*National Heart, Lung, and Blood Institute*
*Office of Research on Women's Health*
*Giovanni Lorenzini Medical Science Foundation*

INTERNATIONAL POSITION PAPER

*on*

# WOMEN'S HEALTH AND MENOPAUSE:

## A COMPREHENSIVE APPROACH

NATIONAL INSTITUTES OF HEALTH

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*and*

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# Preface

*Women's health and menopause is a rapidly expanding field of medical practice and scientific investigation. It is a field of great social importance and impact, nationally and globally, in developed as well as developing countries.*

*Menopause is a normal event in a woman's life. Some women view it as a positive and liberating experience. Others think of it as a negative event. Today, most women live long enough to become postmenopausal. In the developed world, the percentage of women over 50 years of age has tripled in the last 100 years. During this period, women's life expectancy in the United States has increased from 50 to 81.7 years, meaning that more than one third of life will be lived in postmenopause.*

*This "International Position Paper on Women's Health and Menopause: A Comprehensive Approach" is based on extensive international review and evaluation of the scientific evidence for current clinical practices as presented in the published literature. The purpose of this international and multidisciplinary monograph is to enhance the composite health of menopausal and postmenopausal women on a global basis, with consideration of sociocultural concerns and economic issues.*

*The monograph represents the culmination of 7 years of cooperation between the National Heart, Lung, and Blood Institute (NHLBI) and the Giovanni Lorenzini Medical Science Foundation (Milan, Italy and Houston, TX) in a public/private partnership in the development and cosponsorship of four international conferences on Women's Health and Menopause since the mid-1990s. The first three conferences were held in Italy, and the most recent one was held in May 2001 in Washington, DC. The last two conferences were also cosponsored by the Office of Research on Women's Health (ORWH), National Institutes of Health (NIH). These conferences have addressed not only cardiovascular disease, but also other health problems, such as cancer, osteoporosis, and Alzheimer's disease, as well as the use and impact of hormone replacement therapy.*

*Menopause offers the primary care health provider an opportunity to assess a woman's health, her concerns, and her needs for health promotion and disease prevention measures worldwide. Given the multifactorial approaches needed for women during their middle and older years, the NHLBI, the ORWH, and the Giovanni Lorenzini Medical Science Foundation, in a cooperative venture assembled an international panel of experts on menopausal health.*

*The individual chapters of the International Position Paper, prepared by panel members and invited authors, evaluate published research studies to establish relevant background information and compile strategies for management. These were reviewed by internationally acknowledged leaders in their fields. The volume describes and references relevant clinical information and provides evidence-based recommendations for best clinical practices as well as recommendations for future research. Importantly, the goal of this monograph is that the materials be reproduced and translated in individual countries for optimal global dissemination, which will be furthered by presentations at topic-related scientific meetings.*

*On behalf of the NHLBI, I would like to thank Nanette K. Wenger, M.D., chair of the Executive Committee of the International Position Paper; Rodolfo Paoletti, M.D., cochair; Vivian W. Pinn, M.D., cochair; the panel members; the nonpanel coauthors; and the experts who reviewed the preliminary versions of the individual chapters and of the composite document for their valuable scientific contributions and dedication during this 4-year effort to critically review and evaluate extensive international databases on women's health and menopause. I hope that the readers will come away with a sense of appreciation for what biomedical research has accomplished in this important field and anticipation of the many opportunities and needs for future research.*

*Claude Lenfant, M.D.*
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*National Institutes of Health*

# Chapter 1: Executive Summary

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## 1. Introduction

Today, most women live long enough to become menopausal. In the developed world, the percentage of women over 50 years of age has tripled in the last 100 years. Mean female life expectancy has increased from 50 to 81.7 years, meaning that more than one-third of life will be lived in postmenopause. The absolute and relative numbers of older people in both developed and developing countries substantially increased during the 20th century, and the mean age of the population of the world will increase much faster in the next half century. It is projected that there will be almost 2 billion (1,970 million) older persons in 2050, compared with 580 million in 1998; the majority of these elderly are women. The quality of life of older women in the aging population will depend in large measure on the ability of societies to cope with the economic, social, and medical challenges of the postmenopausal years.

Menopause is not a disease, but rather a normal physiologic event in a woman's life. It can be associated, however, with health complaints, a decrease in quality of life, and an increase in risk for illnesses, such as osteoporosis and coronary heart disease (CHD). Studies of menopause are numerous but largely recent. Although many clinically relevant questions remain unanswered, women seeking advice about menopause currently have more options and better interventions for healthy menopausal years than ever before. Menopause is a time in a woman's life when the primary health care provider should assess a woman's health and her need for health promotion and disease prevention measures.

***Menopause is a time in a woman's life when the primary health care provider should assess a woman's health and her need for health promotion and disease prevention measures.***

Given the multifactorial approaches needed for women during their middle and older years, the National Heart, Lung, and Blood Institute (NHLBI) and the Office of Research on Women's Health of the National Institutes of Health (NIH) in Bethesda, MD and the Giovanni Lorenzini Medical Science Foundation of Milan, Italy, and Houston, TX, in a cooperative venture assembled

an international panel of experts on menopausal and postmenopausal health. Through a collaboration that included a series of meetings from November 1998 to July 2000, the Executive Committee and Panel members evaluated published information to determine management strategies that would constitute evidence-based recommendations on menopause for best clinical practice. Evidence statements and recommendations were categorized by a level of evidence ranging from A to D as shown in table 1–1 and indicated within square brackets in the text. Additional participants in document development were referees and reviewers, selected by the Executive Committee in cooperation with the panel members. The resulting multichapter monograph addresses a spectrum of evidence to provide a multidisciplinary approach to the enhancement of menopausal and postmenopausal health globally. Although the evidence reviewed is disease specific, the monograph is designed to enhance the composite health of menopausal and postmenopausal women and is not intended to medicalize menopause.

***Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.***

The terms "*estrogen replacement therapy (ERT)*" and "*hormone replacement therapy (HRT),*" along with their initialisms ERT and HRT, are well established; nevertheless, the panel concurs with critics who view *replacement* as suggesting that menopause is a disease state and that hormonal status should be restored to that of the reproductive years. In the absence of scientific consensus regarding a more appropriate term, the panel has decided to use the term HRT for the present monograph, since HRT is now the most common in use by the medical profession and familiar to the general public. Possible benefits and risks of HRT are summarized in table 1–2.

## 2. Menopause and Aging

- Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathologic or physiologic cause. At present, it can be recognized only retrospectively.
- Endocrine changes will have begun years earlier. Changes in serum concentrations of follicle-stimulating hormone (FSH) and estradiol are maximal in the year of the final menstrual period (FMP). FSH elevation, while a harbinger of menopause, is a poor predictor of age at menopause; the clinician cannot draw any conclusions about the timing of an individual woman's menopause on the basis of the presence or degree of FSH elevation.
- The endocrine changes of menopause do not include any acute decrease in androgens. After menopause, estrone, rather than the more potent estradiol, is the major circulating estrogen. It is produced primarily by peripheral aromatization of androgens, so that fat cells become the major source of endogenous estrogen after menopause.
- There is considerable individual and racial/ethnic variation in age at natural menopause, in climacteric signs and symptoms, and in what may be considered menopause-related sequelae.
- There is a lack of consensus as to whether changes in health occurring during the climacteric or presenting later in life are attributable to menopause and reduced ovarian function or to aging.

## TABLE 1–1

## Evidence Categories

| Evidence Category | Sources of Evidence | Definition |
|---|---|---|
| A | Randomized, controlled trials (rich body of data) | Evidence is from endpoints of well-defined RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A, therefore, requires substantial numbers of studies involving substantial numbers of participants. |
| B | Randomized, controlled trials (limited body of data) | Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post hoc or subgroup analysis of RCTs or meta-analysis of RCTs, controlled trials. In general, category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation. |
| C | Nonrandomized trials and/or observational studies | Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies. |
| D | Expert judgment | Expert judgment is based on the authors' synthesis of evidence from research described in the literature that does not meet the above-listed criteria, taking into consideration critical advice by other members of the international panel of experts, external referees, and external reviewers. The category is used only in cases in which the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C). |

*Source:* Adapted from the NIH. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* Bethesda, MD, 1998; NIH publication no. 98–4083.

## TABLE 1–2

## Possible Benefits and Risks of Hormone Replacement Therapy, With Evidence Categories

| | ***Regimen*** | |
|---|---|---|
| | **Estrogen Alone** | **Estrogen Plus Progestin** |
| ***Possible Benefits*** | | |
| Hot flushes | Significant reductions [A] | Same [A] |
| Symptoms of vulvovaginal atrophy | Improvements, with topical as well as systemic administration [A/C] | Improvements with systemic preparation (only available preparation) [A/C] |
| Decreased sexual function* | Variable success; data inconclusive [B] | Estrogen and androgen: same [B] |
| Urinary flow problems | Alleviation in many cases of urgency, urge incontinence, frequency [B], nocturia, and dysuria [D]; may worsen genuine stress incontinence [A] | Same |
| Urinary tract infection | Reduction in frequency, with local as well as systemic administration [D] | Same [D] |
| Osteoporosis | Maintenance of bone density and favorable effects on markers of bone resorption [A]; marked reduction in risk for vertebral fracture [B]; non-vertebral fracture [C] | Same |
| Oral bone loss* | Possible benefit [C/D] | Same [C/D] |

*Note:* Evidence categories are shown in square brackets. A = randomized clinical trials (rich body of data); B = randomized clinical trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgment. (See also table 1–1.)

* Because clinical data are sparse or inconclusive, consideration of potential benefit would ordinarily be overridden by the extent to which benefits and risks of HRT are well characterized for other organ systems or disorders.

† All findings belong to evidence category C, as they address side effects rather than interventions. This should not weaken the significance of the results.

**TABLE 1–2 *(continued)***

| | ***Regimen*** | |
|---|---|---|
| | **Estrogen Alone** | **Estrogen Plus Progestin** |
| ***Possible Benefits*** | | |
| Neurologic function and mental health* | Possible preservation of certain cognitive skills during the period immediately after induced menopause [B] and during the aging process [C]; possible reduction in risk for Alzheimer's disease with replacement therapy begun after menopause [C], with no effect when begun after the onset of dementia symptoms [B]; possible benefit in certain sleep disorders occurring during the climacteric [C]; possible positive effect on mood [B] | Possible preservation of certain cognitive skills during the aging process [C]; possible reduction in risk for Alzheimer's disease with therapy begun after menopause [C]; possible benefit in certain sleep disorders occurring during the climacteric [C]; possible positive effect on mood [C] |
| Eye* | Little evidence of an effect on age-related maculopathy, cataract, and dry eye [C] | Same [C] |
| Colorectal cancer*† | Possible reduction in risk | Same, but less information available |
| ***Possible Risks*** | | |
| Period-like symptoms, including vaginal bleeding | Vaginal bleeding may occur [A] | May improve, remain the same, or worsen depending on the specific formulation (e.g., MPA versus norethindrone acetate), dose, or schedule (sequential versus combined continuous) of the progestin [A] |
| Mastalgia | Significant increase in breast tenderness [A] | Same or increased discomfort [A] |
| CHD events | Apparent increase in risk in the first 1 or 2 years of therapy [A]; no definitive evidence-based rationale to recommend for prevention of disease | Same |
| Stroke | Conflicting results; no overall effect on stroke risk [B] or possible increase in risk and possible decrease in stroke mortality [C] | Same |

**TABLE 1–2 *(continued)***

| | ***Regimen*** | |
|---|---|---|
| | **Estrogen Alone** | **Estrogen Plus Progestin** |
| ***Possible Risks*** | | |
| Venous thromboembolic events in legs and lungs | Increase in risk, perhaps fourfold increase in RR initially, with a persistent twofold increase thereafter [A] | Similar [A] |
| Breast cancer*† | No appreciable risk association with short-term (< 5 years') use; moderate excess risk with longer use for current users but not for former users | Possible higher risk compared with unopposed estrogen |
| Endometrial cancer*† | Significant increase in risk | Not related to a major excess risk when progestins are given for more than 10–14 days per cycle |
| Ovarian cancer*† | Possible increase in risk | No adequate information |
| Gallbladder disease | Apparent increase in risk [B/C] | Apparent increase in risk [B/C] |
| Asthma | Possible increase in risk with CEEs [C] | No data |

- Estimates of the median age of menopause range from 45 to 55 years worldwide. Understanding of the factors that influence age at menopause is limited. Familial or hereditary factors appear to be the most predictive. Of other variables studied, the most consistent relation is for cigarette smoking, which advances menopause by 1 to 2 years. The timing of menopause may substantially influence subsequent morbidity and mortality.
- Contraception is still needed during the menopausal transition.

## 3. SYMPTOMS AND THE MENOPAUSE

- The climacteric* is sometimes but not always associated with symptoms. There is debate as to whether the term "*symptoms*" should be used when referring to events of the climacteric. The term is used here to refer to those bodily perceptions presented as complaints by the individual woman. The presence of occasional symptoms does not indicate their impact on the woman and may not be clinically relevant or indicative of treatment needs.
- Conflicting findings as to the causes of symptoms in midlife reflect some of the methodologic difficulties inherent in menopause research as well as specific issues pertaining to the measurement of symptoms. General methodologic issues relate to sample selection, validity of

symptom measures, cultural factors, determination of menopausal phase, lack of systematic hormonal level assessment, age at baseline and length of followup, separation of the effects of natural menopause transition from those of induced menopause, and statistical and experimental design. A number of studies suggests that symptom experience is likely to be worse when women have undergone surgical menopause. There is a risk that stereotypes will become operative in menopause research when subjects know the topic of the research.

- Individual women may view menopause as negative and troublesome or positive and liberating. Importantly, the knowledge base on menopause is narrow in that most studies have been carried out on white women of northern European ancestry; relatively little is known about the range of climacteric experiences in women of other racial/ethnic groups. Only studies of women derived randomly from a general population provide findings that can be confidently generalized to be the experience of most women of that particular culture and geographic location.
- The following generalizations about climacteric symptoms can be made.
  - When symptom checklists are used, middle-aged women are highly symptomatic.
  - Age-related symptoms have to be differentiated from those related to the menopausal phase.
  - It is important to consider whether reported symptoms reflect a change relative to a baseline level.
  - Only vasomotor symptoms, vulvovaginal atrophic symptoms, and breast tenderness consistently vary with the phase of the climacteric and are significantly affected [A] by the administration of hormones.
  - Other symptoms, such as insomnia and changes in mood, may be affected by the presence of bothersome vasomotor symptoms.
  - Symptoms are influenced by psychosocial and lifestyle factors.

### 3.1 Vasomotor Symptoms

In North America and Europe, most women have at least some menopausal hot flushes (also called hot flashes). While menopausal hot flushes have been described in a limited number of studies in a variety of other cultures, the prevalence varies widely. There is consensus about the marked temporal relation of vasomotor symptoms to the climacteric. They begin to increase in the menopausal transition, peak 1 to 2 years after the FMP, and may remain increased for several years. A number of studies have shown a statistical relation between hot flushes and night sweats, and some show a relation between those vasomotor symptoms and insomnia. The mechanism of menopausal flushing remains unclear. Core body temperature elevations precede the menopausal hot flush and serve as one trigger of the heat loss phenomenon, but what is responsible for the core temperature elevation is uncertain.

***The knowledge base on menopause is narrow in that most studies have been carried out on white women of northern European ancestry.***

- ***Hormone replacement therapy.*** Estrogen therapy is effective in reducing hot flushes [A]. The use of continuous or sequential progestins with estrogen does not reduce the efficacy of estrogen in the reduction of hot flushes.
- ***Other pharmacologic agents.*** Other agents reported to be more effective than placebo in decreasing hot flushes include megestrol acetate, veralipride, opipramol, venlafaxine, sertraline, paroxetine, and tibolone [B].

* Perimenopause comprises the period of time immediately before menopause (when the endocrinologic, biologic, and clinical features of approaching menopause commence) and the first year after menopause. The climacteric incorporates perimenopause by extending for a longer, variable period of time before and after it.

- ***Physical activity.*** Evidence is conflicting as to whether increased physical activity affects menopausal symptoms.
- ***Foods and beverages.*** Avoidance of hot beverages, foods containing nitrites or sulfites, spicy foods, and alcohol may help limit hot flushes.
- ***Phytoestrogens.*** Although some evidence suggests that dietary supplementation with phytoestrogens yields improvements in hot flushes, the issue remains unclear because of methodologic limitations of the studies.

***Estrogen therapy is effective in reducing hot flushes.***

- ***Gamma-linolenic acid.*** Gamma-linolenic acid provided in evening primrose oil, a popular alternative therapy, appears to offer no benefit over placebo in the treatment of vasomotor symptoms [B].

#### 3.2 Vulvovaginal Atrophic Symptoms

Atrophic changes of the vulva, vagina, and lower urinary tract are common causes of complaints among menopausal women. Only vulvovaginal atrophic changes can be clearly related to menopause; findings as to whether disorders of urinary tract atrophy are menopause or age related are conflicting. (See also "Lower Genital and Urinary Tract Atrophy" in "Gynecologic and Urinary Aspects" below.) With estrogen loss, the vagina shortens and narrows, and its walls become thinner. Decreased production of lactic and acetic acids alters the normal low vaginal pH, to create a milieu that does not favor continued growth of the normal flora. A decrease in estrogen-supported lubrication causes vaginal dryness, which can lead to vaginitis, vaginismus, and dyspareunia. Cystocele and rectocele are also common problems in postmenopausal women.

- ***Hormone replacement therapy***. Estrogen therapy is effective in relieving vulvovaginal atrophic symptoms, and local estrogen preparations are as effective as systemic ones [A]. In observational studies, ERT reduces the frequency of urinary tract infections in the menopausal years [D].

#### 3.3 Mastalgia (Breast Soreness/Tenderness)

In clinical trials, mastalgia has been related to estrogen and progestin concentrations [A]. Mastalgia that is related to the menstrual period often resolves with menopause. Compliance with HRT can be limited by the side effect of mastalgia.

## 4. Sociocultural Issues

- Attitudes toward and beliefs about menopause vary historically and among cultures [C].
- Cross-cultural comparisons demonstrate that reported symptoms can vary significantly among countries and among ethnic groups within countries in type (e.g., vasomotor, psychologic) and in the degree of distress caused [C].
- Difficulties in integrating findings from cross-cultural studies stem from a number of limitations. Among these are differences among cultures in language used to describe symptoms, use of different methodologies in study design and in instruments used to measure symptoms, and differences in diet and other lifestyle factors that make it difficult to establish cultural versus biologic causes of symptom expression.
- A better appreciation of cross-cultural differences in the experience of menopause may derive from an emerging interdisciplinary model in which symptoms are seen as a result of increased vulnerability due to hormonal changes in interaction with psychologic and sociocultural factors.

## 5. Physiological Role of Estrogen and Estrogen Receptors and Pharmacologic Modulation of Estrogen Receptor Activity

- The two known estrogen receptor (ER) subtypes, ERα and ERβ, mediate many biologic effects of estrogens and antiestrogens.
- Different ligands induce different ER conformations.
- Different mechanisms of target gene regulation affect the agonist/antagonist profile of a ligand. Selective ER modulators (SERMs) have a tissue- and gene-specific mixed agonist/antagonist effect.
- Of interest are the SERMs (third-generation HRT), nonsteroidal agents that behave as agonists in target tissues such as bone and liver and as antagonists or partial agonists in reproductive tissues [A/B].
- Both subtypes are also important for normal ovarian follicular development and female fertility.
- Available data suggest that ERα plays an important role in bone maturation and homeostasis in both women and men, and that ERβ has a specific role in bone physiology in women.
- ERα and ERβ are expressed in vascular endothelial cells, vascular smooth muscle cells, and myocardial cells. Beneficial effects of estrogens on cardiovascular function and reactivity stem from direct effects on cells in the vascular system and also from effects on liver and on circulating monocytes/macrophages.
- In the central nervous system (CNS), estrogen is linked to a variety of functions, including learning, memory, awareness, fine motor skills, temperature regulation, mood, reproductive functions, and depression. The predominance of expression and localization of ERβ in rat neocortex, hippocampus, and nuclei of the basal forebrain suggests an important role for ERβ in learning and memory.
- Estrogen and inhibins produced by the ovaries are important feedback regulators of the hypothalamic-pituitary axis and serum concentrations of luteinizing hormone (LH) and FSH. ERα seems to be more involved than ERβ in the LH, FSH feedback loop.
- Increased knowledge of the structure of ERs and of the mechanisms of the receptors' synthesis and their interaction with key elements of the transcription apparatus is facilitating the synthesis of new pharmacologically active molecules.
- ERα- and ERβ-selective SERMs in development might provide improved therapy. Since both ER subtypes are expressed in human breast cancer, measurements of both ERα and ERβ may help in the selection of appropriate breast cancer therapy.

### 5.1 Hormone Replacement Therapy and Related Therapies

***The two known ER subtypes, ERα and ERβ, mediate many biologic effects of estrogens and antiestrogens.***

The regimens most commonly used to treat climacteric symptoms and to intervene against menopausal and postmenopausal health risks are 17β-estradiol, esterified estrogens, and conjugated equine estrogens (CEEs) in combination with a progestin, for example, medroxyprogesterone acetate (MPA). The awareness of undesired effects and serious health risks (breast cancer, endometrial cancer, and venous thromboembolism) with existing HRT call for alternatives with improved safety profiles.

Alternative regimens for women who do not wish to take estrogen exist. Non-ER subtype-selective SERMs display tissue-selective estrogen agonism. They do not increase the risk of breast and endometrial cancer but aggravate hot flushes and increase the risk of venous thromboembolism. The existence of two ER subtypes provides the oppor-

tunity to develop ER subtype-selective ligands; such agents will likely have improved therapeutic profiles. Novel synthetic steroidal ER agonists hold promise because of agonist activity for progesterone and androgen receptors.

## 6. Sexuality

***Multiple population-based studies imply a decrease in female sexual function associated with the midlife years.***

Multiple population-based studies imply a decrease in female sexual function associated with the midlife years, and there is growing evidence that the decrease reflects hormonal changes of the menopausal transition rather than increasing age. Hormonal change is only one of many factors that affect sexual function. Other factors include presence of a sexual partner, partner's age and health, length of the relationship, feelings toward the partner, level of past sexual function, social class, educational level, experience of physical or psychologic ill health, stressors, employment, personality factors, and negative attitudes toward menopause.

- Declining sexual function is common but not universal with aging. There may be an additional decrement associated with the menopausal transition.
- The causes of decreased sexual activity are multiple and include physiologic, psychological, and social factors.
- Definitions and Classification of Female Sexual Dysfunction given by the consensus panel of the Sexual Function Health Council of the American Foundation for Urologic Disease provide a standardized system for clinical diagnosis and treatment and are recommended for use by health care professionals [D].
- Sexual interest, behavior, and activity should be routinely assessed at office visits on a regular basis, and a plan should be developed to address the woman's concerns.
- HRT (estrogen or estrogen plus androgen) and behavioral therapy have had variable success in the treatment of sexual dysfunction [B] but should be considered in patients who desire treatment.
  - ***Hormone replacement therapy***. Although estrogen is effective in relieving vulvovaginal atrophic symptoms, including increasing vaginal lubrication, HRT has not been consistently shown to increase sexual desire or activity [B].

## 7. Cardiovascular and Pulmonary Disease

- Cardiovascular disease (CVD) remains the commonest single cause of female mortality and morbidity in the western world [C]. Despite the protection apparently offered by endogenous sex hormones in their premenopausal years, the longevity of women exposes them to a lifetime risk for coronary and other vascular diseases similar to that of men. There is a wide variation in CHD incidence among countries. In countries in which the incidence is high in men, it is also high in women; likewise, the incidence is low in women and men in countries with low rates of CHD. Because CVD tends to develop at a later age in women than in men, women are more likely to have complicating comorbidities, such as hypertension and diabetes mellitus, which contribute to poorer short-term outcomes after coronary events or revascularization.

### 7.1 Coronary Heart Disease

- Major modifiable risk factors for atherosclerotic CHD are similar in women and men and include dyslipidemia, hypertension, diabetes mellitus, cigarette smoking, lack of physical activity, and obesity (especially abdominal obesity) [C].

The atherogenic risk profile of older women is appreciably more adverse than that of younger women, although it is uncertain whether age or hormone status is the primary determinant of the evolution of the adverse risk profile.

- Large randomized, placebo-controlled clinical trials have shown that beta-blockers, aspirin, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), and angiotensin-converting enzyme (ACE) inhibitors reduce risk for CHD events in women as well as in men [A]. For some of these therapies, the evidence derives largely from secondary prevention trials; in general, therapies that work in secondary prevention will work in primary prevention as well. Treatment effects appear to be similar in women and men. For example, meta-analysis of data from several major lipid-lowering statin trials showed a 29-percent reduction in risk for major CHD events in women, similar to the 31-percent reduction observed in men.
  - HRT has consistently been shown to improve the blood lipoprotein profile markedly, and many large observational studies found that menopausal women who chose to use hormone therapy had a 35- to 50-percent lower risk for CHD than nonusers. In contrast, no hormone benefit on hard cardiovascular outcomes, such as myocardial infarction (MI) or cardiac death, has been demonstrated in clinical trials [B]. In fact, there appears to be an excess risk for cardiovascular events in the first year or two of treatment [A], although coronary benefit over the long term remains possible [B].
    - In the Heart and Estrogen/progestin Replacement Study (HERS), the first published large trial conducted in postmenopausal U.S. women with CHD, those assigned to daily oral CEE plus MPA had an increased relative risk (RR) versus placebo for nonfatal MI and coronary death during the first year and did not have coronary benefit across the average followup of 4.1 years. Also, more women in the hormone replacement group experienced venous thromboembolic events and gallbladder disease [A].
    - The large Women's Health Initiative (WHI) trial of HRT in the United States includes predominantly women without prior CVD and includes women treated with daily CEEs alone or daily CEEs with MPA, versus placebo. All WHI participants were informed of an increased risk associated with active treatment for heart attack and stroke, during the first 2 years after enrollment (www.nhlbi.nih.gov/whi/hrt-en.htm). The majority of participants did not have prior CVD, and the subgroup with prior disease did not account alone for these findings. The trial is continuing to assess long-term benefits and risks of HRT [B].

***Major modifiable risk factors for atherosclerotic CHD are similar in women and men and include dyslipidemia, hypertension, diabetes mellitus, cigarette smoking, lack of physical activity, and obesity.***

    - In the angiographic Estrogen Replacement and Atherosclerosis (ERA) study, there was no coronary angiographic lesion benefit from either estrogen or estrogen plus progestin replacement therapy compared with placebo [A].
    - Preliminary results from the PHASE trial of transdermal HRT for secondary prevention have not shown cardioprotective benefit to postmenopausal women taking estrogen or estrogen plus a progestin compared to the placebo group [B].[1]

A lack of benefit may be due to countervailing adverse changes in coagulation or inflammatory mechanisms. In view of sex differences in atherosclerotic plaque and the vascular remodeling effects of estrogen and progesterone, other doses, preparations, or routes of administration may prove to have an important role in the prevention of CVD in women.

- ***Hormone replacement therapy.*** There is no definitive evidence-based rationale to recommend HRT for the prevention of CHD [A].
  - At present, prevention of CHD should rely on identifying and treating the classic risk factors, such as dyslipidemia, hypertension, diabetes mellitus, smoking, obesity, and sedentary lifestyle [A]. Vigilant management of risk for CHD in women is imperative.

***There is no definitive evidence-based rationale to recommend HRT for the prevention of CHD.***

  - Instead of HRT, HMG-CoA reductase inhibitors (statins), beta-blockers, ACE inhibitors, and aspirin should be recommended to all eligible women with CHD or diabetes mellitus [A].
- ***Phytoestrogens and selective estrogen receptor modulators.*** There are insufficient data to make recommendations regarding the use of soy phytoestrogens or SERMs for prevention of CHD [C].

### 7.2 Stroke

Despite similar stroke rates, women are more likely than men to die of stroke. The main risk factors for stroke are not gender dependent. Although strokes are more closely related to hypertension (which is probably their most important risk factor) than to hypercholesterolemia, HMG-CoA reductase inhibitors (statins) reduce risk for stroke, as do antihypertensive medications.

- ***Hormone replacement therapy.*** HRT has not been consistently linked to stroke protection. In the HERS trial of continuous CEEs combined with MPA in women with prior CHD, HRT was not significantly associated with risk of nonfatal or fatal stroke or transient ischemic attack [B]. Results of the first clinical trial of HRT in women with prior stroke indicate no reduction in the risk for recurrent stroke and death and suggest increased risk for more severe strokes in the first few months after initiation of HRT [B].[2]

### 7.3 Peripheral Vascular Disease

Peripheral vascular disease occurs fairly commonly in women, and, as in all atherothrombotic CVD incidence increases with age in women. Smoking is the most prevalent risk factor for peripheral vascular disease, as it is in men. Peripheral vascular disease carries with it an increased risk for CHD, which is not gender dependent.

- ***Hormone replacement therapy.*** The effect of HRT on peripheral vascular disease is unknown.

### 7.4 Venous Thromboembolism

Modifiable risk factors for venous thromboembolism include the presence of hemostatic disorders, immobilization, and perhaps obesity. Although most cases of venous thrombosis are not fatal, death from pulmonary embolism can occur, and postthrombotic syndrome occurs in as many as one-fourth of patients with deep venous thrombosis. Venous thromboembolism remains a major cause of morbidity and mortality after gynecologic surgery.

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[1] Clarke S, Kelleher J, Lloyd-Jones H, et al. Transdermal hormone replacement therapy for secondary prevention of coronary artery disease in postmenopausal women. *Eur Heart J* 2000;21(Abstract Supplment):212.

[2] Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243–9.

- ***Hormone replacement therapy:*** Findings from recent observational studies and data from clinical trials show a consistent increase in risk for venous thromboembolic events in women taking estrogen compared with those that do not [A]. These studies indicate that there may be a fourfold increase in RR initially, with a persistent twofold increase in risk thereafter. The increased risk for venous thromboembolism was similar in women using an estrogen plus progestin [B]. Similar risk is associated with the SERM raloxifene.[3]

### 7.5 Pulmonary Disease

Estrogen may play a role in the pathophysiology of asthma. Observational studies suggest a positive dose response for use of CEEs and risk for asthma. Otherwise, there appears to be little impact of menopause or HRT on the pulmonary system, although further research is warranted.

## 8. Osteoporosis and Oral Bone Loss: Risks and Therapy

### 8.1 Osteoporosis

- Osteoporosis affects a large proportion of the population of elderly women throughout the world. More women than men are affected. The overall lifetime risk for fractures in women in the United States and most European countries is from 30 to 40 percent, but there is clear variability across cultures. Worldwide for women and men, about 1.26 million hip fractures occur each year, a number expected to double by 2025.
- Rates of osteoporosis and related bone fractures increase with age. Low bone mass at menopause can be due to insufficient bone acquisition during growth or bone loss during adulthood. Ovarian failure heralds dramatic changes in skeletal homeostasis. Bone loss accelerates for a few years after natural menopause or oophorectomy, and continues at a lower rate for the remainder of life. The mechanism of how loss of estrogen at menopause contributes significantly to skeletal bone loss is not completely understood. Postmenopausal bone loss may be exacerbated by low levels of physical activity and poor nutrition, especially low calcium intake. Severe bone loss and fractures are not natural consequences of aging and can be prevented or substantially delayed.
- The principal method for making the diagnosis of osteoporosis is evaluation of the skeleton by using a noninvasive measurement of bone mineral density (BMD). Fracture risk is the most important determinant in patient selection for treatment or intervention for osteoporosis, although bone density is only one of many risk factors that contribute to risk for fracture. Although there has been major progress in methods for assessing risk for osteoporotic fracture, identifying individuals at greatest need for treatment remains a problem.

***Osteoporosis affects a large proportion of the population of elderly women throughout the world.***

#### *8.1.1 Nonpharmacologic Interventions*

Adequate nutrition—in particular, but not exclusively, from intake of calcium and vitamin D—and adequate physical activity are requisite preventive efforts against osteoporosis throughout life. Avoidance of tobacco use and moderation in alcohol intake are obvious.

- ***Calcium***. Adequate calcium intake in older adults can retard bone loss and reduce risk for fracture. While it is recommended that calcium be obtained from the diet, not all

[3] Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE *randomized* trial. Multiple Outcomes of Raloxifene Evaluation [published erratum appears in *JAMA* 1999;282:2124]. *JAMA* 1999 281:2189-97.

individuals are able to increase calcium intake in this way. In such individuals, supplementation may be encouraged. In the United States, it is recommended that an average intake of about 1,200 mg of calcium per day should be achieved by adults ≥ 51 years of age [Dietary Reference Intake (DRI)].

- ***Vitamin D.*** Because it is inexpensive to provide vitamin D and because many of the controlled studies of calcium also used vitamin D supplementation, supplements of vitamin D are recommended for at-risk populations, especially those 65 years of age and older. For at-risk populations, 700 to 800 IU (international units) of vitamin D per day may be sufficient.

***ERT maintains bone density and favorably influences markers of bone resorption.***

- ***Physical activity.*** Bone density responses to increased physical activity in adults have been fairly modest. The type of exercise that promotes bone response may be different from the type recommended for aerobic fitness: Muscle building, weight bearing, resistance exercise is required to alter bone density [A]. Where not medically contraindicated, increased physical activity should be encouraged for all.

#### *8.1.2 Pharmacologic Interventions*

A decade ago estrogen and injectable calcitonin were the only available pharmacologic therapies for menopausal women with osteoporosis. Now there are new bone-specific drugs (e.g., bisphosphonates and parathyroid hormone (PTH)) and broad-spectrum drugs (e.g., SERMs) that combat osteoporosis and have potentially beneficial effects in other organ systems, as well as calcitonin delivered as an intranasal spray.

- ***Hormone replacement therapy.*** ERT maintains bone density and favorably influences markers of bone resorption [A].[4] Long-term and continuing use of estrogen markedly reduces risk for fracture; discontinuation allows bone loss to occur, and fracture protection wanes [B].
- ***Selective estrogen receptor modulators.*** The SERM raloxifene exerts effects similar to those of estrogen in the skeleton and has been shown to prevent vertebral fractures [A].
- ***Bisphosphonate therapy.*** The first-generation bisphosphonate, etidronate, reduces vertebral but not nonvertebral fractures. Newer and more potent bisphosphonates have been shown to reduce risk for vertebral fracture by approximately 45 percent and to reduce risk for nonspine fracture to a lesser but clinically important degree [A].
- ***Salmon calcitonin.*** Salmon calcitonin can reduce resorption and help preserve bone mass. Vertebral fracture rates may be reduced [A/B]. Benefit in peripheral fracture risk has been suggested, but data are not conclusive.

Choosing among estrogen preparations, raloxifene, bisphosphonates, and calcitonin is challenging for individual patients. Considerations are the need for prevention versus treatment, the need for bone-specific versus broad-spectrum effects, patient acceptability and tolerance, and cost. The long-term effects of many of the newer agents (SERMs and bisphosphonates) are not known.

### 8.2 Oral Bone Loss

Oral bone, like the rest of the skeleton, comprises both trabecular and cortical bone and undergoes formation and resorption throughout the lifespan. When oral bone loss exceeds gain, it manifests as either loss of tooth-anchoring support or a diminu-

[4] Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;285(22):2891–7.

tion of the remaining ridge in areas of partial or complete tooth loss.

The prevalence of oral bone loss is significant among adult populations worldwide and increases with age for both sexes. Oral bone loss and attendant tooth loss are associated with estrogen deficiency and osteoporosis [C]. As a consequence, women's experiences with postmenopausal osteopenia may affect the need for, and outcome of, a variety of periodontal and prosthetic procedures, including guided tissue regeneration and tooth implantation [D]. Furthermore, it is possible that oral examination and radiographic findings may be useful signs of extraoral bone diminution [C].

#### *8.2.1 Interventions*

Nonpharmacologic approaches to preserving oral bone include oral hygiene self-care behaviors, such as brushing and flossing; professional dental services, including oral examination, tooth scaling, and polishing; and smoking cessation. Calcium and vitamin D supplementation and pharmacologic therapies for osteoporosis, including HRT and bisphosphonates, may yield positive oral bone effects [C].

## 9. Gynecologic and Urinary Aspects

Atrophic changes of the vulva and vagina are discussed in "Vulvovaginal Atrophic Symptoms" above ("Symptoms and the Menopause"). The present section highlights the assessment of uterine bleeding in older women, the occurrence of lower urinary tract atrophy, and abnormalities of pelvic floor and urinary tract.

### 9.1 Assessment of Uterine Bleeding

- During the menopausal transition, women request consultation for gynecologic evaluation when cycle irregularities start or when hot flushes and other complaints related to hypoestrogenemia occur. The gynecologist may be the only medical contact for healthy women.
- Different patterns of uterine bleeding can be confusing when they occur in older women, and physicians must be alert to the possibility of genital tract pathology. Endometrial bleeding can be linked to endometrial pathology (atrophy, polyps, submucosal leiomyoma, hyperplasia, adenocarcinoma) or to general pathology, dysfunctional conditions, or drugs. Dysfunctional uterine bleeding is common between ages 40 and 50 years. The associated endometrial histology is highly variable. In some patients with bleeding, the endometrial histologic findings appear out of phase with endocrine events. In many, the endometrium will be hyperplastic and may be secretory until the year before menopause. In postmenopausal women, endometrial atrophy is the most common histologic finding.
- Cancer is not the most common cause of abnormal bleeding in perimenopausal women, but abnormal uterine bleeding occurring during perimenopause should be considered secondary to malignancy until proven otherwise. The most important risk factors for endometrial cancer are obesity and menopausal use of unopposed estrogen, even at low dosages. See "HRT, Related Therapies, and Cancer Epidemiology" below, for a discussion of HRT and risk for endometrial cancer. Endometrial hyperplasia is a premalignant lesion, particularly when atypia is present. Endometrial hyperplasia but not atypia can be reversed by the administration of progestin.

***Different patterns of uterine bleeding can be confusing when they occur in older women, and physicians must be alert to the possibility of genital tract pathology.***

- Bleeding during the estrogen-only phase of sequential combined HRT is much more likely to be associated with endometrial pathology than bleeding during the progestin phase. No

available hormone formulation suits all women. Prolonged and/or heavy cyclical bleeding may be due to excess estrogen or insufficient progestin in the sequential formulation or to endometrial pathology. Breakthrough bleeding is associated with a hyperplastic endometrium but may also occur with an atrophic endometrium. Continuous administration of progestins with estrogens has been suggested to prevent the cyclical withdrawal bleeding associated with hormone regimens. A high incidence of irregular bleeding episodes (50 percent) has been observed during the first year.

***In observational studies, ERT reduces the frequency of urinary tract infections in the postmenopausal years.***

- Transvaginal ultrasonographic measurement of endometrial thickness provides a noninvasive clinical indicator of endometrial status. Endometrial thickness < 4 mm usually corresponds to histologically atrophic endometrium; thickness greater than 4 to 7 mm correlates with increased incidence of endometrial pathology in postmenopausal women. The exact level is uncertain in women receiving HRT whose endometrium is often thicker than in untreated postmenopausal women. Present-day ultrasound scanning cannot replace histopathologic assessment of the endometrium in women receiving HRT. Management of bleeding during HRT includes observation, surgery, and specific changes in the treatment regimen.

### 9.2 Lower Genital and Urinary Tract Atrophy

- The epithelium of the inner layer of the vagina has high levels of ERs and undergoes progressive loss of cells during menopause due to estrogen depletion. Estrogen-dependent secretions decrease, leading to vaginal dryness and, in some women, vaginitis, vaginismus, and dispareunia. Local estrogen proved as effective as systemic in treatment for vaginal dryness [A].
- Loss of glycogen-producing cells, a consequence of vaginal and urethral atrophy, causes decreased production of lactic acid and an environment that favors vaginal and urethral infection. It is important to identify and treat patients with recurrent infections to prevent significant morbidity, which includes risk for renal impairment.
- In observational studies, ERT reduces the frequency of urinary tract infections in the postmenopausal years [D]. Its beneficial effects can partially be explained through its support of normal vaginal flora.

### 9.3 Pelvic Floor and Urinary Incontinence

- All four functional layers of the urethra—epithelium, connective tissue, vascular tissue, and muscle—are affected by estrogen status. Estrogen deficiency causes atrophic changes of the urethral epithelium and of the submucosa.
- Urinary incontinence (UI) is defined by the International Continence Society as involuntary loss of urine that is objectively demonstrable and is a social or hygienic problem.
- The relationship between menopause and UI is unknown and not well studied. Limited data are available to support the hypothesis that menopause is a major risk factor for incontinence, especially for stress and urge incontinence.
- Established UI can usually be divided as follows: stress incontinence, which occurs in the absence of detrusor activity; urge incontinence, when detrusor muscle contracts during the filling phase of the bladder; mixed incontinence, which is a combination of both stress and urge incontinence; and overflow incontinence, which is the result of bladder obstruction or injury. Other factors that can cause UI include decreased mobility, cognitive impairment, or medications.
- Evaluation and treatment for incontinence is dependent on the type of incontinence and the person's age, medical history, and desire for therapy.

#### 9.3.1 Interventions

- In many cases, urine leakage can be prevented or improved by improving pelvic muscle tone through different kinds of exercises. Pelvic floor exercises (including Kegel exercises), vaginal weight training, and pelvic floor electrical stimulation significantly reduce incontinence in RCTs [A].
- Behavioral therapies can help patients regain control of bladder function. *Bladder training* teaches people to resist the urge to void and gradually expand the intervals between voiding. *Toilet assistance* uses routine or scheduled toileting, habit training schedules, and prompted voiding to empty the bladder regularly to prevent leaking.
- Pharmacological therapies for the treatment of UI vary accordingly to the kind of incontinence that needs to be treated.
    - ***Muscarinic receptor antagonists.*** Both tolterodine tatrate and oxybutinine significantly increased volume-voided/micturition and decreased micturition and incontinence episodes per 24 hours compared to placebo, but tolterodine only was significantly better than placebo in reducing micturition frequency [A].
    - ***Hormone replacement therapy.*** Uncontrolled trials showed subjective improvement of incontinence upon estrogen treatment, while no objective improvement in measures of urine loss was found in RCTs [A]. HERS found HRT to be associated with worsening of stress UI [A]. By reducing potential afferent stimuli from the bladder, such as lower urinary tract infections, estrogen may benefit urge incontinence [C].
    - ***Bulking injections.*** Periurethral injection of collagen in women with genuine stress incontinence and intrinsic sphincter deficiency has a low short-term cure rate and has not been shown to improve stress incontinence long-term [A].
    - ***Surgical treatment.*** This intervention can be very effective in improving or curing stress incontinence.

## 10. Menopausal Therapies and Cancer

Experimental, clinical, and epidemiological data support an important role for reproductive hormones in the aetiology of some human cancers, including breast, endometrium, and ovary. Whereas for common adult cancers, such as lung and colon cancers, incidence rises continuously and progressively with age, the slope of increase slows around the time of menopause for most hormone-dependent cancers. Worldwide, breast cancer is by far the most frequent invasive cancer in women and the leading cause of cancer death in women, accounting for more than 300,000 deaths each year. Ovarian cancer adds another 100,000 deaths each year, and cancer of the corpus uteri adds 40,000. The issue of the effect of menopausal therapies on risk for cancer is a critical one.

### 10.1 Hormone Replacement Therapy

Most of the potential favourable and adverse effects of HRT on cancer risks are restricted to current users.

- ***Breast cancer.*** In observational studies, there is no appreciable association between less than 5 years of use of HRT and risk for breast cancer. Longer use is associated with a small but significant excess breast cancer risk for current users but not for former users. Combined HRT may be associated with higher breast cancer risk compared with unopposed estrogen.

***Worldwide, breast cancer is by far the most frequent invasive cancer in women and the leading cause of cancer death in women.***

- ***Endometrial cancer.*** Estrogen use is strongly related to increased risk for endometrial cancer. When progestins are given for 10 days or more per cycle, combined HRT is not related to a major excess risk for endometrial cancer.
- ***Ovarian cancer.*** Results of observational studies of HRT and ovarian cancer have been inconsistent. Available findings include the possibility that HRT increases risk for cancer of the ovary.
- ***Colorectal cancer.*** Observational studies suggest that HRT may reduce risk for colorectal cancer. No clinical trial data are available.
- ***Other cancers.*** There is no consistent relationship between the use of HRT and liver cancer, other digestive neoplasms, or melanoma.

### 10.2 Selective Estrogen Receptor Modulators

Given the recognized adverse effects of HRT, much recent attention has focused on assessing alternative approaches to treating menopause, including use of tamoxifen and other SERMs. SERMs may offer many of the advantages of HRT while eliminating some of the disadvantages.

- ***Breast cancer.*** SERMs may reduce risk for breast cancer. Tamoxifen has been shown to reduce the risk for breast cancer by almost 50 percent. One clinical study of raloxifene showed a strikingly reduced risk.[3] Further studies of tamoxifen and raloxifene are in progress.

## 11. Neurologic Function, Mental Health, and Eye

The CNS and eye are among the many tissues thought to be affected by hormonal changes around the time of menopause. In the brain and eye, as in other target organ systems, estrogen interacts with specific intranuclear receptors and putative membrane receptors to regulate intracellular processes. HRT with estrogen or other sex steroids has the potential to influence brain and eye functions.

Few clinical characteristics or diagnostic procedures identify subgroups of women who can benefit from HRT for the prevention or treatment of disorders of neurologic function, mental health, or the eye [D]. Despite a strong biologic rationale, clinical data are sparse. Thus, recommendations regarding HRT to prevent or ameliorate the disorders are necessarily limited.

### 11.1 Cognitive Decline

Memory and other cognitive abilities change over time during adult life. Changes that represent «usual» or «normal» accompaniments of aging are not viewed as pathologic. Modest cognitive decrements initially detectable in middle age are accentuated at elderly age. Many studies suggest that sex hormones influence brain function throughout life, but there is little evidence that menopause per se initiates cognitive deterioration, and serum estrogen concentrations in postmenopausal women do not appear to be closely related to cognitive skills.

- ***Hormone replacement therapy.*** ERT may help preserve specific cognitive skills (e.g., verbal memory) immediately after induced menopause [B]. Clinical trial data of cognitive function with HRT during normal aging are limited and inconsistent [C].

### 11.2 Alzheimer's Disease and Other Neurologic Disorders

A number of neurologic conditions are associated with aging.

- ***Hormone replacement therapy***
  - Alzheimer's disease. HRT begun after menopause may reduce risk of Alzheimer's disease [C]. In contrast, ERT begun after the onset of dementia does not improve Alzheimer symptoms [B].
  - Stroke. HRT does not appear to modify substantially the risk of stroke in older healthy women [A].
  - Other neurologic disorders. For many neurologic disorders, including epilepsy, migraine headache, multiple sclerosis, and

Parkinson's disease, no overall positive or negative impact of menopause or HRT on neurologic symptoms or disability has been described [C].

- Sleep disorders. Some sleep disturbances occurring during the climacteric may benefit from HRT [C].

### 11.3 Mental Health

Women of all ages have higher rates of depression than men, and geriatric depression is a particularly important public health concern. Hot flushes and other climacteric symptoms clearly affect the quality of a woman's life. The menopausal transition does not appear to represent a time of heightened vulnerability to affective disorders.

- ***Hormone replacement therapy***
  - Mood. Hormonal changes associated with menopause have little direct impact on mood [C]. Limited data from studies of women without clinical depression suggest a beneficial effect of estrogen on mood [B].

### 11.4 Eye

Increasing age is often accompanied by visual loss or blindness, and diminished visual acuity among older persons affects women more often than men. Some observational studies suggest the potential relevance of estrogen in eye disease.

- ***Hormone replacement therapy***
  - Maculopathy, cataract, and dry eye. There is little evidence that HRT alters risk for certain types of age-related maculopathy, cataract, or dry eye [C].

## 12. Future Needs

As life expectancy continues to increase, a challenge for the future will be to maintain and improve the quality of life in women as they age through better management of menopausal symptoms and health risks associated with menopause. Despite exciting new research in the field of menopause, including the availability of more choices for intervention and major breakthroughs in the understanding of ER-mediated effects, much work remains to be done. The increasing number of postmenopausal women and their increasing longevity highlight the importance of women's health and well-being.

Key needs for the field of menopause in the near future are outlined in table 1–3.

***Limited data from studies of women without clinical depression suggest a beneficial effect of estrogen on mood.***

**Note:**
The Women's Health Initiative, NHLBI, NIH, is referred to throughout this International Position Paper. As this document went to press, the NHLBI stopped an important component of the WHI on the basis of recommendations by the study's Data and Safety Monitoring Board (DSMB), an independent advisory committee. The reasons for stopping this major clinical trial of estrogen plus progestin early were due to an increased risk of invasive breast cancer as well as increases in coronary heart disease, stroke, and pulmonary embolism in participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefits. The study, which was scheduled to run until 2005, was stopped after an average follow-up of 5.2 years. However, because the balance of risks and benefits of estrogen alone is still uncertain, the DSMB recommended that that component of the WHI be continued unchanged.

Because of the importance of the information from the estrogen plus progestin study, the results were released early in an expedited article on July 9, 2002 on the JAMA Website. Links to the JAMA article and a related editorial, can be found at http://www.nhlbi.nih.gov/whi/hrtupd/.

## TABLE 1–3

## Women's Health and Menopause: Future Needs

### Menopause and Aging

- Conduct more research on the biologic and psychosocial processes of menopause.
- Conduct additional longitudinal studies using prospective observational designs and large cohorts on the natural history of menopause representing women from a broad array of racial/ethnic and socioeconomic backgrounds.
- Undertake additional menstrual diary research with concurrent hormone measures, to establish biomarkers of women's proximity to menopause.
- Undertake additional research on fertility and contraception in the perimenopause.
- Further understanding is needed about the reciprocal influences of lifestyle, decision to use HRT, and quality of life.
- Providing women and their families with balanced information about menopause, fostering positive attitudes towards aging and menopause, and encouraging healthy lifestyles may improve their health and quality of life related to menopause.

### Symptoms and the Menopause

- Better document the natural menopausal transition through prospective investigations to distinguish menopause-related changes from those of aging or disease.
- Conduct questionnaire studies validating phytoestrogen intake against metabolic measures of metabolites in different cultural settings.
- Conduct a larger RCT of phytoestrogen supplementation, including metabolic measures of metabolite levels.

### Sociocultural Issues

- Undertake better controlled population-based studies using standardized instruments adapted to the culture studied.
- Develop an interactive psycho-bio-cultural model of menopause.
- Disseminate research results within cultures under study, so that women can make their own decisions about the need for and choice of interventions and treatment strategies.
- Conduct more interdisciplinary research for a better understanding of interactive factors.

### Physiological Role of Estrogen and Estrogen Receptors and Pharmacologic Modulation of Estrogen Receptor Activity

- Further characterize a possible antiproliferative role of ERβ in the uterus and mammary gland.
- Determine the physiologic functions of ERβ in the ovary (role in polycystic ovarian syndrome?), bladder, urethra, bone, cardiovascular system, immune system, and CNS.
- Develop ERα- and ERβ-specific agonists and antagonists for experimental and therapeutic purposes.
- Attain different profiles of action for exogenous estradiol through use of different formulations.
- Obtain higher specificity of action by identification of new target molecules involved in gene transcription.
- Increase knowledge of the mechanisms involved in ER activation through membrane receptors to develop new pharmacologic compounds acting along these pathways.

**TABLE 1–3 *(continued)***

### Sexuality

- Improve understanding of the natural hormone changes that occur with aging and menopause, and of the roles of endogenous estrogens and androgens in women's sexuality.
- Develop standardized methods to measure libido in women.
- Better define the determinants of sexual health, including sexual desire and arousal, in postmenopausal women.
- Increase knowledge about the effects of medications on female sexuality in postmenopause, including the role of therapeutic hormonal and nonhormonal agents in the treatment of sexual dysfunction.
- Improve the transmission of information to postmenopausal women about sexual health.

### Cardiovascular and Pulmonary Disease

- Conduct urgently needed randomized controlled clinical trials to investigate the potential benefits and risks of different hormone preparations in women with and without prior CHD.
- Investigate low dosages of oral estrogen, nonoral preparations, SERMs, and androgens in randomized trials with clinical outcomes.
- Except for asthma, very little data exist on the effect of menopause or HRT on the respiratory system, and investigation of the effects on important disease entities should be considered.

### Osteoporosis and Oral Bone Loss: Risks and Therapy

- Develop noninvasive tools to measure bone quality or bone strength inexpensively.
- Develop pharmacologic agents that will stimulate bone formation and restore lost bone. All currently approved drugs are antiresorptive.
- Develop new pharmacologic agents for osteoporosis that are bone-specific and that can be used indefinitely.
- Improve knowledge of the association between oral bone and the rest of the skeleton, in particular as related to therapeutic benefit.

### Gynecologic and Urinary Aspects

- Obtain additional data on the determinants of endometrial function and the specific effects of ovarian hormones on skin and different urogenital mucosae.
- Develop new ERα and ERβ agonists and antagonists as well as new progestins.
- Develop sensitive methods for early diagnosis at the molecular level of estrogen defects in various tissues.
- Develop noninvasive methods of endometrial testing.
- Improve knowledge of the relationship between HRT and the pelvic floor, including UI.
- Develop reliable, easy-to-use diagnostic indexes for pelvic floor and urinary syndromes.
- Develop new pharmacologic agents for the treatment of UI.
- Design clinical trials to properly assess the relationship between SERMs and pelvic organ prolapse.

**TABLE 1–3 *(continued)***

### Menopausal Replacement Therapies and Cancer Epidemiology

- Further quantify the breast cancer risk of estrogen and estrogen-progestin regimens.
- Improve understanding of the relation between the use of HRT and risk for breast cancer according to age.
- Further investigate the (potentially favorable) biologic effects of HRT on the biologic characteristics of breast tumors.
- Undertake additional studies on the use of HRT in women with a diagnosis of breast cancer.
- Better quantify risk for endometrial cancer with combined HRT.
- Obtain additional data on the use of HRT and risks for cancers of the ovary, colon and rectum, lung, liver, and melanoma.
- Conduct additional research regarding cancer risks of the use of tamoxifen and other SERMs, as well as so-called natural therapies for postmenopause.
- Conduct RCTs to obtain data for the effects of SERMs on risks of various cancers.

### Neurologic Function, Mental Health, and the Eye

- Explore the possibility that SERMs may act as estrogen antagonists as well as agonists in the brain or eye.
- Conduct cohort studies from representative populations and randomized controlled clinical trials to assess potential hormonal effects on age-associated cognitive decline, risk for Alzheimer's disease and vascular dementia, mood, macular degeneration, and other disorders of neurologic function, mental health, and eye.
- Evaluate the effectiveness of combination replacement therapy with estrogen plus a cholinomimetic drug in RCTs for women with Alzheimer's disease.
- Evaluate in RCTs the potential effects of HRT on primary prevention of Parkinson's disease and on symptoms of Parkinson's disease.
- Determine in RCTs whether estrogen combined with antidepressants or antipsychotic drugs might enhance effects of these medications in depressive disorders and schizophrenia, respectively.
- Determine in long-term RCTs whether HRT might reduce incidence of age–associated maculopathy, cataract, or dry eye.
- If beneficial effects of HRT are confirmed, undertake basic and clinical research to define mechanisms of action, optimal choice, timing of therapy and duration of usage of estrogen or SERMs, and potential modifying effects of progestin cotherapy.

# Chapter 2: The Menopause and Aging

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***Dramatic increases in life expectancy have led to women expecting to live more than a third of their lives after menopause.***

## Key Points[a]

1. Dramatic increases in life expectancy have led to women expecting to live more than a third of their lives after menopause.
2. The onset of menopause may affect progressive age-related changes in function and structure of body tissues and systems.
3. There is a lack of consensus as to whether the biological and psychological changes occurring during the menopause transition or presenting later in life are attributable to menopause and reduced ovarian function or to aging.
4. The timing of menopause may substantially influence subsequent morbidity and mortality.
5. Menopause cannot be said to have occurred until there have been 12 months of amenorrhea for which there is no other obvious pathological or physiological cause. Contraception is still needed during the menopause transition.
6. Endocrine changes begin years earlier. FSH and estradiol changes are maximal in the year of the FMP.
7. The endocrine changes of menopause do not include any acute or sudden decrease in androgens.
8. Menopause research has to address identified methodologic difficulties.
9. There is considerable individual and racial/ethnic variation among women in the age of menopause and in their manifestation of perimenopausal signs, symptoms, and menopause-related sequelae.
10. Influences of the menopause on health may affect a woman's quality of life.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.)

## 1. Introduction

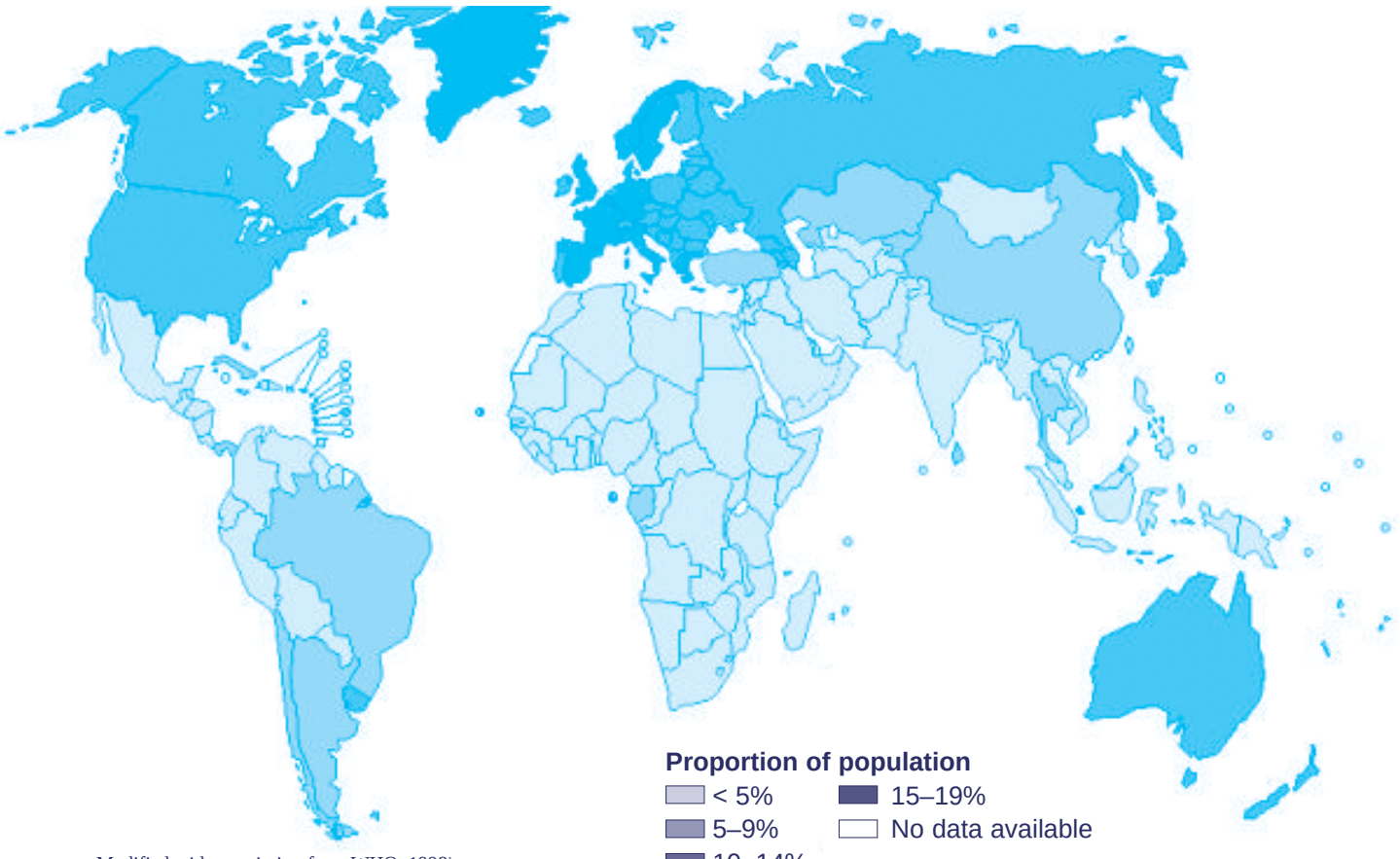
The third millennium begins with vast potential from unprecedented advances in medicine, technology, and public health. Major achievements over the past century in the conquest of infectious and parasitic diseases, progress in nutrition and education, reductions in maternal and infant mortality, although occurring unevenly on a global scale, have resulted in dramatic increases in life expectancy and burgeoning numbers of older individuals (figs. 2–1 and 2–2).[1] Although the world's elderly have been increasing in number for some time, the pace of population aging has accelerated during the past century, resulting in the "graying" of societies across the world as striking reductions in mortality have combined with declines in fertility to produce a rate of expansion of the older population that has outpaced total population growth.[2]

***…Remarkable increase in the proportion of women over fifty in the population, which has tripled since the turn of the 19th century.***

In the industrialized nations of Europe, Asia, and North America, this phenomenon has been a prominent issue. However, accelerated population aging in less-developed countries, where increases in the rate of growth of the older population are surpassing those in more-developed nations, has been underappreciated. Accommodating increases in the proportion of older individuals may be especially challenging to countries that are less-devel-

### Figure 2–1

### An Aging Population: Population Aged 65 and Above, 1996




Modified with permission from WHO, 1998[1]

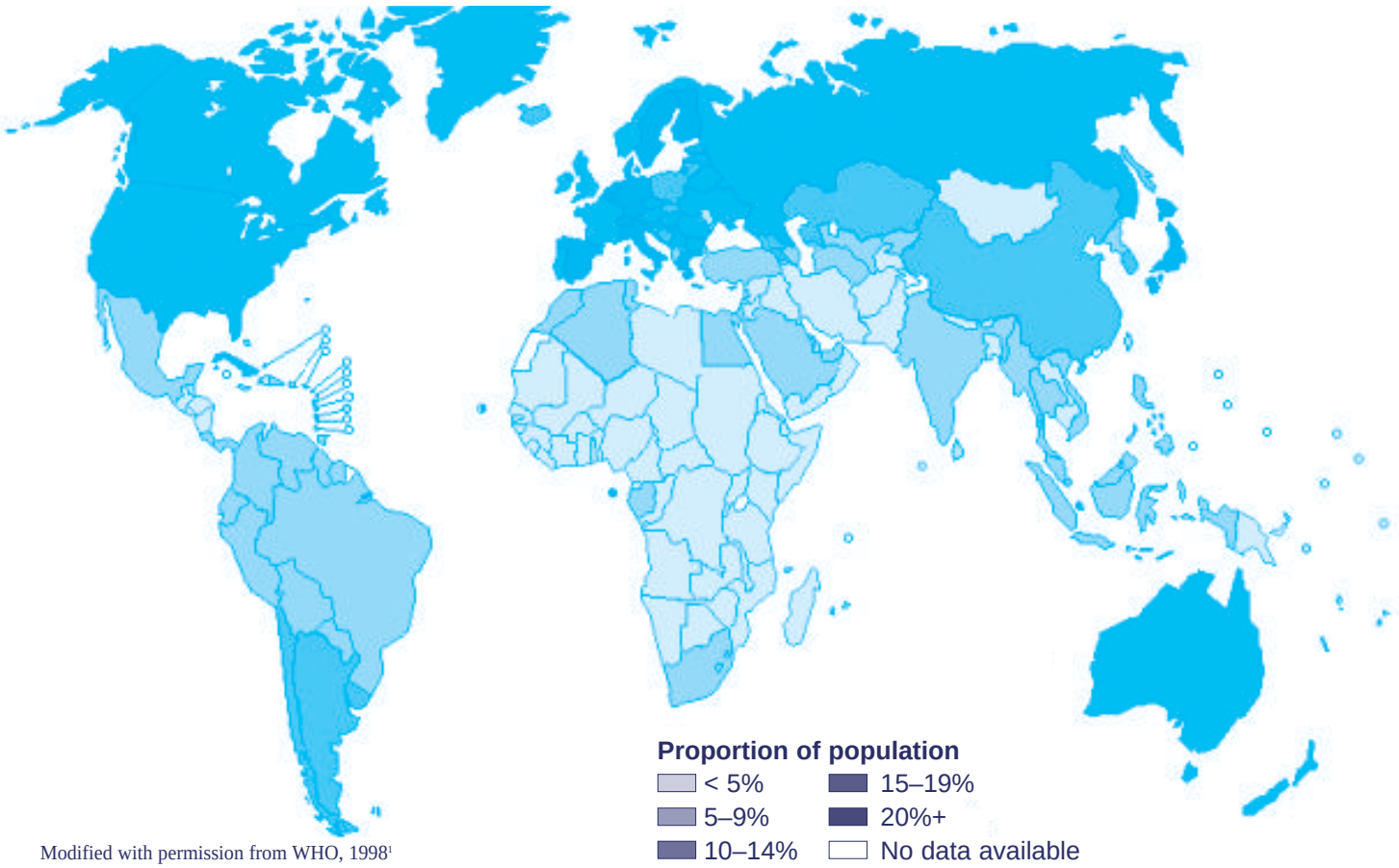
oped and are less prepared to address the economic, social, cultural, and medical uncertainties, competing priorities vis-à-vis enhanced life expectancy, and the desire to maintain quality of life into the very late years of life.[2]

In the developed world, mean life expectancy for women since 1900 has increased from 50 to 81.7 years. Particularly striking is the remarkable increase in the proportion of women over fifty in the population, which has tripled since the turn of the 19th century.[2] Population projections estimated approximately 467 million women in the world to be aged 50 years and older in 1990. By the year 2030, this number is expected to grow dramatically to 1,200 million. The numbers of postmenopausal women in the developing world are anticipated to increase much more rapidly than those in the industrialized world. From 1990 to 2030, the rate of growth of the postmenopausal population will decrease from 1.5 to 1.0 percent in the industrialized world, while averaging between 2 and 3.5 percent in less-developed countries. Therefore, during this period, the proportion of postmenopausal women in more developed countries is expected to decline from 40 to 24 percent, whereas it will increase from 60 to 76 percent in less-developed countries.

Accelerated population aging has led to a major epidemiological transition in the leading causes of death from infections and acute diseases to the chronic and degenerative diseases of old age (such as malignant neoplasms (see ch. 11), cardiovascular and cerebrovascular diseases (see ch. 8), osteo-

## Figure 2–2

### An Aging Population: Population Aged 65 and Above, 2020

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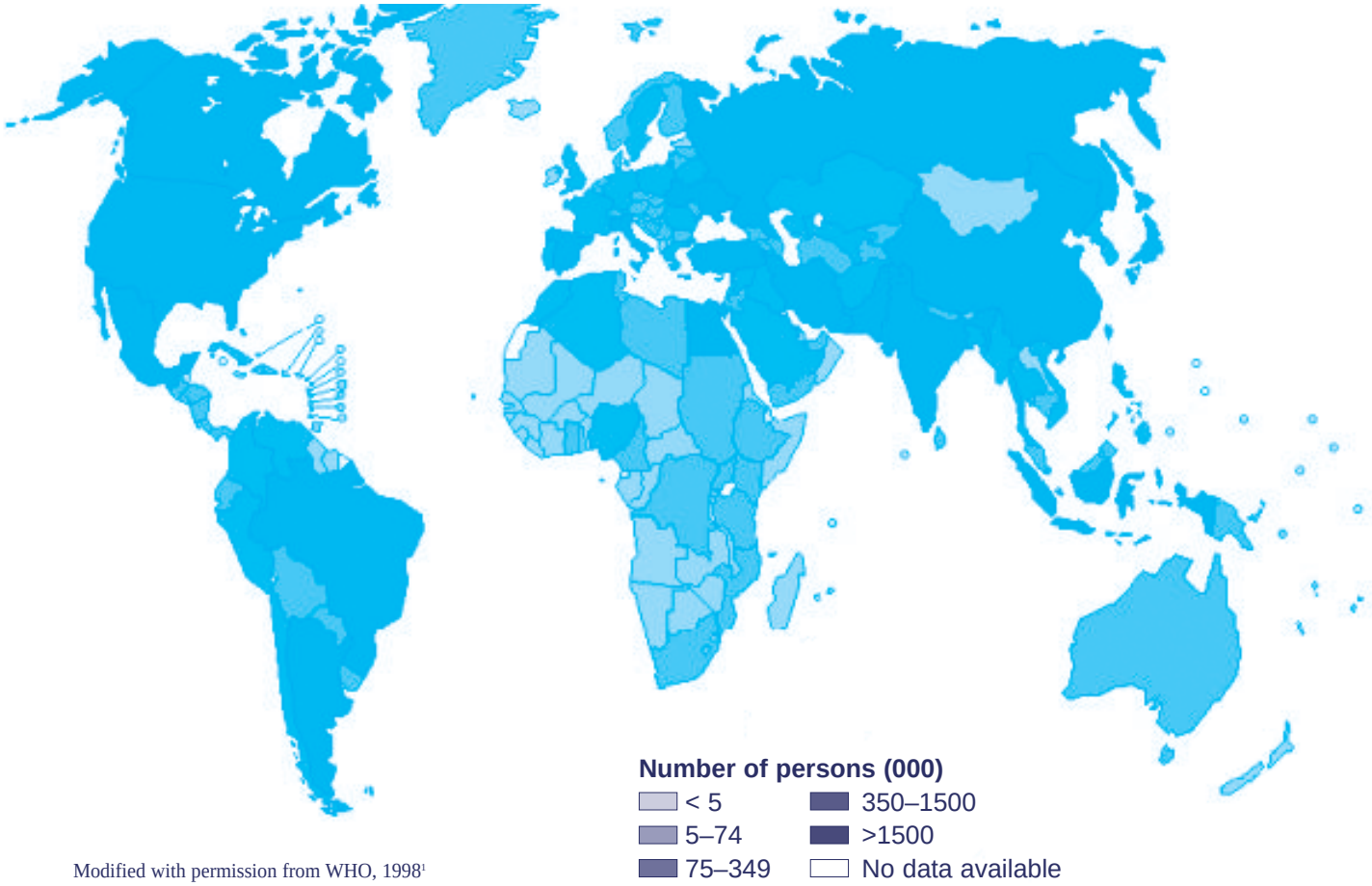
## FIGURE 2–3

### Diabetes Mellitus. Estimated Prevalence Among Adults, 1997

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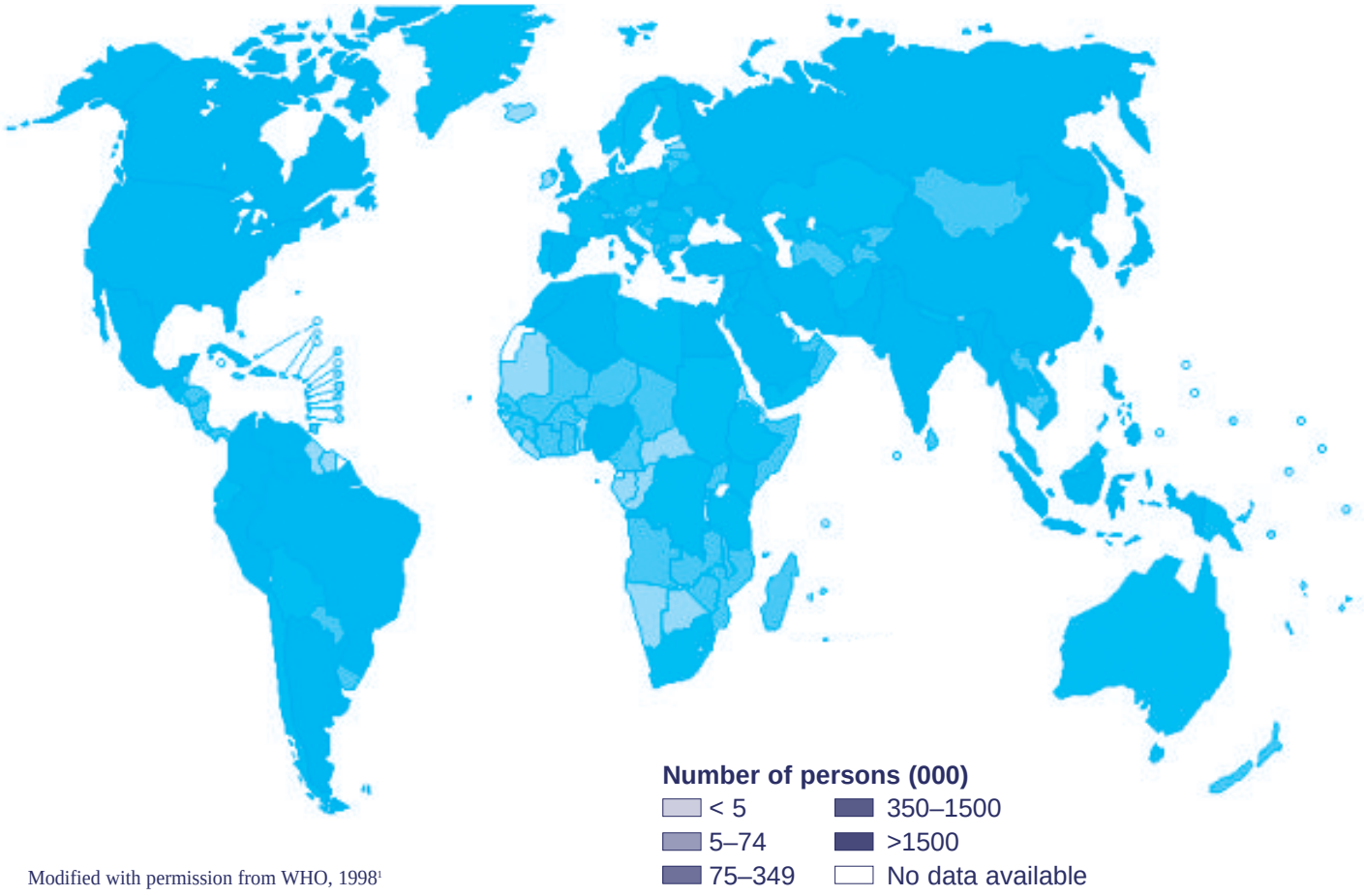
***Approximately 467 million women in the world … aged 50 years and older in 1990. By the year 2030, this number is expected to grow dramatically to 1,200 million.***

porosis (see ch. 9), and dementia (see ch. 12). The incidence of some metabolic diseases, such as diabetes mellitus, is increasing (figs. 2–3 and 2–4).[1] Degenerative processes, such as macular degeneration or progressive lens opacity, have been linked to prolonged estrogen deficiency.[3] Another study shows that HRT has a positive influence on intraocular pressure increasing with age.[4] However, increasingly sophisticated research in aging since the mid-1970s has led us to challenge the concept of an inevitable, inexorable, unified progression toward debility and infirmity before death. Now aging is appreciated as the heterogeneous product of a genetic disposition being revealed under variable environmental, behavioral, psychosocial, and economic conditions, many of which are amenable to profound change with existing as well as emerging new strategies.

Aging is associated with progressive structural, functional, endocrine, and metabolic alterations in a variety of tissues and systems, many of which have been implicated in subsequent impairments in physiological, physical, psychosocial, and cogni-

## Figure 2–4

### Diabetes Mellitus. Estimated Prevalence Among Adults, 2025

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tive functioning. A critical tenet in aging research, which is aimed at understanding, modifying, or preventing age-related morbidity, disability, and death, is the importance of differentiating changes due to disease and other pathologic processes from those attributable to aging *per se*. To better understand the etiology of age-related disease in women, it is important to additionally ascertain the independent role of menopause and its interaction with aging. There is little consensus as to the significance of menopause in healthy aging, and considerable controversy exists as to the scope of the physiological and psychological changes surrounding menopause or presenting later in life that are attributable to menopause and reduced ovarian function. Future advances in preventing and managing diseases and disorders in middle-aged and older women will require more careful delineation of those diseases and disorders that are attributable to menopause and reduced ovarian hormone levels versus those diseases that are not. Such advances are critically needed to clarify ambiguities in the presentation of age-related disease, to improve diagnosis and treatment, and to constrain health care costs.

The most profound and universal alteration in the mature aging endocrine system occurs in women and is due to menopause. However, while menopause is a universal phenomenon in women,

there is considerable individual variation among women in the age of menopause and in the manifestation of perimenopausal signs and symptoms as well as what may be considered menopause-related *sequelae*. The perimenopausal and postmenopausal experience encompasses a complex interaction of sociocultural, psychological, and environmental factors as well as biological changes relating strictly to altered ovarian hormone status or deficiency. In the United States and many Western countries, the perimenopausal experience is usually perceived largely in negative terms—as a transitional phase dominated by disturbing physical and mental symptoms. It has been suggested that highly negative characterizations of menopause may be due to an over-sampling of clinic-based populations of perimenopausal women, who, seeking treatment for symptoms, were more readily available for study and whose experiences represented the extremes of a difficult transition. Importantly, our knowledge base on menopause is extremely narrow in that the majority of studies have been of white women (of northwest European ancestry); very little is known about the range of perimenopausal experiences in women of other racial/ethnic groups. The sociocultural and behavioral antecedents and consequences of menopause have also not been well addressed, and major gaps exist in understanding factors that may profoundly influence the perception of, and response to, perimenopausal symptoms and *sequelae*. (See ch. 4).[5]

***Smoking is associated with a menopause which occurs 1 to 2 years earlier than in nonsmokers.***

The age of menopause and the timing of the onset of changes in the endocrine milieu may have profound implications for subsequent morbidity and even mortality. Women reporting an earlier menopause are reported to be at greater risk of CVD disease[6] and osteoporosis[7] but at a reduced risk of breast cancer.[8] However, data are conflicting, and methodological difficulties in assessing the relationship between age at menopause and the risk of subsequent conditions and diseases of aging abound in the literature base.

Although estimates for the median age of menopause range from 45–55 years of age worldwide[9] and between 50 and 52 years of age in white women from industrialized countries, our understanding of the determinants of, or factors which influence the age at, menopause is limited, with conflicting findings between studies commonly found. A prominent role appears to be played by race/ethnicity and lifestyle and sociocultural factors.[10] Recent studies have suggested that compared to white women, menopause is experienced at a later age in Japanese women and at a younger age in African-American[11] and Latin American[12] women and in women living in less-developed countries. Of all the variables studied, the most consistent relationship has been for smoking, which is associated with a menopause which occurs 1 to 2 years earlier than in nonsmokers.[13] Reproductive variables, including later age at menarche, oral contraceptive use, longer menstrual cycle length, and parity, have been (albeit inconsistently from study to study) associated with an older age at natural menopause. Other studies have shown an earlier menopause to be associated with lower socioeconomic status, lower educational attainment, low body mass index (BMI), or being on a weight-reducing diet.[14]

## 2. Aging In Women

Aging is associated with profound changes in body composition. For reasons that are incompletely understood, as they age, both men and women lose bone and muscle and increase their proportion of fat mass. These changes are of great public health significance, particularly as their associated structural (e.g., diminished muscle and bone strength) and metabolic (e.g., glucose intolerance, hyperinsulinemia) *sequelae* have been implicated in the development of frailty and morbidity (including heart disease, hypertension, osteoporotic fractures, and osteoarthritis).

Sarcopenia, defined as reduced muscle mass, is a well-known consequence of aging and occurs in parallel with reductions in muscle strength and, to some extent, muscle quality.[15] Importantly, decreased muscle mass and strength can impair physical performance in the elderly and are associated with an increased risk of physical frailty, declines in functional capacity, impaired mobility, and falls.[16]

A recent study suggests that the menopause transition is associated with deleterious changes in body composition and fat distribution, promoting the selective accumulation of fat in the intra-abdominal compartment. However, while increases in total and central adiposity were observed, no differences in fat-free mass were noted, which suggests that menopause may have less impact on the processes promoting muscle loss.[17]

As both men and women age, collagen synthesis is reduced, and the skin becomes progressively thinner and wrinkled. The decrease in collagen synthesis is similar in other connective tissues and in tissues rich in collagen, such as the conjunctiva and articulation capsules. Although ERs are present in the skin,[18] thus defining this tissue as a target tissue—and it is widely believed that estrogen deficiency affects epithelial tissues—there is a dearth of prospective observational data using validated methods to assess skin quality in different racial/ethnic groups exposed to varying environmental factors. Importantly, the ability to differentiate the effects of menopause from those of aging is very limited as skin quality can be substantially influenced over time by genetic, smoking, and environmental influences, particularly ultraviolet exposure, which can cause premature aging of the skin. There is evidence from experimental studies that estrogen can stimulate collagen biosynthesis and maturation in animal models[19] and increase skin collagen content in humans.[20] Estrogen use in humans has been associated with greater collagen content, thickness, elasticity, and vascularization.[21] Increases in facial hair, temporal hair loss, and deepening of the voice often observed in elderly women have been linked to the relative androgen dominance after menopause. Evidence suggests that estrogen administration can prevent hair loss,[18,22] and the frequent complaint of "dry eyes" (*keratoconjunctivitis sicca*).[23] However, there have been few RCTs demonstrating major benefits of HRT on the skin, hair, or sensory organs, such as the eye.

***Recent studies have suggested that compared to white women, menopause is experienced at a later age in Japanese women and at a younger age in African-American and Latin American women and in women living in less-developed countries.***

Because aging is associated with decrements in both skin thickness and BMD, it has often been postulated that measurement of the thickness of skin can be used to predict the risk of osteoporosis after menopause. However, despite significant statistical correlations between skin thickness and bone mineral content (BMC), the risk for osteoporosis cannot be accurately deduced from skin thickness in an individual patient.[24, 25]

## 3. Definitions

The word "menopause" ("ménespausie") was used for the first time in 1816 by Gardanne.[26] Initially, the phenomenon of menopause was explained as a deficiency of ganglionic regulatory functions. In 1910, Marshall[27] recognized that the ovary should be classified as an endocrine organ. From the endocrine perspective, the menopause represents a primary ovarian insufficiency and has an inception between the ages of 40 and 56 years, with a mean age of 51 years.[28] From a scientific perspective, natural menopause coincides with the FMP, and this cannot be determined until there have been[12] months of amenorrhea.[9] This definition is based on clinical epidemiological evidence that the probabil-

ity of resumption of menstruation after 12 months of amenorrhea is vanishingly small.[29,30]

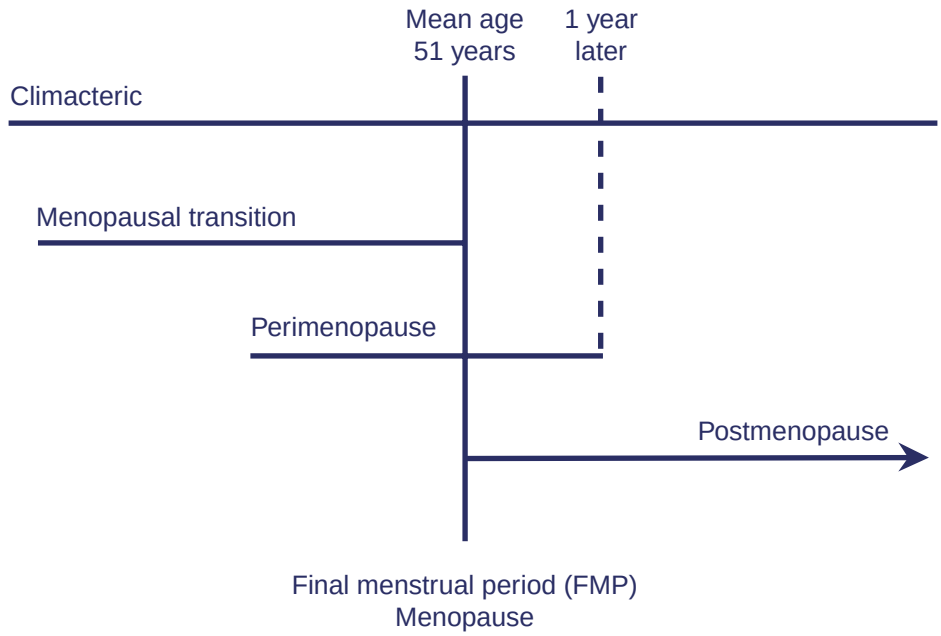
Much confusion has been caused by differing definitions used in relationship to changing ovarian status. Definitions were provided by the World Health Organization (WHO) Scientific Group on Research on the Menopause in the 1990s.[9] More recently, these definitions and others were considered by the Council of Affiliated Menopause Societies (CAMS) of the International Menopause Society (IMS). The only change recommended to the WHO definitions was the inclusion of the term "climacteric," considered by many clinicians to be descriptive of this phase of life. The list of menopause-related definitions given below was approved by the IMS in October 1999, in Yokohama, Japan.[31]

| TERMS | SOURCE |
|---|---|
| *Menopause (natural menopause)* | **WHO** |

The term "natural menopause" is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the FMP, which is known with certainty only in retrospect a year or more after the event. An adequate biological marker for the event does not exist.

## FIGURE 2–5

### Relationships Between Different Time Periods Surrounding the Menopause



***Perimenopause*** **WHO**

The term "perimenopause" should include the period immediately prior to the menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause.

***Menopausal transition*** **WHO**

The term "menopausal transition" should be reserved for that period of time before the FMP when variability in the menstrual cycle is usually increased.

***Climacteric*** **IMS**

This phase in the aging of women marks the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.

***Climacteric syndrome*** **IMS**

The climacteric is sometimes, but not necessarily always, associated with symptomatology. When this occurs, it may be termed the "climacteric syndrome."

***Premenopause*** **WHO**

The term "premenopause" is often used ambiguously to refer to the 1 or 2 years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. The group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period up to the FMP.

***Postmenopause*** **WHO**

The term "postmenopause" is defined as dating from the FMP, regardless of whether the menopause was induced or spontaneous.

***Premature menopause*** **WHO**

Ideally, premature menopause should be defined as menopause that occurs at an age more than two standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cutoff point, below which menopause is said to be premature.

***Induced menopause*** **WHO**

The term "induced menopause" is defined as the cessation of menstruation, which follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or radiation).

Figure 2–5 shows the relationships between different time periods surrounding the menopause.

## 4. Physiology

The process of the menopausal transition appears to take about a decade. The earliest signs of this transition are (1) shorter menstrual cycles by 2–3 days and (2) infertility. After birth, the number of oocytes continuously decreases. At puberty, 1 million oocytes are left.[32] This number decreases to 0.3 million by the age of 20 years.[32] Menopause is marked by the exhaustion of the ovarian supply of oocytes.[33] Although only approximately 400 follicles or less than 0.01 percent of all oocytes proceed through ovulation between menarche and menopause,[33,34] long-standing amenorrhea or the prolonged intake of a contraceptive pill does not seem to postpone menopause.[13] Reduced fertility due to the aging process of the oocytes and to abnormal follicular maturation is the first sign of ovarian aging. After the age of 40, about 30–50 percent of all cycles show an abnormal basal temperature.[35,36] Two to eight years before menopause, the incidence of luteal insufficiency and anovulatory cycles increases,[37] resulting in a higher incidence of persisting follicles and dysfunctional bleeding. Shorter menstrual cycles appear to be detectable at about age 38–40.[38,39] The subtle but common shortening of the intermenstrual interval is clinically valuable, as it seems to be predictive of other perimenopausal changes.

Subtle reproductive hormonal changes occur in the face of these minor cycle changes. FSH appears to rise throughout reproductive life, but the elevation becomes obvious in the late thirties/early forties in women.[40] Although it is elevated for most of the menstrual cycle, early follicular phase FSH concentrations are most easily discriminated from "normal" concentrations on cycle days 2–5. An elevated FSH is a harbinger of menopause, although it may still be many years away, and has clearly been shown to augur poorly for future fertility.[41] It is a poor predictor of age at menopause, however, and the clinician cannot make any conclusions on the timing of an individual woman's menopause based upon the presence or degree of FSH elevation.[42]

On the other hand, as long as the active follicular phase permitting the maturation of healthy follicles remains stable and the luteal phase normal, fertility is maintained. Therefore, contraception is still needed during the menopause transition, despite moderately elevated FSH levels. An isolated elevated serum FSH level is not proof of the occurrence of menopause and is not sufficient to consider a perimenopausal woman infertile so that she could cease reliable contraception.[43]

### 4.1 Clinical Factors

Environmental influences may alter the ovarian aging process. Smoking advances the age of menopause by about 2 years.[28] Recent studies suggest that high levels of galactose consumption may do the same. However, most of the determinants of menopause are innate. Familial and genetic factors appear to be the most predictive at present.[44] One recent study described an ERα polymorphism that is associated with a 1.1 year advancement in the age at menopause and a nearly threefold RR of hysterectomy for benign disease.[45] Ovarian surgery, adhesions, and pelvic endometriosis appear to be associated with poor ovarian stimulation for in vitro fertilization and perhaps are also risk factors for early age at menopause.[46]

Menstrual cyclicity is currently the best indicator of menopausal status. The large variability in intermenstrual intervals that occurs at this time of life probably reflects a combination of short cycles[38] and skipped cycles. Treloar et al.[37] reported a detailed analysis of intermenstrual intervals of women encompassing over 20,000 menstrual cycles. Variability of cycle length was enormous in both the perimenarcheal years and the years of menopausal transition. Cycle length shortening is probably due to elevated FSH levels in the early follicular phase/late luteal phase of the cycle.

The classic characterization of the menopause transition was provided by Sherman and Korenman (1975).[47] Six women were followed in detail up to and including the actual last menstrual period. Their data described the key features of the menopause transition, which are still under investigation today, almost 20 years later: (1) a monotropic rise in FSH secretion, (2) continued folliculogenesis and evidence of ovulation up to the FMP, and (3) periods of hypoestrogenemia concomitant with large FSH rises. The loss of inhibin restraint was first hypothesized by this group.

Metcalf followed perimenopausal women longitudinally throughout their forties and fifties.[48] This characterization of the perimenopause included the observation that the key feature of passage "through" menopause was the subsequent complete absence of luteal activity. Therefore, a permanent failure of ovulation is the cardinal observation. Within the first year after a woman's FMP, variable estrogen excretion was observed; thereafter, estrogen excretion was abidingly low and basal.[48,49] These results have been confirmed by others in serum studies.

Using 6 years of prospective annual measures, Burger et al. reported that mean FSH levels began to increase from about 2 years before the FMP, increasing most rapidly about 10 months before the FMP, and had virtually plateaued by 2 years after the FMP.[50] Mean estradiol levels started to

decrease about 2 years before the FMP, decreased most rapidly around the time of the FMP, and had virtually plateaued by 2 years after the FMP.

Klein et al. reported the endocrinology of follicles and peripheral hormones in women in their early forties.[51] Shortened follicular phases, apparent accelerated folliculogenesis, and a monotropic FSH rise were all confirmed in these women. Follicle fluid was aspirated and compared to younger controls. Follicle fluid in reproductively aged women contained more estradiol and less insulin-like growth factors than younger women, despite fewer granulosa cells per follicle.[51] Oocytes contained aberrant meiotic spindles in abundance, evidence for chromosomal damage to the oocyte either due to its age alone or to inappropriate paracrine/endocrine cues.[52] These data emphasize that reproductive aging begins earlier than previously believed (as early as age 40) and is happening in a very significant way before menstrual cycles become irregular and certainly before women notice any symptoms. This becomes particularly poignant in the office setting when healthy women in the older reproductive age group are informed of their poor fertility potential despite their robust, asymptomatic status.

Santoro et al.[53] observed a small cohort of women in the mid-perimenopausal years when menstrual cyclicity was beginning to deteriorate. Compared to younger women, these perimenopausal women had evidence of greater estrogen excretion in conjunction with elevated FSH and LH concentrations and decreased luteal phase progesterone metabolite excretion.[53] Irregularities of menstrual cyclicity were characterized by occasionally dramatic excursions of estrogen well beyond the normal range for younger women. Thus, "skipped" cycles in the perimenopause may be due to either failure of folliculogenesis and hypoestrogenemia or accelerated and sustained estrogen secretion. These findings have recently been confirmed in a larger, epidemiologic sample of perimenopausal women.[54] The common gynecological problems of women in the perimenopause, such as dysfunctional uterine bleeding, growth of uterine leiomyomata, and the frequent utilization of dilatation and curettage (D&C) and hysterectomy for women in this age group, may be explained by the persistence of these hormonal patterns.

### 4.2 FSH, Inhibins, and Reproductive Aging

The monotropic rise in FSH that accompanies the onset of the menopause transition has been known since the 1970s.[47] At that time, the prevailing notion was that a lack of inhibin "restraint" of FSH caused the elevation, the so-called "inhibin hypothesis."[47] Inhibins are molecules in the transforming growth factor-β (TGF) peptide superfamily. (See also ch. 5, sec. 6.) They are produced by the granulosa cells of the ovary. They are heterodimeric, consisting of a common alpha subunit and a specificity-providing beta subunit. Inhibin A appears to be expressed in large, dominant follicles and the corpus luteum while inhibin B appears to be a product of small follicles.[55] Although they were believed to act via specific binding to a cell surface receptor, inhibin receptors have only recently been identified.[56]

***The available data shows that after hysterectomy menopause occurs earlier.***

Thus, two decades after it was proposed, the inhibin hypothesis has been confirmed by measurement. Diminished inhibin A and B have been reported in the circulation of older reproductive-aged women.[57–60] Elevated FSH in perimenopause may be more tightly linked to this loss of inhibitory tone, rather than to decreased estradiol production by the perimenopausal ovary. At the early stages of the menopause transition, women appear to be estrogen replete and do not demonstrate evidence of decreased estradiol until they are within several years of their FMP.[50–53] In fact, in some perimenopausal women, the elevated FSH may lead to "overshoot" and the consequent production of supraphysiological amounts of estradiol.[53–61] Follicular phase inhibin B appears to be detectably decreased

in the early perimenopause, concomitant with the rise in FSH.[50] As the transition progresses, follicular phase inhibin A declines detectably as well, perhaps as a later event.[50]

In addition to these early changes in inhibin A and B, activin A has been shown to be elevated in perimenopausal women.[58,60] Activins are the beta homodimers of the inhibin molecules and exist as activin A and B. While they clearly play a local role in pituitary FSH secretion, their ability to act as endocrine factors influencing the production of FSH is not established. Moreover, activins circulate bound to follistatin, their serum-binding protein. The relatively high affinity of follistatin for activin, as well as its abundance in serum, suggests that activin may exert most of its effects in a paracrine or autocrine, and not endocrine, fashion.

***Considering the high incidence of hysterectomy in some countries, this observation is clinically relevant.***

#### *4.2.1 Androgens in the Perimenopause*

Circulating androgens in women reflect contributions from adrenal, ovarian, and peripheral sources. When relatively stable adrenal hormones, such as dehydroepiandrosterone sulfate, are measured, a dramatic decline is observed across the adult lifespan.[62, 63] An independent effect of the process of menopause on circulating adrenal androgens has not been observed.

Together with the age-related decline in adrenal androgen production, ovarian androgens, particularly testosterone and androstenedione, decrease throughout adult life as well.[64,65] Metabolites of dihydrotestosterone demonstrate the most precipitous declines between the ages of 20 to 40 years.[63] While some studies suggest that a small menopause-associated decrease in testosterone occurs,[66,68] other longitudinal, prospective studies have not documented any acute decrease in testosterone or androstenedione associated with the menopause transition.[69,70] The modification of testosterone bioavailability by sex hormone binding globulin (SHBG) may play a role in perimenopausal physiology; however, it is controversial as to which direction SHBG changes across menopause, with some studies observing a decline[67,70] and others an increase.[69] It seems clear that the major decline in circulating testosterone occurs well before the menopause transition.[65] Based upon current well-designed studies and including observations about both adrenal and ovarian androgens, the medical "myth" that menopause is associated with an acute drop in androgens does not appear to be tenable any longer.

#### *4.2.2 Neuroendocrine Changes*

The loss of "positive feedback," that is, the ability to respond to an estradiol challenge with an LH surge, appears to be another feature of the perimenopause which leads to potential morbidity for women.[71] It is unclear why this ability is lost, as it appears to be regained in the postmenopause, when LH surges in response to estrogen challenge have been well documented.[72,73] Perhaps the other concurrent abnormalities of the endocrine milieu predispose women to this temporary state. It may be the result of enhanced susceptibility to the negative feedback of estradiol.[60,74]

Whereas in young premenopausal women estradiol is the major circulating estrogen, estrone becomes the dominant estrogen after menopause. Estrone is produced primarily by peripheral aromatization of androgens.[75] Aromatization takes place in the adipose tissue, muscle, bone marrow, skin, brain, and other tissues. Estrone is less potent than estradiol. The postmenopausal concentration (20 to 60 pg/mL) of estrone equals or surpasses the range observed in healthy premenopausal women. The conversion of androgens to estrogens (mostly estrone) increases from approximately 1.4 to 2.7 percent in premenopausal compared to postmenopausal women.

### 4.3 Menstrually Defined Menopausal Status

Most observational studies of changes in health outcomes related to menopause have tried to subcharacterize the perimenopausal years based on changes in menstrual status.[76] The Korpilampi Workshop in 1985[77] defined the boundary between the premenopausal and perimenopausal states by the reporting of changes in menstrual flow and/or regularity. They identified that the reliability of such definitions for predicting the further movement to postmenopause had not been sufficiently studied.

Brambilla et al.[29] proposed a method for operationally defining the onset of perimenopause as (1) a self-report of 3 to 12 months of amenorrhea, and (2) for those without amenorrhea a self-report of increased menstrual irregularity. They stated that validation of this definition would require the examination of longitudinal hormonal changes with changes in the menstrual cycle.

Using prospective data, the Melbourne Women's Midlife Health Project[76] found that women who reported not having had a menstrual period in the last 3–1 months were older, had lower estradiol and inhibin levels and higher FSH, and were more likely to report hot flushes and to self-rate themselves as having started the menopausal transition, compared with women who had menstruated in the last 3 months. Subsequent analysis from the same project compared retrospective self-reports of menstrual status with prospectively kept menstrual diary data[78] for women reporting at least one menstrual period during the previous 3 months. This study found that no significant agreement exists between retrospective self-reports and prospective diary-based measures of change for cycle frequency nor for flow. Thus, retrospective self-reports at interview of changes in menstrual frequency and flow should not be regarded as reliable measures for the purpose of determining menopausal status.

#### *4.3.1 Hormone Measures*

Relatively few studies have undertaken any hormonal determinations. Endocrine change occurs for some years prior to the cessation of menopause,[50] so it is important to acquire measures while women are still menstruating regularly, some years before menses cease. Other issues involved in hormone measures have been those of the frequency of sampling (annual versus daily or weekly), type of sampling (plasma, urine, salivary), phase of the cycle sampled, and the presence of floor effects due to the lack of sensitivity of assays at the lower levels of estradiol and inhibin, which occur in the postmenopause.

#### *4.3.2 Age and Length of Followup*

Age at baseline and length of followup are important issues. Followup has often been only in the order of 3 years.[79–81] The Melbourne Women's Midlife Health Project found that after 3 years of followup, only 12 percent of women had become naturally postmenopausal (12 months of no bleeding after reaching their FMP). At the end of 7 years of followup, only 39 percent of the women in this cohort were naturally postmenopausal, reflecting splintering of the sample as well as length of followup.

***Whereas in young premenopausal women estradiol is the major circulating estrogen, estrone becomes the dominant estrogen after menopause.***

### 4.4 Natural Menopausal Transition Versus Induced Menopause

A major problem in menopause research has been to establish the health experiences associated with natural menopause and how these may differ when menopause is induced. A number of studies suggest that symptom experience is likely to be worse when women have undergone surgical menopause.[82] Documentation of medical treatment, which may impact ovarian functioning (surgery, chemotherapy, irradiation), and documentation of medication

taken by women are needed so that these women may be treated separately in the analysis. The available data show that after hysterectomy menopause occurs earlier. The mean age of ovarian failure in the hysterectomized group was 45.4 ± 4.0 years (standard deviation) and was significantly lower than the mean age of 49.5 ± 4.04 years in the nonhysterectomized control group ($p < 0.001$).[83] Considering the high incidence of hysterectomy in some countries, this observation is clinically relevant. In the United States, one woman in three undergoes hysterectomy by age 65. The rate in the European Union nations ranges from 6 to 20 percent.[84] In the 1980s, of a total sample of women in six European countries, 11.4 percent had undergone hysterectomy, the highest percentage being found in Italy (15.5 percent) and the lowest in France (8.5 percent).[85] In Europe, the prevalence of surgical procedures is higher in privately insured persons than in persons with only basic insurance. Among 25- to 74-year-old privately insured women, the lifetime prevalence of a hysterectomy is 30 percent with low educational status and 13 percent with high educational status ($p < 0.001$).[86] A European woman without education has a RR of 2.2 (1.1–4.4) for hysterectomy compared to an educated woman.[87] Similar data are reported from the United States.[88] In the United States, hysterectomy rates increased with age, and rates for black women slightly exceeded the rates for whites.[89] Hysterectomy with ovarian preservation is associated with increased risk of high diastolic blood pressure, diagnosis of hypertension, and increased BMI but is not associated with other heart diseases.[90] Women who underwent hysterectomy reported more discomfort and frequent symptoms of urogenital atrophy.[91]

### 4.5 Exogenous Hormones

Exogenous hormones may mask the effects of changing ovarian function, so that women taking the oral contraceptive pill or any HRT must also be treated separately in analyses. In many countries, an increasing number of women are choosing to adopt HRT, and this may lead to a splintering of the sample and even to insufficient numbers to examine the effects of the natural menopausal transition. Holte reported that sample size in a longitudinal study over 5 years was reduced from 200 to 56.[92]

Prospective studies allow the profile of those who adopt HRT to be compared with that of nonusers, in order to elucidate any biases which are related to hormone selection and which may affect the endpoint.[93]

## 5. Qualtiy of Life and Menopause

Concepts of quality of life vary from measures of subjective well-being, symptoms, or other indicators of health status to that of functional status. Assessing the impact of a condition on quality of life is particularly relevant. A range of measurement tools are available for monitoring how climacteric symptoms affect patients with regard to their well-being, sleep disturbance, other somatic symptoms, and cognitive and sexual functioning. Only standardized and well-validated measurement tools should be used.

The close association between lifestyle and health is generally recognized. Much is still to be learned about the reciprocal influences of lifestyle, decision to use HRT, and quality of life. The most relevant factors influencing a woman's quality of life during the menopause transition appear to be her previous emotional and physical health, her social situation, her experience of stressful life events (particularly bereavements and separations), as well as her beliefs about menopause and aging. Those who seek medical help for menopausal problems tend to report more physical and psychological problems in general. They are more likely

to be under stress and to hold particular beliefs about the menopause.[94]

Health and quality of life related to menopause may be enhanced by providing: (1) balanced information about the menopause to women and to their families; (2) discussion of attitudes towards the menopause, with the promotion of positive attitudes towards aging and menopause; and (3) health promotion sessions focusing upon healthy lifestyles of balanced diet, daily exercise, and cessation of smoking.[94]

## 6. Future Needs

- Markers of a woman's proximity to menopause are lacking. More menstrual diary research studies with concurrent hormone measures are needed to identify biomarkers of menopausal status.
- More research is needed on fertility and contraception in the perimenopause.
- Further understanding is needed about the reciprocal influences of lifestyle, decision to use HRT, and quality of life.
- Providing women and their families with balanced information about menopause, fostering positive attitudes towards aging and menopause, and encouraging healthy lifestyles may improve their health and quality of life related to menopause.

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# Chapter 3: Symptoms and the Menopause

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## Key Points[a]

1. Conflicting findings regarding which symptoms are related to hormonal changes of menopause reflect different research methodologies and their limitations.
2. When symptom checklists are used, middle-aged women are highly symptomatic.
3. Age related symptoms may be differentiated from those related to the menopausal phase.
4. Only vasomotor symptoms, vaginal atrophic symptoms, and breast tenderness consistently vary with the phase of the menopause transition and are significantly affected by the administration of hormones in double blind RCTs [A].
5. Other symptoms, such as insomnia and mood, may be affected by the presence of bothersome vasomotor symptoms.
6. Symptoms are influenced by psychosocial and lifestyle factors.

***Conflicting findings regarding which symptoms are related to hormonal changes of menopause reflect different research methodologies and their limitations.***

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1).

## 1. Introduction

A large number of symptoms have been variously linked with the menopause transition. Important clinical questions include the following:

1. What are the most frequent symptoms experienced by middle-aged women?
2. Which of these are related to the hormonal events reflected in the different phases of the menopausal transition, and which relate to aging?
3. What is the role of other psychosocial and lifestyle factors in determining women's experience of symptoms?
4. What evidence is there for the effectiveness of treatment interventions for symptoms linked to the transition to menopause?

## 2. Quality of Life and Symptoms

***Symptoms are influenced by psychosocial and lifestyle factors.***

The term "quality of life" refers to a subjective perception on the part of both researcher and subject. Areas covered range from health status (SF–36),[1] life satisfaction,[2] coping,[3] and depression (Center for Epidemiologic Studies Depression scale)[4] to scales measuring symptoms thought to be characteristic of specific states, such as menopause. This breadth of coverage and absence of a single, widely accepted definition may be a limiting feature of the concept of quality of life.[5] There are two different types of measures: global quality of life or aspects specific to a particular disease (such as osteoporosis) or a physiological state such as the hormonal changes underlying the menopause transition. Scales designed to measure the latter make the assumption that the more symptoms are present and the more severe those symptoms are, the lower is the ensuing quality of life. Yet there has been surprisingly little research linking symptom presence with the other more global aspects of quality of life described above.

There is debate as to whether the term "sign" or "symptom" should be used when referring to the events of the menopausal transition. The term "sign" is often used to refer to objective clinical manifestation of a disease, such as a lump or a bruit, whereas the term "symptoms" is used to refer to those bodily perceptions presented as complaints by the individual. This chapter uses the term "symptom" in this context.

## 3. Methodological Aspects of Measuring Symptoms

Conflicting findings as to the etiology of symptoms in midlife reflect some of the methodological difficulties inherent in menopause research as well as specific issues pertaining to the measurement of symptoms, such as sample selection, validity of symptom measures, age at baseline and length of followup, separation of the effects of the natural menopausal transition from that of induced menopause, statistical and experimental design. The most obvious methodological issue is the potential to confuse studies evaluating the effects of estrogen or differences between estrogen users and nonusers on various outcomes as "studies of menopause." In order to distinguish menopause-related changes (due to changes from altered levels of estrogen and/or other sex hormones) from those of aging or disease, it is necessary to elucidate the processes of the transition from premenopause to postmenopause. Although there is an abundance of studies and findings on the effects of ERT on various physiological and psychological outcomes, the actual processes and mechanisms of follicular depletion which underlie the transition to menopause are poorly understood.

### 3.1 Study Type

Clearly a number of different research modes can be used to explore whether the menopause transition affects quality of life, varying from studies of primates (often involving extirpative surgery and then hormonal intervention), to clinical trials of

women who may have reached natural menopause or had menopause induced. However, clinical experience is based on a small proportion of self-selecting, predominantly ill women and may not be representative of most women's experience of the menopause.[6,7] Population-based studies have demonstrated that women who seek treatment differ in systematic ways from those who do not.[6,7] Patient-based samples are biased in terms of education, socioeconomic status, other health problems, and incidence of general depression.[8] Clinical trial samples often included women who had undergone surgical menopause, and the hormones administered were usually synthetic, so these studies do not inform us of the relationship of symptoms to the natural menopause transition. Only studies of women derived randomly from the general population provide findings which can be confidently generalized to be the experience of most women of that particular culture and geographic location. Reliable transcultural comparisons are rare because rating scales and questionnaires cannot be easily translated to other languages: a specific term may not exist in the target language or may have a slightly different meaning. This problem exists even for translations within the group of western languages and points to the importance of validation.

There are intercultural and intracultural differences in symptom reporting. Kaufert and Syrotuik[9] describe how stereotypes held by differing social and cultural groups act as a framework within which an individual can select and organize and label experience. Moreover, in menopause research there is a risk that stereotypes will become operative whenever subjects know the topic of the research.

### 3.2 Rating Scales

Health outcomes and their determinants can be measured by validated rating scales. The failure to use adequately validated scales has been a major problem in menopause research. In the classical Kuppermann Menopausal Index,[10] a numerical summation of 11 menopausal complaints derived from clinical experience in New York in the 1950s, as well as in other rating scales, the importance of "neurovegetative symptoms" is overestimated, whereas other changes are neglected. This particularly applies to the measurement of sexuality and of symptom experience. For example, with regard to sexuality, relatively few of the population-based studies of the menopause transition have made any inquiry about sexual functioning. Differing measures of sexual functioning have been used but studies often fail to offer any data on the validity or reliability of these measures in their local population. The research process itself may result in response bias. This includes interviewer bias in the phrasing of questions and specification bias if the variable under study is not well specified to the full understanding of the subject.

### 3.3 Symptom Measure

A major methodological issue is that of the symptom measure utilized and its validity and reliability for the cultural group studied. The standard method used for collecting information on the prevalence and severity of symptoms has been a checklist of symptoms. But the checklist in itself introduces a number of biases, including the problem of elicitation. For example, Wright,[11] interviewing women of the Navajo tribe, found that virtually all respondents reported no bodily changes since menopause in relation to open-ended questions, but most responded positively to symptoms in the checklist. Holte[12] noted that the sounder the methodology, the lower the prevalence of symptoms. When frequency or bothersomeness of complaint are included, the reporting rate goes down further: irritability was reported by 57 percent of premenopausal women as being present occasionally, but only 10 percent of the same women reported that it was there frequently.[12] The presence of symptoms "occasionally" does not indicate their impact on the woman and may not be clinically relevant or indicative of treatment needs. Porter et al.[13] assessed the impact and prevalence of symp-

toms in a Scottish postal survey of 6,096 women aged 45–54. Fifty-seven percent of the cohort had experienced a hot flush, but only 22 percent said that it had been a problem. Similar disparity existed for night sweats (55 percent and 24 percent) and dry vagina (34 percent and 14 percent). Only 4 percent had experienced none of the symptoms.

The most frequently used checklist has been based on a numerical summation of 11 menopausal complaints, the Kupperman Menopausal Index, derived from clinical experience in New York in the 1950s. The index was a combination of self-report and physician ratings. The index included 11 symptoms (vasomotor, paraesthesia, insomnia, nervousness, melancholia, vertigo, weakness (fatigue), arthralgia and myalgia, headaches, palpitations and formication) rated on a 4-point scale. In a critical review, Alder[14] noted that terms were ill defined, categories included overlapping scores, and scores were summed without being based on independent factors. Symptoms seemed to be arbitrarily selected; omitted were measures of vaginal dryness, dyspareunia, and breast tenderness. The following year Kupperman and coworkers, including Blatt,[15] described a modification, which allowed for some symptoms to be weighted more than others. Weighting was used without statistical justification. Later, investigators, such as Neugarten and Kraines,[16] extended the list to 28 symptoms but found that only 9 of these distinguished menopausal women from those at other developmental phases. These authors, and many since, arbitrarily categorized groups of symptoms. Greene[17] was the first to use factor analysis as the basis for categorizing symptoms into three factors, vasomotor, somatic, and psychological. But Greene's study contained a number of flaws. Although his 30-symptom list was constructed from the scale of Neugarten and Kraines,[16] he failed to include breast pain, somewhat curiously as Neugarten and Kraines had found this symptom to be associated with menopausal women. Nor did he include symptoms of vaginal atrophy. These symptoms (mastalgia and atrophy) were still not included in a later amended 20-item list.[18]

Whether psychological complaints vary with the menopause transition has been a key concept, yet the capacity of most symptom checklists to adequately measure psychological morbidity is unknown.[9] In their Manitoba study, symptoms measuring psychological morbidity had to conform to scales used by psychological epidemiologists, and concurrent validity was sought. The symptom checklist was not restricted to items with an association with menopause but was embedded in an 18-item general symptom list adapted from one used in a community health survey. The 11 symptoms forming the menopausal index were derived from the International Health Foundation studies (hot flush, night sweats, dizziness, rapid heart beat, pins and needles in hands and feet, tiredness, irritability, headaches, depression, nervous tension, and insomnia). Interestingly, the list did not include vaginal atrophy symptoms, yet the International Health Foundation list was supposedly chosen as a "succinct summary of the core symptoms as described in the clinical literature." Four factors were found. Hot flushes and night sweats group together as a separate factor, and five symptoms burdened on a psychological factor. These were five of the six symptoms in the International Health Foundation arbitrary classification of "symptoms of the nervous system." A strong association was found between the five psychological symptoms and the two standardized measures of psychological morbidity used for concurrent validity.

Greene[18] compared the findings of seven factor analytic studies. Despite different methodologies and sampling, he found that vasomotor symptoms (hot flushes, night sweats) always formed a separate cluster, totally independent of other symptoms. There was also agreement that a number of symptoms cluster together to form a general somatic or perhaps psychosomatic factor: pressure or tightness in head or body, muscle and joint pains,

numb-tingling feelings, headaches, feeling dizzy or faint, breathing difficulties, and loss of feeling in hands or feet. A further group of symptoms cluster together to form a psychological factor, which in some studies can be subdivided into anxiety and depression.

### 3.4 Cross-Sectional Versus Longitudinal Design

As indicated above, observational studies of population-based samples are the best way to determine the symptom experience of women in relationship to the phases of the natural menopause transition. However, they often suffer from being cross-sectional in design[19] rather than having the power of longitudinal analysis of the same women through the menopause transition.[20] Cross-sectional studies can only indicate whether associations exist and are unable to determine causality. Cross-sectional studies have certain advantages. They are more convenient and less expensive to carry out. Subjects are only asked to participate on one occasion so that the response rate is likely to be higher than when subjects are asked to contribute time for assessments on a regular basis. Those who accept to participate in a longitudinal study may differ in certain systematic ways from those who decline and this may introduce bias into the sample.[21] Thus, the sample participating in a cross-sectional study may be more similar to a general population sample than that of a longitudinal study sample.

Splintering of the study population can continue for other reasons during the accrual process.[22] From the target group, only those persons available to the investigator are potentially eligible for study. Further splintering occurs after applying inclusion and exclusion criteria. After being admitted to the study, the subject's records must be properly filled in: missing data on some variables can lead to exclusion of the subject with some analytic techniques. If the reason for drop-out or premature early termination of the study is related to the studied endpoint, this can induce further bias. Another source of error is that of confounding, which necessitates the need for multivariate analytic methods to control for the influence of the various factors that can affect an outcome. The majority of community-based studies have been cross-sectional and thus limit researchers to inferring apparent associations. Cross-sectional studies cannot control for premenopausal characteristics nor separate the effects of aging from those of menopause.

These studies are less satisfactory than longitudinal studies in which the same women are followed over time with the same instruments, so that what is being observed is change in the same population with time. Longitudinal cohort designs facilitate the identification of causal pathways and allow the effects of aging to be disentangled from those of menopause.[8] However, most longitudinal studies have used inadequate statistical methods, often resorting to a cross-sectional approach to data, which, as repeated measures, are no longer independent in nature.[23] Longitudinal collection of data reduces reliance on memory for long recall periods. The length of the recall period in cross-sectional studies can lead to further inaccuracy of data. This is not only true for the studied endpoints, but also for possible covariates at the time of occurrence. In longitudinal studies, there is the opportunity for measures to be made prospectively (such as menstrual diaries) rather than relying on self-recall, which may be substantially less accurate. When change over time is the key concern, a prospective design is mandatory.

### 3.5 Statistical Analysis

Most studies have only utilized univariate analysis and thus been unable to take into account the role of confounding or interacting factors. The findings of these studies are thus often contradictory. A major problem in the longitudinal studies has been the lack of a sensitive enough statistical analysis, which would use a within-subject-repeated-measures method, allowing for the various factors which may affect the quality-of-life measure, changes in those factors, and interactions with the menopausal transition to be identified.[23]

The analysis of longitudinal studies becomes more complex as the temporal dimension is added to the other possible components of the study. Many statistical approaches are possible. A simple and powerful technique is to calculate mean values prior to and following an event such as the FMP. To allow for the influence of multiple factors, linear regression is preferred to logistic regression where continuous data are available. For more information about evolution in time, more complex techniques are needed. A suitable technique is repeated measures multivariate analysis of variance using a number of contrasts to estimate various effects. Simple split plot or randomized block designs cannot be recommended as they often violate compound symmetry assumptions. For series involving more than 100 observations for each subject, time series and spectral analysis techniques should be considered. Structural equation modeling is recommended for examination in detail of a range of factors that may influence the studied endpoint, the presence of feedback and of latent or nonmeasurable variables.

In reviewing the extensive observational literature in this field accessible in Medline, we will concentrate on those studies which use adequate study design.[24] These include random sampling; describing the study as a general health survey, so that bias caused by emotional response to menopause is lessened; collecting information on current symptomatology, so that the problem of recall bias is minimized; utilizing an age range that encompasses the menopause transition, for example, 45–55 years for cross-sectional studies or a younger (mean) age group for longitudinal studies of the menopause transition, to ensure that women are premenopausal at outset; longer followup in longitudinal studies; and collection of data on menstrual status, hormone usage, and induced menopause, so that the phase of the menopause transition can be adequately determined. Where there are methodological problems such as poor response rate, these are outlined.

## 4. Prevalence of Symptoms in Middle-Aged Women: Relationship to Hormonal Events of the Menopause Transition and Aging

A few studies have tried to address this question by examining different symptom experiences for women of different age groups and menopausal status.

Two studies compared symptom checklist results for men and women of different age groups using lists from general practices. Results were presented by age groups rather than by menopausal status. Bungay et al.,[25] in a United Kingdom postal survey, found that four different patterns occurred by age and sex. Peaks of prevalence of flushing and sweating were closely associated with the mean age of the menopause. Less impressive peaks of minor mental symptoms were associated with an age just preceding the mean age of menopause. Complaints about aching breasts, irritability, and low backache diminished after menopause. Male and female curves were parallel for loss of appetite, crawling or tingling sensations on skin, headaches, difficulty with intercourse, indigestion, constipation, diarrhea, shortness of breath, coldness of hands and feet, dryness of skin, dryness of hair, aching muscles, aching joints, feelings of panic, feelings of depression, and stinging on passing urine.

A Dutch national study[26] of the symptoms in the Kupperman index experienced by men and women aged over 25 years, reported female/male ratios for each symptom. Only transpiration (excessive sweating) showed a significant increase at age 45–54, compared to younger age groups and then remained raised. No other symptom showed a significant increase in the age group 45–54, including the General Health Questionnaire score of mental health.

Most observational studies using symptom checklists find that middle-aged women are highly symptomatic. An Australian study[27] of women aged 45–54 found the symptoms most commonly experienced in the prior 2 weeks to be very dry skin (68 percent), backache (49 percent), forgetfulness

(47 percent), problems sleeping (39 percent), irritability (37 percent), and mood swings (36 percent). Hot flushes were reported by 25 percent of women (rank order 10) and sweating attacks by 13 percent (rank order 19). Vaginal dryness and discomfort was reported by 16 percent (rank order 17).

As noted earlier, there is consensus about the marked temporal relationship of vasomotor symptoms to menopause.[28] These begin to increase in perimenopause, reach a peak within 1–2 years of the FMP,[12] and remain elevated for up to 10 years.[29–31] McKinlay et al.,[32] in a followup study over 4 years of 1,178 premenopausal women, found increasing hot flushes—10 percent in early premenopause, 30 percent in early perimenopause increasing to 50 percent of women 1 year prior to the FMP—coinciding with late perimenopause, with reports of hot flushes starting to decline significantly 2 years after FMP and reaching 20 percent of women 4 years after FMP. Thus, hot flushes are not the most frequent symptoms reported, nor are they pathognomonic of menopause, being reported by younger menstruating women. A number of studies have shown an association between hot flushes and night sweats,[33] and some show an association between these vasomotor symptoms and insomnia.[34] Women who had an artificially induced menopause were more likely to still report flushing than were naturally menopausal women and to report more symptoms.[34] Only a few studies included any reported measure of dryness of the vagina. Oldenhave reports that dry vagina increased in the perimenopause to postmenopause, with a slight decrease > 10 years postmenopause, which may be explained by lack of a partner.[31] This complaint is related to hot flush reporting. There was less consistency regarding other symptoms. A number of cross-sectional studies, including the two Ede studies,[29,31] report a small but transient increase in nonvasomotor symptoms in perimenopause. There was no attempt to differentiate whether any increase in such symptoms is due to distress caused by vasomotor symptoms. A Norwegian 5-year prospective study found that vasomotor symptoms, vaginal dryness, heart palpitations, and social dysfunction increased with the menopausal transition, but that headache and breast tenderness decreased.[35] However, these results were based on only 59 of the 200 premenopausal women selected for the study. The author notes that the finding of heart palpitations must be treated with caution since it differs from all previous factor analytic studies.[35] Recently released results from the cross-sectional phase of the Study of Women's Health Across the Nation (SWAN) study have also found an increase in vasomotor symptoms and in psychological and psychosomatic symptoms related to menopause.[36] Analyses of data from 14,906 women aged 40 to 55 years found vasomotor symptoms burden on a different factor to psychosomatic symptoms. Perimenopausal and postmenopausal women, HRT users, and women who had a surgical menopause were all significantly more likely to report vasomotor symptoms compared to premenopausal women, with postmenopausal women having the higher OR. Psychosomatic symptoms (tense, depressed, irritable, forgetful, headaches) were reported more often by perimenopausal women, hormone users, and women with a surgical menopause than by premenopuase or postmenopausal women. A number of other studies, including recent longitudinal studies using validated mood scales, have not found an association between mood and menopausal status.[37]

The Melbourne Women's Midlife Health Project reported on the analysis of those women who after 7 years of followup had progressed through the menopause transition. Annual measures included a 33-item symptom checklist. Increasing significantly from early to late perimenopause were the total number of symptoms, hot flushes, night sweats, and dry vagina. Breast soreness/tenderness (mastalgia) decreased significantly with the menopause transition. Trouble sleeping showed a smaller increase, which was found to in part reflect bothersome hot

flushes.[38] (See figs. 3–1 to 3–5.) The onset of hot flushes was found to be related to decreased estradiol levels ($p < 0.01$), and the onset of night sweats was related to the change in estradiol level ($p < 0.05$).[38] Interestingly, breast tenderness was not included in the SWAN study reported above. The SWAN study found that vaginal dryness was related to vasomotor symptoms but did not reach the criteria for inclusion in the factor analysis, and results were not reported by menopausal status.[36]

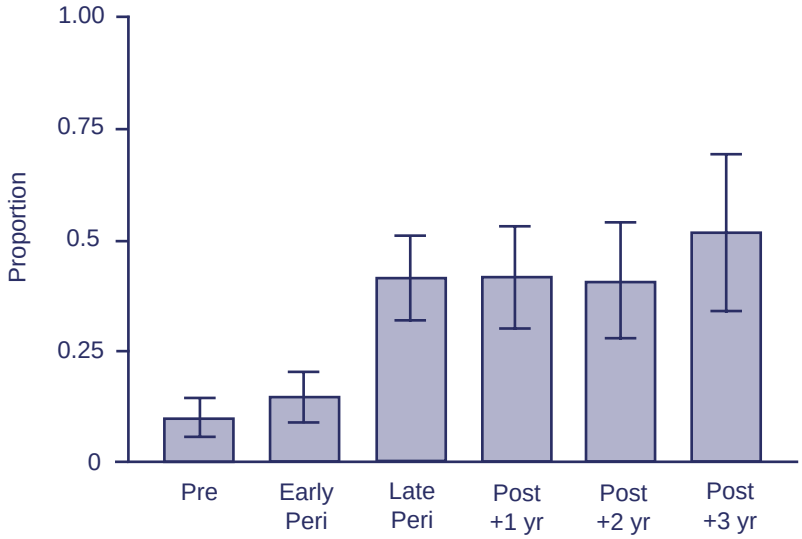
***Epidemiological studies have found that only vasomotor and vaginal atrophic symptoms significantly increase as women pass through the natural menopause transition.***

Longcope et al.[39] also report a significant negative association of hot flushes with estrone and estradiol levels amongst their sample of 241 Massachusetts women followed for 3 years. Thus, a number of epidemiological studies have found that only vasomotor and vaginal atrophic symptoms significantly increase as women pass through the natural menopause transition.

Although many theories have been suggested to explain the mechanism of menopausal flushing, none provide a satisfactory explanation.[40] Core body temperature elevations precede the menopausal hot flush and serve as one trigger of this heat loss phenomenon.[41] What is responsible for the core temperature elevation is a matter of speculation. Although vasomotor symptoms are associated with increasing FSH and decreasing estradiol levels,[38,42] it may be that vasomotor symptoms relate to the activity of another substance, in whose absence the activity of the thermoregulatory center is disturbed.[42] This substance may be common to both ovaries and testes and explain the fact that the male flushes after orchidectomy and the woman after ovarian failure. Each hot flush is accompanied by a gonadotrophin-releasing hormone (GnRH) pulse with a consecutive episode of FSH and LH secretion.[43] Because hypophysec-

## FIGURE 3–1

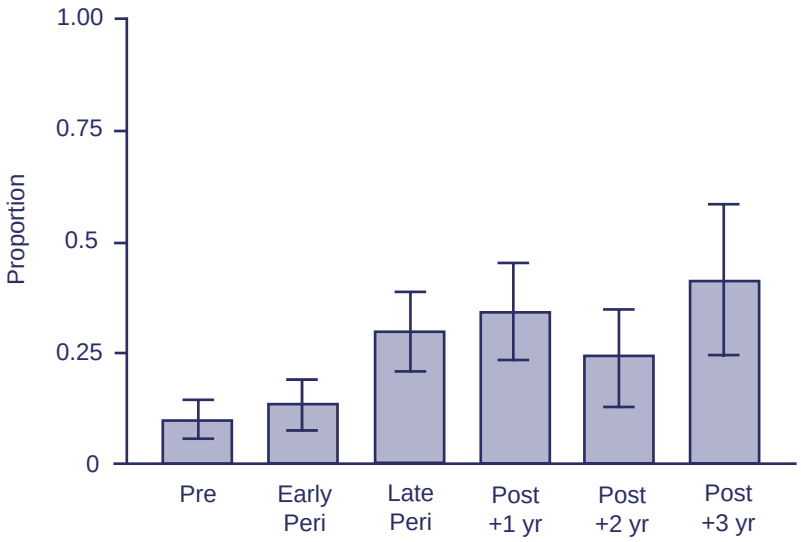
### Proportion of Women Bothered by Hot Flushes by Menopausal Status




pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

## FIGURE 3–2

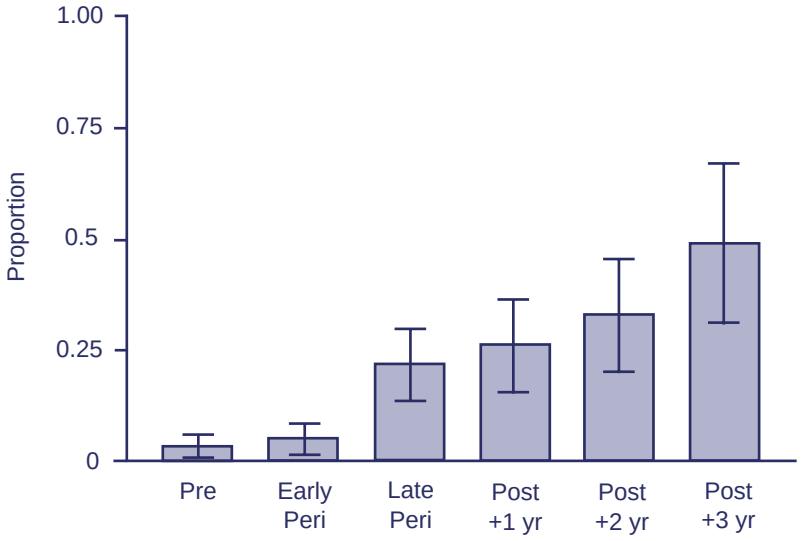
## Proportion of Women Bothered by Night Sweats by Menopausal Status




pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

## FIGURE 3–3

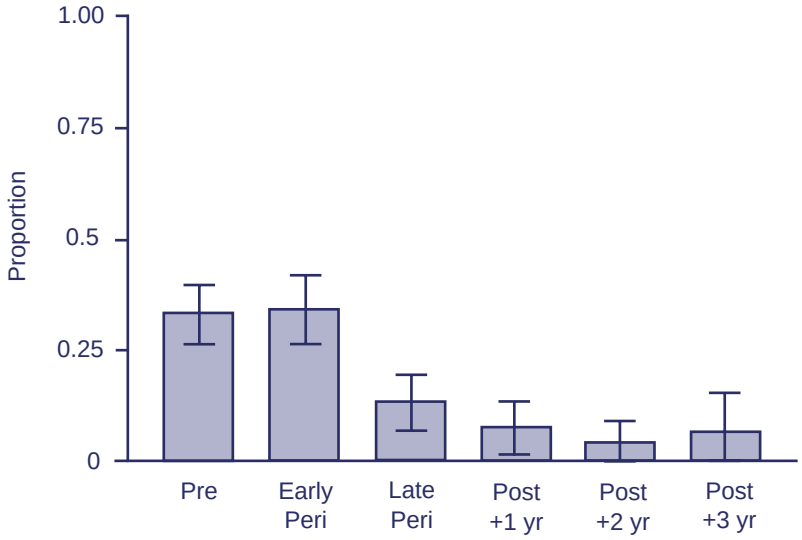
## Proportion of Women Bothered by Dryness of Vagina by Menopausal Status




pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

## FIGURE 3–4

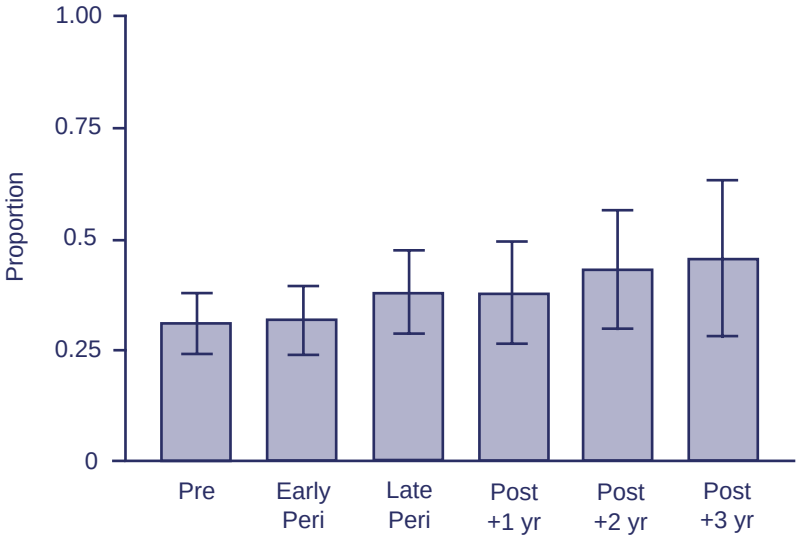
## Proportion of Women Bothered by Breast Soreness by Menopausal Status




pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

## FIGURE 3–5

## Proportion of Women Bothered by Trouble Sleeping by Menopausal Status




pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

tomized hypogonadotropic women experience hot flushes in the same way as women with an intact pituitary, vasomotor instability is induced by a common higher cerebral center and not by the gonadotropin-pulse. The vasodilatation occurring during hot flushes leads to an increase of skin temperature and finger volume and to an augmented oxygen consumption.[44] Due to peripheral vasodilatation, there is an increase of the pulse rate by about 15 percent. Body core temperature then decreases. The increase of finger perfusion starts 1.5 min before the start of the hot flush and lasts for several minutes after its subjective end. Serum LH levels increase only after the beginning of peripheral vasodilatation and reach their maximal value approximately 12 minutes later. Most likely as a consequence of the cooling down of the body core temperature, an elevation of adrenocoticotropic hormone (ACTH) and of human growth hormone (hGH) occurs respectively 5 and 30 minutes after the rise of skin temperature. Because hot flushes occur not only after menopause, but also during the down-regulation by GnRH analogues, the primary decrease of serum estradiol is essential for vasomotor symptoms. Anorexia nervosa or other conditions of hypothalamic amenorrhea do not provoke hot flushes. Furthermore, hot flushes are only observed in women previously exposed to endogenous or exogenous estrogen activity. The pathophysiological mechanism provoking hot flushes involves catecholamines, catecholestrogens, serotonin, histamine, endorphins, and prostaglandins. The endorphin neurons are inactivated by low estrogen levels, a phenomenon that is reversible.

## 5. Role of Psychosocial and Lifestyle Factors in Determining Women's Experience of Symptoms

Cross-sectional studies have explored associations between symptom experience and a large range of other factors. In keeping with other studies from Australia, North America, Scandinavia, and Europe, an Australian study found lower symptom experience in the midlife years to be associated with increasing years of education, better self-rated health, the use of fewer nonprescription medications, absence of chronic conditions, a low level of interpersonal stress, not currently smoking, exercise at least once per week, and positive attitudes to aging and to menopause.[45]

A previous history of premenstrual complaints was reported to be associated with the occurrence of vasomotor symptoms during menopause in cross-sectional analyses of this population-based sample of midlife women.[42,46] Longitudinal analysis of the same cohort found that a prior history of both physical and psychological premenstrual complaints was associated with a more symptomatic perimenopause characterized by dysphoria, skeletal, digestive, and respiratory symptoms.[47]

The cross-sectional phase of the SWAN study found that reports of vasomotor symptoms were negatively associated with educational level and self-assessed health and positively associated with difficulty in paying for basics. Psychosomatic symptoms decreased with age and were reported less often by those with better self-reported health and with less difficulty in paying for basics.[36]

***Cross-sectional studies have explored associations between symptom experience and a large range of other factors.***

Longitudinal population-based studies are best able to establish the likely relationship between experience of symptoms, psychosocial and lifestyle factors. The Massachusetts Women's Health Study found that prior physical and psychological symptoms explained physical symptoms, while psychological symptoms were explained by low education and perceived health.[6] A further analysis of the 454 women from this sample who were premenopausal at baseline and postmenopausal by the

6th followup found that variables related to greater frequency of vasomotor reporting included a longer perimenopause, more symptoms reported prior to menopause, lower education, and more negative attitudes to menopause prior to menopause.[48] Symptom bothersomeness was related to a greater frequency of vasomotor symptom reporting, smoking, and being divorced. Variables that predicted consultations were greater frequency and bothersomeness of symptoms, higher education, and greater health care utilization.[48] Women with negative attitudes to menopause were more likely to subsequently experience bothersome symptoms.[49]

A British study[50] found that women who had experienced an early natural menopause had a strongly increased risk of vasomotor symptoms (hot flushes or night sweats), sexual difficulties (vaginal dryness or difficulties with intercourse), and trouble sleeping. However, there was little or no excess risk of the other somatic or psychological symptoms studied. In contrast, all types of symptoms were more common among women who had had a hysterectomy or were users of HRT. Using prospective data collected when the women were 36, symptom reporting was predicted by low education, stressful lives, or a previous history of poor physical and psychological health. Adjustment for these factors in a logistic regression model did not affect the relationship between symptoms and current menopausal status. For vasomotor symptoms, postmenopausal women had an adjusted OR of 4.7 (95 percent confidence internval (CI) 2.6–8.5), and perimenopausal women had an adjusted OR of 2.6 (95 percent CI 1.9–3.5) compared with premenopausal women. Corresponding adjusted ORs for sexual difficulties were 3.9 (95 percent CI 2.1–7.1) and 2.2 (95 percent CI 1.4–3.2) and for trouble sleeping were 3.4 (95 percent CI 1.9–6.2) and 1.5 (95 percent CI 1.1–2.0).

A postal survey of men and women aged between 49–55 years and registered with a London general practice[51] found no gender differences in reporting of self-rated health, life satisfaction, and health-related quality of life, although women reported more physical problems. Menopausal status was not significantly related to life satisfaction or to health-related quality of life. Significant predictors of health-related quality of life were serious illness, employment, and marital status. Sample size was relatively small in this study (n = 189), response rate was only 47 percent, and the age range may have meant that most women were already in the menopausal transition.

Using structural modeling of data from the first 6 years of followup of the Melbourne Women's Midlife Health Project, the presence of bothersome symptoms was found to adversely affect well-being.[52] Repeated measures multivariate analysis of covariance also found that bothersome symptoms adversely impacted negative mood.[37]

Greene[28] suggested a vulnerability model to explain the role of psychosocial factors in symptom experience during the menopausal transition. The Greene vulnerability model hypothesizes that adverse psychosocial factors render women vulnerable to develop nonspecific physical and psychological symptoms at this time. Response to stress interacts with personality and sensitivity to biological changes to determine the actual symptoms experienced.

Hot beverages can cause flushing through counter current heat exchange mediated through the thermoregulation center of the anterior hypothalamus. Foods containing nitrites and sulphites and spicy foods, such as those containing the active agent in red pepper or capsaicin, may also provoke severe flushing. Alcohol intake is also associated with flushing reactions, although there are no controlled trials examining the effect of alcohol intake on the severity of menopausal symptoms, in particular vasomotor symptoms. The mechanism of alcohol-provoked flushing is complex but is probably related to the fact that fermented alcoholic beverages contain tyramine or histamine, which induces flushing.[53]

### 5.1 Exercise

It has been suggested that physical activity may have a beneficial effect on reducing vasomotor symptoms in menopausal women. Physical exercise involving increased energy expenditure increases hypothalamic β-endorphin production, and β-endorphins are reported to stabilize thermoregulation.[54] However, conflicting evidence exists as to whether exercise has an effect on menopausal symptoms.

In a cross-sectional study of a population-based sample of 728 Australian-born women,[55] physical activity had no significant effect on women's experience of troubling symptoms, including those symptoms associated with their menopausal status, such as vasomotor symptoms. Hammar et al.[56] reported that women who participated in organized physical exercise on a regular basis had a lower prevalence of moderate to severe vasomotor symptoms compared with women of the same menopausal status from the population. A further study by these researchers[54] reported that from a population of 793 women, only 5 percent of highly physically active women experienced severe vasomotor symptoms as compared with 14–16 percent of women who had little or no weekly exercise. The latter study collected data on physical habits and on current and previous experience of vasomotor symptoms. There is the risk of women overestimating the time spent in physical activities as well as the problems of retrospective reporting of vasomotor symptoms. A prospective or intervention study would avoid these problems. However, the fluctuating nature of the experience of vasomotor symptoms and the expectations of participants could affect such studies. A case-control study[57] (82 cases and 89 controls) found that habitual exercise prior to the FMP did not reduce the likelihood of experiencing vasomotor symptoms during the perimenopause.

## 6. Effectivemess of Treatment Interventions for Symptoms Linked to the Transition To Menopause

Available treatments aimed at reducing symptoms related to the menopausal transition include HRT, phytoestrogens, and natural therapies, which have been shown to possess different degrees of efficacy.

### 6.1 Hormone Replacement Therapies (HRT)

Most RCTs of HRT have been carried out on postmenopausal women, many of whom have already received HRT and may have undergone a surgical menopause. Nevertheless, there is considerable consensus in findings that the symptoms which consistently respond to HRT are the vasomotor and vaginal atrophic symptoms. These beneficial effects of HRT persisted after adjusting for baseline symptom level and uterine status.[58]

***Conflicting evidence exists as to whether exercise has an effect on menopausal symptoms.***

There is a substantial body of evidence showing that HRT is effective in reducing hot flushes. Randomized double-blind placebo controlled trials have reported that CEE at dosages of 0.3, 0.625, and 1.25 mg/day significantly reduced hot flushes compared with placebo.[59–61] Similarly, other preparations of estrogen, administered either orally or by transdermal patch, have also shown effectiveness in the relief of vasomotor symptoms.[62–70] Gordon et al.[67] compared the efficacy of estradiol patches and oral conjugated estrogen and found no statistically significant difference between the preparations with regard to their effect on the reduction of hot flushes. The response to the 0.1 mg estradiol patch was greater, and the response to the 0.05 mg estradiol patch was less than the response to conjugated estrogens, although these differences were not statistically different. Percutaneous estradiol delivered in an alcohol-water gel has been reported to be effective in treating vasomotor symptoms.[71] The

use of either continuous or sequential progestins with estrogen does not reduce the efficacy of the preparation in the reduction of hot flushes.[58,65,72] Recently, an intranasal 17β-estradiol spray has been shown to be significantly better than placebo and similar to oral estradiol in reducing hot flushes and is also well tolerated.[73]

***Considerable consensus in findings that the symptoms which consistently respond to HRT are the vasomotor and vaginal atrophic symptoms.***

Vaginal symptoms related to atrophy have been reported to be alleviated by ERT. Local low-dose treatment with a small vaginal tablet of 25 micrograms of 17β-estradiol was shown to significantly relieve postmenopausal symptoms related to vaginal atrophy when compared to placebo.[74] Preparations of estradiol vaginal cream have a similar effect[75] and also result in an increase in plasma levels of estradiol. Percutaneous, transdermal, and oral estradiol treatments have all been reported to improve the vaginal cytology profile in comparison with placebo therapy.[67,71,76] Sleep disturbances do not appear to be helped by transdermal or oral ERT.[69,77] The benefits and risks of HRTs are discussed in other chapters.

A number of nonestrogen preparations have been evaluated for their effects on menopausal symptoms with varying results. The progestational agent megestrol acetate (20 mg twice daily) has been reported to significantly decrease the frequency of hot flushes in women with a history of breast cancer.[78] Veralipride, an antidopaminergic treatment, reduced vasomotor symptoms and was significantly more effective than placebo in three trials.[79–81] Other dopamine agonists and antagonists have also been found to be more effective than placebo in alleviating hot flushes.[78] In one trial, opipramol treatment was reported as being significantly better than placebo in reducing hot flushes.[82] Trials with clonidine,[83] propranolol,[84] and dong quai[85] have shown these treatments to be no more effective than placebo in controlling hot flushes. Dong quai did not have any effect on vaginal cell maturation.[85] More promising results for non-hormonal treatment of hot flushes have come from trials of antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs) and related drugs such as venlafaxine. Pilot studies presented at conferences have found significant reduction in hot flush frequency and severity, but evidence from larger double-blind randomized trials is needed.[86]

Studies of the effects of HRT on mood, cognitive and sexual functioning are discussed elsewhere. The symptom of breast soreness/tenderness (mastalgia) has been shown in clinical trials to be related to estrogen/progestin balance.[58] The Postmenopause Estrogen/Progestin Intervention (PEPI) trial[58] found a significant reduction in muscle and joint pain in women who adhered to estrogen- and progestin-containing regimes. This beneficial effect on muscle and joint pain was not evident in intention-to-treat analyses. Aches or stiff joints were reported by over 40 percent of women in the Melbourne Women's Midlife Health Project at each phase of the menopause transition,[38] although there was no demonstrable variation with the menopause transition. Given the prevalence of these symptoms among middle-aged women, further research is needed.

### 6.2 Phytoestrogens

Phytoestrogens are plant compounds that have a close similarity in structure to estrogens. Evidence for the effects of phytoestrogens on reducing menopausal symptoms, hot flushes, and vaginal dryness come from two main sources—observational studies and clinical trials. The first source is from epidemiological data of populations who have high dietary intakes of phytoestrogen compounds and who have a very low rate of hot flushes (for example, 5–10 percent of Japanese women report hot flushes compared with 70–80 percent of Western women).[87] Japanese women are reported

to consume 20–150 mg/day of isoflavones[88] compared to Western women, where less than 5 mg/day is consumed.[89]

The second source is from placebo-controlled clinical trials. Five studies[90–94] have reported improvement in hot flushes after dietary supplementation with phytoestrogens. In three of these studies,[90,93,94] there was no significant improvement in these symptoms in subjects in the treatment compared to the placebo group. In one study,[93] there was an increase in urinary isoflavone excretion in the placebo group. There was a strong negative correlation between the level of urinary isoflavone excretion and the incidence of vasomotor symptoms in both treatment and placebo groups. This further emphasises the problem with intervention studies using naturally occurring dietary compounds.

There are problems with both sources of information. Whether Japanese women do in fact experience a significantly lower frequency of hot flushes has been challenged,[95] and there is no data from this population on the prevalence of vaginal dryness. Evidence from controlled trials is limited by several problems—finding an effective control group, as phytoestrogens are present in so many foods that it is difficult to eliminate them from the diet, and the fact that natural improvement of menopausal symptoms occurs with time. Of five studies that looked at changes in vaginal cytology with and without phytoestrogen supplementation, there was a significant improvement in three instances[91,96,97] but not in two.[90,98] The variations in response may depend on populations studied, source of phytoestrogen, and study design, particularly with respect to duration of exposure.

### 6.3 Natural Therapies

Evening primrose oil, containing gamma-linolenic acid, has been evaluated as a therapy for treating hot flushes and sweating associated with menopause in a randomized, double-blind, placebo-controlled trial.[99] Although there is no good scientific rationale for the use of this preparation in treating hot flushes and although neither clinicians nor the pharmaceutical industry have ever promoted evening primrose oil for this purpose, there is a current view among the lay public that it is effective in the control of menopausal symptoms. Chenoy and colleagues[99] reported that gamma-linolenic acid provided by evening primrose oil offers no benefit over placebo in treating menopausal flushing.

## 7. Future Needs

Clearly there has been a great deal of research documenting the relationship of symptoms of the menopause transition. In this section, we expand on those areas that require further detailed studies.

In the field of observational studies, there is a need for better documentation of the processes of the natural menopause transition using prospective investigations to distinguish menopause-related changes from those of aging or disease. Design features needed in these longitudinal epidemiological studies are:

- Randomized population sampling including minority women of the country concerned
- Baseline age 45 or less, so that women are more likely to be premenopausal
- Symptom checklists which include all symptoms shown to vary directly (vasomotor, vaginal atrophic, breast tenderness) or indirectly (insomnia, mood) with hormonal change
- Validated measures of psychosocial and lifestyle factors which may mediate hormonal effects
- Prospectively kept menstrual calendars so that phase of the menopause transition can be determined without bias of retrospective recall
- Regular hormonal measures
- Power analysis for sample size, so that effects of hormones and other factors can be delineated

- Long-term followup until women are at least 10 years postmenopausal, so that longer term effects can be studied, including the natural history of untreated symptoms
- Studies of different populations worldwide, representing women from a broader array of racial-ethnic and socioeconomic backgrounds

In the field of treatment interventions, there have been many RCTs of different forms of HRT on symptoms, and larger studies are in progress. On the other hand, there is a need for—

- Questionnaires validating phytoestrogen intake against metabolic measures of metabolites in different cultural settings before either RCTs or observational studies of the role of phytoestrogens can proceed
- A larger RCT of phytoestrogen supplementations, including metabolic measures of metabolite levels

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# Chapter 4: Sociocultural Issues in Menopause

*Aila Collins, Ph.D.**

***Cross-cultural comparisons demonstrate that reported symptoms can vary significantly among countries and among ethnic groups within countries.***

## Key Points[a]

1. Attitudes toward and beliefs about menopause vary historically and among cultures [C].
2. Cross-cultural comparisons demonstrate that reported symptoms can vary significantly among countries and among ethnic groups within countries in their type (e.g., vasomotor, psychological) and in the degree of distress caused [C].
3. Difficulties in integrating findings from cross-cultural studies stem from a number of limitations. Among these are differences among cultures in language used to describe symptoms; use of different methodologies in study design and in instruments used to measure symptoms; and differences in diet and other lifestyle factors that make it difficult to establish cultural versus biologic causes of symptom expression.
4. A better appreciation of cross-cultural differences in the experience of menopause may derive from an emerging interdisciplinary model in which symptoms are seen as a result of increased vulnerability due to hormonal changes in interaction with psychological and sociocultural factors.

## 1. The Meaning of Menopause

The sociocultural aspects of menopause have not been the focus of attention or research interest to the same extent as menopause as a physiological event. Historically and cross-culturally, perspectives on menopause have varied widely. The 19th-century Victorian image was an aging woman with a decaying body, prone to illness and insanity.[1] In contrast, the view of menopause among Asian women has focused on freedom from pregnancy and a sense of liberation.[2] Bowles emphasized that women's experience of and attitude toward menopause are influenced by beliefs and expectations inherent in the prevailing sociocultural paradigm.[3] Thus, factors such as cultural beliefs, values, and attitudes toward menopause determine the experience of individual women of that stage of life as negative and troublesome or positive and liberating.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgment. (See also table 1–1.)

Hällström wrote that the psychological significance ascribed to menopause in Western countries should be regarded as a sociocultural myth.[4] By generating expectations in women, the myth can act as a self-fulfilling negative prophecy. Reproduction and child-rearing have been the primary roles defined for women. Osofsky and Seidenberg argued that many of those writing about the psychology of menopause assumed, on the basis of their own cultural biases, that women derive greater meaning from and place greater significance on their reproductive capacity than do men.[5] Barnett and Baruch emphasized the need to revise our view of women's roles, including broadening our concept of midlife by taking into account women's roles in the workplace as well as the social contexts within which they live.[6]

***Menopause research needs multidisciplinary teams to address its different aspects.***

Research on menopause has long been polarized. The medical model of menopause has focused on identifying symptoms of the climacteric syndrome. Endocrinologists have defined menopause as a deficiency disease requiring treatment, with symptoms believed to be directly linked to the lack of estrogen. Social scientists, on the other hand, have emphasized the social and cultural construct of menopause, holding that whether and how climacteric symptoms are experienced is influenced by that meaning. There is evidence, for instance, that negative attitudes and beliefs before menopause may predict depressed mood or other symptoms at menopause.[7,8]

Recent trends in epidemiological research have highlighted the need to integrate these opposing views into an interactive model. Flint suggested a psycho-bio-cultural model of menopause for interdisciplinary research and for a better understanding of the different aspects of women's health.[9] It is being recognized that menopause research needs multidisciplinary teams to address its different aspects. Research from disciplines such as gynecology, endocrinology, neurology, psychiatry, psychology, and anthropology may be integrated to characterize what changes menopause entails and the individual and cultural differences that occur as a result. A central question to be addressed is whether menopause is universally associated with similar physical changes and symptoms or whether there is, indeed, cross-cultural variation. Evidence of cultural diversity in perception of symptoms lends support to the hypothesis that how menopause is experienced is not ubiquitous but distinct according to cultural groups.

It may be difficult to compare the results from different studies because of methodological problems associated with the research. (See also ch. 3, sec. 3.) Many studies have used less than ideal research designs, unvalidated rating scales that have been translated from one language to another, and small clinical samples. Obermeyer et al. in a recent review[10] pointed out shortcomings of many of the studies used for cross-cultural comparisons. She emphasized the need for studies using a longitudinal design, standardized questionnaires, and an agreed-upon definition of menopause, criteria that most of the cross-cultural comparison studies do not fulfill.

## 2. Cross-Cultural Comparisons

Cross-cultural comparative data can help clarify the extent to which the experience of menopause is universal, provide information about symptom variability, and identify important factors influencing symptoms. Prevalence comparisons among countries of somatic symptoms of menopause, such as hot flushes, and of psychological symptoms, such as depression and changes in sexual interest, show considerable, though not always significant, differences. Among the major findings, one of the best known is the marked contrast between the relatively high prevalence of vasomotor symptoms reported in North American and

European women and the low prevalence reported by Asian women.

Lock's classic studies of Japanese perimenopausal women[11–13] have been widely cited. She collected data on these women using a self-administered questionnaire. The study was carried out in southern Kyoto, where the women were employed in factory or other blue-collar jobs; in Nagano, a rural area where the women worked on farms; and in the suburban area of Kobe, where most of the women were homemakers. The prevalence of hot flushes was low: 3 percent of the homemakers and 10 percent of the working women reported them. The Japanese women more often reported shoulder stiffness, headache, and, to a lesser extent, lumbago, symptoms not specifically linked to the menopausal state. The most striking result was that for most of the symptoms in the symptom list about 85 percent of the women gave a negative response.

A comparison of U.S., Canadian, and Japanese women by Avis et al. showed the Japanese women to have the lowest prevalence of hot flushes and of depression as well as the lowest intake of medication.[14] Such findings may lead us to believe that Asian women do not experience the intense symptoms reported by North American, European, and African women. With regard to hot flushes, however, Lock found that the Japanese women did not have a word for the concept, which had to be explained using different words.[12]

Lock's interpretation of these findings was that Japanese women do not think the same way about menopause as, for example, women in the United States. The Japanese word for midlife transition, konenki, has a social rather than biologic connotation. According to Lock, middle age in Japan is thought of foremost as a social process; the biologic changes are generally viewed as playing only a small part. Konenki is seen as a "luxury disease" suffered only by those women who have too little to do. The strong work ethic in Japanese society coupled with a certain moralistic attitude may influence women and make them less likely to complain of any physical discomfort associated with konenki. Lock also noted that women are explicitly encouraged by the government to provide nursing care for elderly relatives, since there is a marked shortage of programs to care for the aged population. Only recently women's groups have begun to debate issues associated with konenki and have argued that middle-aged women ought to focus more on their own health. Among these activists is Albery, who challenged the belief that Japanese women do not suffer from hot flushes.[15] She also advocated a more evidence-based approach to the understanding of female aging as well as endorsement by the government for gynecologists to treat menopausal symptoms using HRT.

Thus, it may be premature to accentuate social factors in the interpretation of Lock's findings. Biologic factors may have an important role. Recent research has shed light on the role of dietary factors. In much of Asia, particularly Japan, the diet is rich in phytoestrogens. Several studies have found a decrease in the frequency of hot flushes frequency in postmenopausal women in response to soy protein supplementation.[16,17] Larger, well-controlled clinical trials are needed, however, to better address the positive and possible negative effects associated with the intake of soy protein.[18,19] (See ch. 3, sec. 6.2.)

Is it possible that Asian lifestyle could have such dramatic effects on women's health? More recent studies in Asia present a somewhat different picture of symptom reporting. Among them is a well-designed, large-scale study by Boulet et al., conducted in Hong Kong, Indonesia, Korea, Malaysia, the Philippines, Singapore, and Taiwan.[20] The climacteric syndrome was, indeed, experienced by the participants, although in a milder form than generally reported in Western countries. The prevalence of hot flushes and of sweating was lower than in Western countries but not negligible. The percentages of women reporting more psychological types of complaint were similar to those in Western

countries. Perhaps, as the authors suggested, distress related to vasomotor symptoms is translated into psychological complaints, which are more frequently considered to warrant consulting a physician.

Other studies of Asian women that compared symptom reporting include a cross-sectional study of Thai women in Bangkok.[21] The women were asked to report symptoms in the prior 2 weeks. They did experience hot flushes, although the most common complaints were dizziness, headache, joint pain, and backache. The sample was not representative, and the conclusions must be considered tentative, because the women were recruited as they accompanied family members or friends to the hospital. In a study of Thai women attending health clinics in Bangkok, 22 percent of the women with irregular menses and 7 percent of the postmenopausal women reported hot flushes, although the most common symptoms were dizziness (45 percent) and irritability (41 percent).[22]

Among perimenopausal Chinese women living in Hong Kong, 20 percent of those surveyed experienced hot flushes, and, again, psychological complaints such as anxiety and nervousness were more prevalent.[23] In another study of urban women, perimenopausal Canadian and Chinese women differed markedly in symptom prevalence: 60 percent and 18 percent, respectively, reported vasomotor symptoms, and the Chinese women ranked other symptoms as more important, including boredom, poor memory, numbness in the hands or feet, change in appearance, and change in ability to see, taste, or smell.[24] Both groups in the study reported sleep-related problems and fatigue. Ho et al. studied perimenopausal Hong Kong Chinese women and found that although 10 percent experienced hot flushes, musculoskeletal complaints were the most prevalent.[25]

Thus, the prevalence of hot flushes appears to be lower in Asian women, although some of the more recent studies have shown rates closer to western figures. Also, the types of symptoms reported and the degree of distress caused are often different. There are no good explanations for the observed differences. Hot flushes were previously thought to be linked directly only to estrogen deficiency and not modulated by other factors. Our study[26] and that of Avis et al.[27] showed that hot flushes are modulated by psychosocial factors, such as satisfaction with work role and stress at work. In an ongoing study, we found that women with high-stress jobs report the most frequent hot flushes (Collins A and Ahs A, unpublished results). Many of the assumed truths about climacteric symptoms may have to be modified. Because all symptoms are individual and modulated by cognitive processes to a certain extent,[28] they can be influenced by cultural factors. A clear, and perhaps related, example of such influences is the cultural variation in pain perception.[29]

There are probably important factors within cultures that can mediate symptom experience. They include differences in expectations and attitudes toward aging and menopause, as well as socioeconomic factors and women's roles and opportunities in society. A very important area of research that has been largely neglected until recently is the study of different ethnic groups within Western countries. Our ongoing population-based longitudinal study has shown that among perimenopausal women residing in the Stockholm area, women born outside Scandinavia report more frequent hot flushes than do Swedish-born women (Collins A and Ahs A, unpublished data). Researchers in the United States found that African-American women were significantly more likely than white women to report hot flushes.[30] The difference remained after adjustment for BMI, educational level, and menstrual and gynecologic history. The authors attributed the difference mainly to psychosocial factors and stress. Despite the high prevalence of symptoms, few African-American women had discussed menopausal management with their physicians.[30] A study[31] of women of the Indian subcontinent living in the United Kingdom showed that the

majority regarded menopause as a natural event. However, only 33 percent were happy about menopause, and 46 percent were worried about possible adverse effects, such as ill health or weight gain. Over 75 percent of the women stated that they would like to seek medical advice about management of menopause. They also stated that they would prefer a female doctor who would be able to communicate with them in their own language. Thus, the overall results suggest a great need for information and education.

The large-scale, population-based SWAN in the United States compared symptom reporting among white, African-American, Chinese-American, and Japanese-American women.[32] The Asian-American women had significantly fewer symptoms than the white women, and the African-American women had the highest prevalence of vasomotor symptoms.[32] At the same time, among premenopausal through postmenopausal women, attitudes toward menopause and aging were found to differ among the ethnic groups; African-American women were the most positive, and Chinese- or Japanese-speaking women who received their schooling outside the United States were the least positive.[33] Menopause was described as a natural transition of life by Chinese-American and Chinese women in the United States.[34] It is important to consider where women obtain their information about menopause. Study results suggest distinct differences among ethnic groups. Several U.S. studies showed that, in general, African-American women and in particular less educated African-American women have less knowledge of menopause, are less likely to discuss menopause with a physician, and have less awareness of and less knowledge about HRT,[35–38] although they are more likely to have had a hysterectomy.[39] There can be distinct biases in prescribing HRT, and African-American women are less likely than white women to use it.[40] The findings should be related to those of a recent ethnographic study by Agee of African-American and Euro-American women of menopausal age.[41] The women were interviewed in depth about the transfer of knowledge about menopause and aging from mother to daughter. The African-American women more than the white women recounted that their mothers had provided them with the knowledge and tools to negotiate difficulties associated with menopause. They relied more on their own capacity to cope with problems encountered during the menopausal transition, and they were more prone to resist a biomedical model and, thus, less willing to follow their doctors' suggestions to start hormonal treatment. Many Euro-American women stated that their mothers had not talked about their menopausal problems, and many felt that their own life experiences set them apart from their mothers. The relative lack of a role model made them more dependent on a medical approach to solving problems related to menopause.

Also, the age at natural menopause differs between white and African-American women; the African-American women reached menopause significantly earlier.[42] In trying to explain the reasons for these differences, the authors focused on marginalization and psychosocial stress as the most significant predictors of earlier menopause among African-American women.

### 3. Ethnographic Studies

The degree of development of a society may also be important, and we may have to look more closely at nonwestern societies that are not as developed as those of Asia. There are unique studies of populations of rural women with a low level of formal education, and living simple lives, who show no signs of distress at menopause. Data collection was adapted to the women's lifestyle and adjusted for traditional expectancies. The findings may provide us with important indications of the role of cultural norms in symptom experience and reporting.

Beyene used a systematic ethnographic approach to collect data on 107 rural Mayan women aged 33 through 57 years.[43] The women lived in southeastern Yucatán, Mexico, where the residents were subsistence farmers practicing traditional Mayan ceremonies. The onset of natural menopause was earlier than in developed Western countries. The Mayan women became menopausal at ages 41 through 45.

The women did not consider menopause a major crisis. In general, they reported looking forward to menopause and likened it to being young and free. Menopause in the rural Mayan culture was largely unrecognized except as marking the end of menstruation and childbearing. The women indicated that the only recognized symptom of menopause was menstrual irregularity followed by the final cessation of menses. None reported hot flushes or cold sweats. The premenopausal Mayan women did not seem to have cultural knowledge or expectations relating to the onset of menopause other than the cessation of menstruation. Mayan women considered menopause to be a life stage free from taboos and restrictions. They reported better sexual relationships with their husbands, because of no risk of pregnancy.

The findings were particularly valuable because of another study's analysis of the hormonal profiles of rural Mayan women.[44] It was hypothesized that their menopause would be endocrinologically distinct. Determination of FSH, estradiol, prolactin (PRL), androstenedione, and testosterone values as well as BMD of 52 postmenopausal and 26 premenopausal rural Mayan women showed the same endocrinological profile as in U.S. women. Even with specific questioning through a native interviewer, however, it was not possible to elicit familiarity with hot flushes.[44] Interestingly, some Mayans who had moved to a nearby city experienced hot flushes.

Beyene also studied rural Greek women.[43] Data were collected from women living in a village in the eastern part of the island of Evia. The villagers were farmers using traditional farming methods, including plowing with horses and mules. Like the Mayans, the Greek women experienced menopause as a life stage free from taboos and restrictions. They, too, reported better sexual relationships with their husbands. They reported that, without risk for pregnancy, they felt more relaxed about sex. However, women also associated menopause with growing old, lack of energy, and a generally downhill course. Premenopausal women reported anxiety, negative attitudes, or anticipation, with some mixed feelings. When asked about experience of menopausal symptoms, 73 percent of the menopausal and postmenopausal women reported having had hot flushes, and 30 percent reported having cold sweats. Unlike Mayans, Greek women understood the concept of hot flush, and the older women even offered the Greek word for this symptom. They were also able to give detailed accounts of the process of hot flushes and the times they most often felt the sensations and changes in their bodies. Women said they experienced more hot flushes at night and around the times they usually expected to have their menstrual periods.

These two cultures are very different from the other cultures studied, since these are rural women living in a village, where the form of life is still very traditional. In both of them, the women were farmers with physically strenuous work. Possible explanations for reduced symptomatology in the rural groups could relate to physical exercise[45] or dietary habits, although studies of such lifestyle components have yielded mixed results. (See ch. 3, sec. 5.1.) Social or socioeconomic status probably plays an important part. Not all women have access to modern medical care. In an interview study of women with spontaneous menopause in Karachi, Pakistan, 6 percent of slum dwellers sought treatment for symptoms, compared with 26 percent of middle class clinic attendees and 38 percent of the most privileged group, wives of retired military officers.[46] Only one-fifth of the slum

dwellers reported symptoms, whereas 57 percent of the middle class and 50 percent of the most privileged group reported hot flushes. In a study in India, women living in a culture in which social status increased with age experienced few symptoms.[47]

A study of menopausal Nigerian women of Yoruba descent found 30 percent to have had hot flushes.[48] Joint pain was the most frequently reported symptom. The authors suggested that the Yoruba women may not have been as aware of hot flushes as white women and that they may have wrongly attributed their sensations to environmental temperature or to fever.

In an ongoing population-based study of Arab women, Obermeyer reported on the occurrence of symptoms and on help seeking by perimenopausal women in Beirut, Lebanon.[49] The proportion of women reporting hot flushes was 45 percent, similar to figures in the United States, Canada, and Sweden. Reported depression was similar to that in Canada but lower than the U.S. figure of 36 percent. The frequency of hot flushes was higher in smokers, and women who were employed reported fewer symptoms. Thirty-nine percent had sought help for their symptoms, and 15 percent reported using HRT, figures the authors interpreted as consistent with the high educational level of Beirut women and the degree of medicalization in the country.

## 4. What Can Cross-Cultural Comparisons Tell Us?

Flint and Samil[50] and Obermeyer et al.[10] in reviews of the literature emphasized the need for integration of the biomedical and developmental views of menopause.

Attempts to verify menopausal symptoms in different cultures have proved difficult. (See ch. 3.) Results from different studies are hard to compare because the quality of data can differ and studies differ in design and subject representativeness. Often, the subjects were patients or volunteers. Much research has used rating scales translated from European or North American studies; concerns have been raised about the appropriateness of translations without consideration of the cultural relevance of the questionnaires' content. Many studies cited above demonstrated that symptom types and patterns vary from country to country. Vasomotor symptoms are the most frequently reported symptoms in Europe and North America, but in Asia psychological complaints appear to be more common. Yoruba women in Nigeria described joint pain most commonly. The interpretation of bodily states and, thus, symptom experience may be different in different cultures. Boulet et al. suggested that Asian women may report vasomotor symptoms less frequently because vasomotor distress is experienced more in psychological terms.[20] There is a need to know how to ask the right questions and a need for more knowledge of the cultures being studied. In addition, more reliable scales are needed, and these have to be developed in a cultural context.

Overall, there is an association between hormonal changes and climacteric symptomatology, and the association is modulated by cultural factors. There is a considerable variation in the prevalence and pattern of symptoms in different countries, a variation probably due to diversity in cultural norms and traditions as well as in diet and other lifestyle factors.

## 5. Access to Health Care

Kaufert developed a model of menopause in which there are important social implications of becoming menopausal that vary from one society to another.[51] The definition of menopause for any culture will be derived from the meaning and consequences of menopause and from how women's roles are defined in that society. Women are aware of these stereotypes and interpret their bodily changes in accordance with what they have learned. The experience of menopause is associated with a woman's health history as well as a wide

range of variables, such as genetic factors, diet, education, marital status, number of pregnancies, the kind of work she has carried out, social support, and access to health care.[52]

***Women need education and balanced information to make personal decisions regarding whether to use HRT.***

Access to health care varies widely among countries. Women's choices around menopause are said to bear consequences for their health in old age. For a long time, hot flushes and night sweats were considered to be core symptoms of menopause and the most important reason for using HRT. More recently, HRT has been widely promoted for prevention against osteoporosis, CVD, and an array of other conditions. Educated women in industrialized countries with well-developed medical care are a privileged group with access to the most recent information on HRT, whereas other groups have less access and less knowledge. On the other hand, medicalization of menopause in cultures in which menopause is not perceived as a problem is an important issue that should be debated. Some critics have questioned the role of the pharmaceutical industry in influencing health care through product promotion.[53] Developing countries with scarce resources are less likely than developed countries to allocate funds for care of menopausal women. In addition, the inequality among social groups within countries can result in very different access to information and care.

Promoting positive attitudes to aging and to menopause could be important in modifying symptoms and improving the health of women.[54] Women need education and balanced information to make personal decisions regarding whether to use HRT. An important goal for health care providers should be to educate women. Such education should lead to greater equality among women in different cultures and social levels and help women control their own health.

## 6. Conclusions

Menopause has long been considered a turning point in women's lives in western cultures. Although menopause as a physiologic event remains constant, attitudes toward and beliefs about menopause vary considerably historically and cross-culturally. In the past decade, there has been a heated debate among biomedical and social scientists as to whether menopause should be seen as a deficiency disease rather than a natural event. Cross-cultural comparisons fuel the debate by showing that the relation between hormones and symptoms is, indeed, complex. There are significant differences in patterns and prevalence of symptoms between countries and, interestingly, in the types of symptom reported in different ethnic groups within countries. It is difficult, however, to draw firm conclusions from available cultural and ethnographic comparison studies because of a number of limitations. Among these are differences among cultures in language used to describe symptoms and in women's inclination to report symptoms; use of different methodologies in study design and instruments used to measure symptoms; and differences in diet and other lifestyle factors that make it difficult to establish cultural versus biologic reasons for symptom expression. (See ch. 3.)

## 7. Future Needs

- As cross-cultural research on menopause has been hampered by methodological difficulties, better controlled, population-based studies are needed which use standardized instruments adapted to the culture studied.
- There is growing recognition that investigators in different disciplines have to work together for a better understanding of women's health at menopause; such collaboration is particularly needed for cross-cultural work.
- An interactive psycho-bio-cultural model of menopause is needed, which recognizes the interplay between the individual and her psychosocial and cultural environment. From such a perspective, symptoms can be seen as the result of increased vulnerability due to hormonal changes interacting with psychological and sociocultural factors.
- Access to health care has been shown to vary among countries and among socioeconomic groups within countries. It is important that research results be disseminated within the cultures under study so that women can make their personal decisions about possible interventions and treatment strategies.

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# Chapter 5: Physiological Role of Estrogen and Estrogen Receptors

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***There are two different ER subtypes, ERα and ERβ, that mediate the biological effects of estrogens and antiestrogens. Different ligands induce different ER conformations.***

## Key Points[a]

1. There are two different ER subtypes, ERα and ERβ, that mediate the biological effects of estrogens and antiestrogens. Different ligands induce different ER conformations.
2. Different mechanisms of target gene regulation affect the agonist-antagonist profile of a ligand. SERMs have a tissue- and gene-specific mixed agonist-antagonist effect.
3. Both ERα and ERβ are expressed in human breast cancer. Measurement of both ERα and ERβ is suggested for selection of appropriate breast cancer therapy.
4. Both ERα and ERβ are important for normal ovarian follicular development and female fertility.
5. ERβ-selective agonists may protect from abnormal prostate growth and may be the therapy of choice for urge incontinence in women.
6. Available data suggest that ERα plays an important role in bone maturation and homeostasis in both women and men but that ERβ also has a specific role in bone physiology in women.
7. ERα and ERβ are expressed in vascular endothelial cells, smooth muscle cells, and myocardial cells. Potential beneficial effects of estrogens on cardiovascular function and reactivity stem from direct effects on cells in the vascular system but also from effects on liver and circulating monocytes-macrophages.
8. Estrogens are linked to a variety of functions in the CNS: learning, memory, awareness, fine motor skills, temperature regulation, mood, reproductive functions, and depression. The predominant expression and localization of ERβ in rat neocortex, hippocampus, and nuclei of the basal forebrain suggest an important role for ERβ in learning and memory.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgment. (See also table 1–1.)

9. Estrogen and inhibins produced by the ovaries are important feedback regulators of the hypothalamo-pituitary axis (HPA) and the serum levels of LH and FSH. ERα seems to be more involved in the LH, FSH feedback loop than ERβ.
10. ERα and ERβ subtype-selective SERMs may better provide the benefits of estrogen replacement therapy (third generation HRT) than currently used treatments.

***Estrogens have an important role in maintaining a balanced bone metabolism.***

## Extended Summary

**Introduction:** Nuclear receptors such as the ER are ligand-dependent transcription factors. There are two different ER subtypes, ERα and ERβ, that mediate the biological effects of estrogens and antiestrogens. ERβ exists in multiple isoforms. Different ligands induce different ER conformations, and there is a dramatic difference in the topology of the ER surface between agonist- and antagonist-bound receptor. Coactivators and corepressors interact with ligand-bound ERα and ERβ and play, together with the receptor, an important role in the regulation of ER target-gene expression. Different modes or mechanisms of target gene regulation affect the agonist-antagonist profile of a ligand. SERMs have a tissue- and gene-specific mixed agonist-antagonist effect. Alternative indirect activation pathways, other than binding of natural or synthetic small organic hormones or drugs, can also modulate the ER activity. Estrogens have also very rapid effects, so-called nongenomic effects. Nonreceptor-dependent antioxidant effects by estrogens have been reported, protecting from neurodegenerative disorders and atherogenesis.

**Breast Tissue:** There is no pubertal breast development in aromatase-deficient women due to lack of or too low levels of circulating estrogens. Estrogen therapy of aromatase-deficient female patients led to normal prepubertal and postpubertal breast development. ERα has been shown to be necessary for mouse mammary gland development. ERβ is abundantly expressed in rat breast. Both ERα and ERβ are present in human breast cancer. Measurement of both ERα and ERβ is suggested for selection of appropriate breast cancer therapy.

**Urogenital Tract:** ERα and ERβ are both expressed in uterus, ovary, testes, and prostate in the mouse. Absence of ERα results in infertility in both male and female mice. Absence of ERβ results in partial infertility in female mice but no impaired fertility in male mice. ERβ-deficient mice display hyperplasia, dysplasia, and prostatic intraepithelial neoplasia (PIN)-lesions of the prostate. Deficiency of aromatase in human females led to ambiguous genitalia and polycystic ovaries. ERT of aromatase-deficient female patients led to resolution of the ovarian cysts and menarche. Male patients with estrogen deficiency or estrogen insensitivity are reported with macroorchidism or oligozoospermia. ERβ-selective agonists may protect against abnormal prostate growth and may be the therapy of choice for urge incontinence.

**Bone:** Estrogens have an important role in maintaining a balanced bone metabolism. In addition, estrogens protect postmenopausal women from bone loss and the development of osteoporosis. Estrogens may play an important role in the maintenance of bone mass in aging men. Estrogens are important for the pubertal growth spurt and epiphyseal closure in girls as well as in boys. There are likely both direct and indirect (systemic) effects of estrogens on bone metabolism and homeostasis. Both ERα and ERβ are expressed in the bone-forming osteoblasts. Estrogen insensitivity in a male patient caused by ERα deficiency led to osteopenia and continuous longitudinal growth due to unfused epiphyses. Male and female patients with aromatase deficiency have increased bone turnover, delayed bone maturation, low

BMD, and tall stature due to unfused epiphyses. ERT of both female and male aromatase-deficient patients resulted in growth spurt, closure of the epiphyses, and increased BMD. Lack of ERβ expression in the female ERβ-/- mice led to a masculinized bone phenotype of the long bones but no effect on the bone phenotype in male mice. Available data suggest that ERα plays an important role in bone in both men and women but that ERβ perhaps has a role in bone physiology only in women.

**The Cardiovascular System:** A number of gender-related cardiovascular differences have been reported, for example, (1) lower risk for young women than for young men to develop atherosclerosis and CVD, (2) higher prevalence of left ventricular hypertrophy in men than in women, (3) significantly greater intimal thickening after vascular injury in men than in women, and (4) the rapid vascular response to estrogen in women but not in men. ERα and ERβ are expressed in vascular endothelial cells, in smooth muscle cells, and in myocardial cells. Both ERα and ERβ can mediate the vascular injury response to estrogens, suppressing smooth muscle cell proliferation and intimal thickening. Estrogens have both genomic and nongenomic effects on vascular tissue. Part of the beneficial effects of estrogen on cardiovascular function and reactivity comes from liver-specific effects of estrogens on the serum lipid/cholesterol profile. ERα most likely mediates the liver-specific effects of estrogens. Also monocytes-macrophages are potential targets for the beneficial effects of estrogens on the cardiovascular system and the development of atherosclerosis.

**Central Nervous System and the Hypothalamo-Pituitary Axis:** Estrogens are reported to influence a variety of functions in the CNS such as learning, memory, awareness, fine motor skills, temperature regulation, mood, and reproductive functions. Estrogens are also linked to symptoms of depression and treatment of depressive illness. Different brain structures and neurotransmitter systems are involved in the different effects of estrogens. The predominant expression and localization of ERβ in rat neocortex, hippocampus, and nuclei of the basal forebrain suggest an important role for ERβ in learning and memory. Estrogen, through effects on the HPA, modulates the expression and secretion of several hormones from the anterior pituitary gland, such as LH, FSH, growth hormone (GH), and PRL. Female and male patients with aromatase-deficiency have elevated levels of LH and FSH and elevated circulating levels of androgens. Substitution with conjugated estrogens in both male and female aromatase-deficient patients resulted in normalization of gonadotropin and testosterone levels. Clinical data on a male patient with an ERα nonsense mutation also showed increased circulating LH and FSH levels despite high estrogen levels. In ERα-/- mice, the serum LH but not the FSH levels were elevated despite tenfold higher circulating levels of estrogen. Available data indicate that estrogens rather than testosterone (in both men and women) together with inhibins are the major regulators of serum gonadotropin levels and that ERα seems to be more involved in this process than ERβ.

**Hormone Replacement Therapy: Traditional Alternatives and Future Perspectives:** The most common regimens in use to treat symptoms of the menopause and postmenopausal health risks are 17β-estradiol, esterified estrogens, or CEEs, each in combination with a progestin, for example, MPA. The awareness of undesired effects and serious health risks (breast cancer, endometrial cancer, and venous thromboembolism) with existing HRT (first generation HRT) warrants alternatives with improved safety profile. Alternative regimens for women who do not wish to take today's first generation HRT exist. Non-ER subtype-selective SERMs (second generation

***ERα and ERβ are expressed in vascular endothelial cells, smooth muscle cells and in myocardial cells.***

HRT) display tissue-selective estrogen agonism. Although the most frequent and serious health risks of first generation HRT are obviated by these SERMs, they still suffer from low efficacy compared to first generation HRT, and they aggravate hot flushes. The existence of two ER subtypes, ERα and ERβ, gives the opportunity to develop ER subtype-selective ligands that will most likely better provide the benefits of ERT, with an improved therapeutic profile (third generation HRT).

## 1. Introduction

Around 1960, Jensen and colleagues came to the conclusion that the biological effects of estrogen had to be mediated by a receptor protein.[1] Since then, two ER subtypes have been cloned, ERα[2] and ERβ.[3] The discovery of rat ERβ was rapidly followed by the cloning of ERβ from other species[4–6] and the identification of several ERβ isoforms with: (1) extended N-termini,[7,8] (2) a variant with an 18 amino acid residue insertion into the ligand-binding domain (LBD), with altered ligand-binding characteristics,[9,10] and (3) C-terminal splice variants unable to bind ligand or activate reporter gene transcription.[11,12] Various alternatively spliced forms have been described also for ERα.[13,14] The biological and physiological significance of different isoforms of ERα and ERβ is unknown and remains to be investigated. Whether there is still another ER subtype (e.g., ERγ) to be found remains an open question. However, the vascular protective effect of estrogen in the absence of ERα and ERβ[15] and the fact that ERα and ERβ double knockout (DERKO) mice survive to adulthood[16] may suggest that yet another unidentified ER exists.

ERα and ERβ are similar in their architecture to the other members of the steroid-thyroid hormone superfamily of nuclear receptors[17,18] in that they are composed of independent but interacting functional domains: the N-terminal A/B domain, the least conserved among nuclear receptors, enables the receptor to interact with members of the transcriptional apparatus; the C domain, involved with binding of DNA, contains two zinc-binding motifs and a dimerization interface that mediates cooperativity in DNA binding; the D domain, also referred to as a "hinge region," necessary to give the receptor some flexibility between the DNA and the LBDs, binds heat shock protein hsp 90, and probably harbors the sequence representing the nuclear localization signal; and the E/F multifunctional domain recognizes and binds a ligand and is involved in receptor dimerization and interaction with transcription factors and cofactors.[19] The gene modulatory effect of a receptor following binding of a ligand depends on the conformational change of the receptor induced by the ligand and the subsequent events, including release of inhibitory proteins (heat shock proteins), receptor dimerization, receptor:DNA interaction, recruitment of and interaction with coactivators and other transcription factors, and the formation of a preinitiation complex.[20]

In particular, two regions in the ERα participate in transcriptional activation of target genes by forming protein:protein contacts with other transcription factors or coactivators, the ligand-independent, N-terminal activation function 1 (AF–1) and the ligand-dependent, C-terminal activation function 2 (AF–2).[17, 20–23] Synthetic ligands with mixed agonist-antagonist activity, so-called SERMs, such as tamoxifen and raloxifene, display a low but significant partial estrogen agonist activity via ERα on an estrogen-responsive element (ERE).[24] In contrast, these mixed agonists-antagonists display pure antagonism via ERβ on an ERE site. The partial agonism of the SERM tamoxifen by ERα is mediated by a slightly different part of the ERα AF–1 region than required for estradiol (E2) signaling.[25] The pure antagonism of tamoxifen by ERβ was recently explained by the lack in human ERβ of this particular function of hERα AF–1.[26] Thus, differences in the amino-terminal regions of ERα and ERβ most likely explain the differences in their response to mixed agonists-antagonists,

such as tamoxifen and raloxifene, on an ERE site. (See also ch. 6, sec. 3.2.4 for mechanism of antagonist action.)

The ER LBD, similar to other intracellular receptors, is made up of 12 α-helices, named H1–H12. Helix 12 (H12), together with amino acid residues in helices H3, H4, and H5, constitute the AF–2 coactivator recruitment and interaction surface.[20,27] The resolution of 3D structures of ERα in complex with agonists and antagonists has given a molecular mechanism for agonism and antagonism, respectively.[28–30] When the ER LBD is complexed with estradiol or diethylstilbestrol (DES), H12 is positioned over the ligand-binding pocket, generating the AF–2 surface that promotes interaction with coactivators[29] and transcriptional activation. In contrast, in the ERα or ERβ LBD-raloxifene complexes[28,30] or in the ERα LBD–4-hydroxytamoxifen complex,[29] H12 was instead positioned in the hydrophobic cleft formed by H3, H4, and H5, foiling the coactivator interaction surface. (See also ch. 6, sec. 3.2.4 for molecular mechanisms of antiestrogen action.) It is evident that different ligands induce different receptor conformations[31,32] and that different conformations of the receptor affect the efficiency by which coactivators and corepressors interact with the liganded receptor[29] and, consequently, the agonist-antagonist profile of ligands.[33]

In recent years, there has been a strong focus on the cloning and characterization of nuclear receptor coactivators, corepressors, and their associated histone acetyl transferases (HATs) or deacetylases, respectively.[20] Integrator molecules like CREB (cAMP responsive element binding protein) binding protein (CBP/p300) and coactivator and corepressor proteins form protein:protein complexes with liganded nuclear receptors, bringing HATs or deacetylases in juxtaposition to chromatin. These events play a key role in the transcriptional regulation of target genes by liganded nuclear receptors and determine the final outcome on target gene expression.

The presence of different ER subtypes and isoforms and different coactivators and corepressors and our increasing knowledge of mechanisms by which ERα and ERβ, respectively, can modulate target gene expression have significantly added to our understanding of the physiology and pharmacology of estrogens and antiestrogens and have given a plausible explanation of why antiestrogens and SERMs sometimes behave more like estrogen agonists than estrogen antagonists. Initially it was believed that the ER affected the transcription of estrogen-sensitive genes only by direct binding of the ligand-activated receptor to EREs on DNA. We now know that ERα and ERβ also can modulate the expression of genes in an indirect manner, either by blocking the ability of a transcription factor to bind to its response element on DNA,[34] thereby inhibiting gene expression, or by stimulating gene expression by indirect binding of ER to DNA response elements through protein:protein interaction with other transcripton factors.[35–38] The different mechanisms by which ERα and ERβ modulate gene expression have changed our view of the pharmacology of estrogens and antiestrogens. The terms “agonism” and “antagonism” should be used with care. Natural or synthetic hormones that we now categorize as estrogen agonists and estrogen antagonists should perhaps not, in general terms, be categorized in this way. The reason for the caution is exemplified by the transcriptional effect of ERα and ERβ via an activator protein 1 (AP1) site in the presence of estrogens and antiestrogens.[39] With ERα, typical agonists such as estradiol and DES but also the antagonist tamoxifen function as equally efficacious agonists in the AP1 pathway, the antagonist raloxifene being only

***The different mechanisms by which ERα and ERβ modulate gene expression have changed our view of the pharmacology of estrogens and antiestrogens.***

a partial agonist. In contrast, with ERβ, estradiol acts as an antagonist inhibiting the agonistic activity of the two antagonists tamoxifen and raloxifene.[39]

In addition to the classical activation of the ERs by natural or synthetic hormones, alternative, indirect activation pathways of the ER (at least α) in the absence of ligand has been described[40–43] as a consequence of the activation of membrane receptors like those for insulin-like growth factor (IGF)-I,[44] epidermal growth factor (EGF)[45] and TGF and dopamine.[46] Still debated is the exact mechanism involved in this process. Several studies utilizing specific inhibitors of trandsduction signals, like ras, and protein kinase A and C (PKA and PKC), have clearly shown that the full activity of these molecules is essential for unliganded ER activation. Furthermore, point mutation studies have shown that two serines located in the N-terminal A/B domain are required for this process.[42] These findings indicate that phosphorylation of ER or of molecules interacting with ER is involved in transcriptional activation of the unliganded ER. More studies are necessary, particularly to better define whether this mechanism is conserved among different cell types. In fact, studies in various cell systems favor the hypothesis of differential mechanisms depending on the system examined.[47,48] The current hypothesis for the physiological significance of these alternative pathways implies that they may be of relevance in those phases of embryologic development in which neither estradiol nor its metabolites are available (e.g., during the maturation of the reproductive and the nervous systems).[47] These mechanisms might also be of pharmacological interest in the treatment of neoplastic forms that express the ER but have lost the responsiveness to treatment with ER antagonists (e.g., certain type of mammary carcinomas).

Another emerging and potentially important pathway involves the very rapid so-called nongenomic effects of ligands on nuclear receptors.[49] In endothelial cells, estrogen-ER complex-mediated membrane effects lead to sequential activation of ras, raf, mitogen-activated protein kinase kinase (MEK) and, subsequently, activation of mitogen-activated protein kinase (MAPK).[50] It is proposed that this may lead to activation of endothelial nitric oxide synthase (eNOS) and stimulated release of nitric oxide (NO). In neurons, membrane effects of estrogen lead to stimulation of src, ras, MEK, and MAPK, resulting in neuroprotection, and in the bone-specific osteoblasts, the membrane effects of estrogen may be involved in control of apoptosis, cell proliferation, and differentiation.[50]

An important aspect of the physiology and pharmacology of estrogens, which does not require the presence of the receptor protein, is their described antioxidant effects, suggested to protect from neurodegenerative disorders caused by oxidative stress, as in Alzheimer's disease or atherogenesis due to excess uptake of oxidized low density lipoproteins (LDLs) by macrophages in the vascular wall.[51,52] Components of CEEs have also been tested for their antioxidant effects.[51] Equilin and its derivatives were reported to be better antioxidants than estradiol in inhibiting peroxidation of fatty acids and cholesterol in LDL particles. Other agents reported to exert neuroprotective or antiatherogenic effects caused by oxidative stress are phenolic compounds, vitamin E, insulin-like growth factor-1, and mifepristone (RU486).[51–55] In the context of antioxidant effects, antiestrogens (trans-hydroxytamoxifen, tamoxifen, and Imperial Chemical Industries PLC [(ICI) 182,780] but not E2 have been shown to activate the transcription of the quinone reductase gene and to increase NAD(P)H:quinone oxidoreductase enzyme activity via an electrophilic/antioxidant response element (EpRE/ARE).[56] Furthermore, E2 inhibited the agonistic effect of the antiestrogens, and ERβ was more efficacious than ERα in stimulating EpRE/ARE-containing reporter gene expression.[35] These findings suggest that antiestrogens are also potent antioxidants and stimulators of phase 2 detoxification enzyme genes, protecting cells from

damage by radicals and other toxic byproducts of metabolic oxidation.

ERα gene polymorphisms may also provide important information about the physiology of estrogen action. Different ERα polymorphic forms have been linked to increased pig litter size[57] and human breast cancer susceptibility,[58] low BMD, osteoporosis,[59] hypertension,[60] spontaneous abortion,[61] and increased body height.[62]

## 2. Breast Tissue

The importance of estrogens in the development of female breast tissue is well documented. Female aromatase-deficient patients, unable to convert $C^{19}$ steroids (e.g., testosterone) to estrogens, showed no sign of breast development at the onset of puberty[63]. Administration of estrogen to the two described female patients led to normal prepubertal and postpubertal breast development.

ERα knockout (ERKO or ERα-/-) female mice have lost their capacity to develop mammary gland tissue beyond the embryonic and fetal stages despite elevated levels of circulating estrogens (17β-estradiol). This impairment of breast development has been attributed to the lack of both direct and indirect (regulation of growth factor, e.g., EGF, and progesterone receptor (PR) expression) stimulatory effects of estradiol on breast epithelial and stromal tissues, due to missing ERα expression.[64] Applying tissue recombinant experiments and making a series of wild-type and ERα-/- breast stromal and epithelial tissue combinations, it was concluded that ERα expression in the stromal cell layer was essential for growth stimulation of the ductal epithelium in the mammary gland in mice.[65] PRL, also expressed and secreted from the anterior pituitary, plays a crucial role in mammary gland physiology. In ERKO female mice, the expression of PRL from the anterior pituitary and the circulating levels of PRL in serum are decreased by twentyfold and fivefold, respectively. It is conceivable that the impaired mammary tissue development in ERKO female mice is also due to decreased levels of PRL, in part due to lack of ERα expression in ERKO pituitary.[57]

More than 70 percent of primary breast cancers in women are ER (should be read ERα) positive and show estrogen-dependent growth that undergoes regression when deprived of supporting hormones. Patients whose breast tumors lack significant amounts of ERα rarely respond to endocrine ablation or treatment with antiestrogens, whereas most patients with ER-containing breast cancers benefit from such treatment.

Immunochemical determination of ER in tumor biopsies has become a routine clinical procedure on which the choice of therapy is based. However, the currently available immunochemical procedures for ER measurements are based on ERα-specific antibodies that do not detect ERβ protein (unpublished observations).

***The importance of estrogens in the development of female breast tissue is well documented.***

ERβ mRNA and protein, together with ERα mRNA and protein, have been detected in human breast cancer biopsies and in human breast cancer cell lines.[66] With the use of receptor-specific antibodies, both ERα and ERβ were found to be expressed in the normal rat mammary gland, but the presence and cellular distribution of the two receptors were distinct.[67] While the level and percentage of cells expressing ERβ was more or less constant during prepubertal and pubertal stages and throughout pregnancy, lactation, and postlactation, the level and percentage of ERα-containing cells varied dramatically. The possible role of ERβ in normal breast tissue development and physiology and in breast cancer development and/or therapy is, however, as yet unknown.[68]

## 3. Urogenital Tract

ERα and ERβ are both expressed in uterus, ovary, testes, and prostate, but with different cellular localization. In the ovary, ERα is mainly expressed in thecal cells and in the prostate mainly in the stromal compartment. ERβ is expressed mainly in glandular epithelium of the uterus, primarily in the granulosa cells of the ovary, and mainly in the epithelium of the testes and prostate.

***ERα and ERβ are both expressed in uterus, ovary, testes, and prostate, but with different cellular localization.***

Aromatase-deficiency in female patients led to excess circulating androgens in the fetus and at puberty, resulting in virilization and ambisexual development. The two aromatase-deficient female patients[63] were reported with ambiguous genitalia at birth, a phenotype that was further pronounced at pubertal age, and with polycystic ovaries, characterized by a disproportionate number of atretic follicles and dense fibrotic subcortical stroma. The elevated serum levels of FSH and LH in these patients, as a result of perturbed estrogen-dependent negative feedback on gonadotropin production, were suspected to be the cause of the polycystic ovaries. Estrogen replacement in these affected female patients led to normalized gonadotropin and androgen levels, resolution of the ovarian cysts, and menarche.[63] Like female aromatase-deficient patients, aromatase knockout (ArKO) female mice had low serum estrogen levels and high testosterone and gonadotropin levels.[69] Female ArKO mice also displayed genital anomalies, with underdeveloped external genitalia and uteri; and the ovaries contained numerous follicles that appeared arrested before ovulation. The stroma of the ovaries was hyperplastic, with structures that appeared to be atretic follicles. No corpora lutea were present.[69]

Male patients with either defective estrogen production[63] and the male patient with estrogen insensitivity caused by a nonsense mutation in ERα gene[70] are reported to have macroorchidism or oligozoospermia and/or decreased sperm viability or motility. The fertility of the aromatase-deficient or estrogen-resistant male patients is not known. Male ArKO mice were initially fertile but developed progressive infertility[71] due to arrested spermatogenesis. These findings suggest that estrogen has a direct effect on male germ cell development and fertility.

Deletion of the ERα gene in mice results in infertility in both females and males. ERα-/- female mice show complete infertility with hypoplastic, estrogen-resistant uteri and hyperemic ovaries with no ovulatory capacity.[64] Similar to the aromatase-deficient female patients, ERKO female mice have elevated testosterone and LH levels. Treatment of these mice with a GnRH antagonist reduced the serum levels of LH and reverted or prevented the cystic ovarian phenotype,[72] in agreement with the disappearance of polycystic ovaries in aromatase-deficient female patients following estrogen substitution and subsequent normalization of serum gonadotropin levels. To challenge the ovulatory deficiency of ERKO female mice, immature mice were treated with exogenous gonadotropins. Although the ovulatory capacity was reduced compared with age-matched wild-type mice, the collected oocytes were fully competent to undergo successful in vitro fertilization,[72] suggesting that ERα is not critical for follicle maturation and ovulation.

ERβ knockout (BERKO or ERβ-/-) mice also have been generated. Female animals showed reproductive defects (20 percent of normal fertility),[64] while males showed normal fertility. The LH and estrogen levels in BERKO females are comparable to wild-type, but their fertility is compromised due to reduced ovarian efficiency. Superovulation of BERKO female mice exhibited several mature but unruptured follicles. The number of corpora lutea was considerably less than in wild-type mice, suggesting an attenuated response to the ovulatory hormone surge in the absence of ERβ.

Female mice unable to express either ERα or ERβ, DERKO mice, exhibited normal reproductive tract organ development but were, as expected, infertile.[16] Similar to ERKO female mice, the DERKO females showed uterine hypoplasia but no polycystic ovaries. The ovaries of prepubertal DERKO females, displayed precocious maturation evidenced by multiple, large antral follicles, not observed in control wild-type females. The very high serum levels of LH in these animals explain the prepubertal, precocious ovary phenotype of the DERKOs.[16] The ovarian phenotype of the adult DERKO female was distinct from the ERKO and BERKO female phenotypes, most notably by the presence of structures resembling seminiferous tubules of the testis. The sex-reversal of the adult DERKO ovary phenotype was judged to be caused by a redifferentiation of ovarian components rather than by a developmental phenomenon.[16] In summary, based on the ovarian phenotype in DERKO females, it was concluded that both ERα and ERβ are required for the maintenance of germ and somatic cells in the postnatal mouse ovary.

Male ERKO mice are infertile, with atrophy of the testes and seminiferous tubule dysmorphogenesis resulting in decreased spermatogenesis and inactive sperm.[64] Recently, a more detailed study of the cause of the infertility of male ERKO mice provided biological evidence that ERα plays an important role in the reabsorption of luminal fluid from the efferent ductules during the transit of spermatozoa from the testis to the head of the epididymis.[64] Concentration of sperm is claimed to improve their survival and maturation during epididymal storage. Administration of high levels of estrogen to men is known to cause infertility. Thus, another possible explanation that may contribute to the nonreproductive phenotype of ERKO male mice is the relatively high levels of estrogens in ERKO mice and the presence of ERβ in seminiferous epithelium, spermatids, and spermatocytes, causing infertility by a direct action on the testes. In contrast to male ERKO mice, male BERKO mice are fertile,[64] suggesting a different role for ERβ compared to ERα in the male reproductive system. As expected, DERKO male mice are infertile, with an 80-percent reduction in the number of sperm produced in the testis.[16]

Estrogens are claimed to be effective in the treatment of urge incontinence in postmenopausal women. It has recently been shown that ERβ is highly expressed in the inner epithelial cell layer of the rat bladder and urethra.[73] These results suggest that female patients with UI might benefit from ERβ-selective agonist therapy.

Estrogens have also been linked to prostate disease. In different species, estrogens synergize with androgens in inducing glandular hyperplasia and dysplasia and in inducing adenocarcinoma in the prostate.[74] Immunohistochemical studies revealed that ERβ is the predominant ER subtype in the prostate, located in the epithelial cells along the ductal network of the prostate. ERα has been detected only in the stromal compartment of the prostate.[73–75] It has been suggested that ERβ is regulated by androgens in the prostate, since the abundance of ERβ mRNA was rapidly reduced following castration but restored after testosterone replacement.[76] Exposure of wild-type mice to the estrogen 5α-androstane-3β,17β-diol, a metabolite of dihydrotestosterone, caused a decrease in the level of androgen receptor (AR) in the prostate.[75] In ERβ-/- mice, however, the level of AR is elevated, and 5α-androstane-3β, 17β-diol was without effect, suggesting that the AR gene is an ERβ target in the prostate.[75] Exogenous estrogens have a negative effect on epithelial cell differentiation, ductal morphogenesis, and prostate growth,[74] and the prostate of adult rats neonatally exposed to estrogens shows hyperplasia, dysplasia, and presence of *in situ* carcinoma. It was hypothesized that ERβ is a marker of epithelial differentiation and that the decline in epithelial cells in neonatally estrogenized rats is a result of altered epithelial cell differentiation.[74,76] ERβ-/- mice display signs of prostatic hyperplasia with aging.[75] This suggests that ERβ may protect against abnormal prostate growth.

## 4. Bone: Development and Homeostasis

It is well established that estrogens exert an important influence on bone physiology; clinically this is manifested by the occurrence of osteoporosis in postmenopausal women. There is also compelling evidence that estrogens protect postmenopausal women from bone loss and the development of osteoporosis, maintaining a balance between bone resorption and bone formation.[77,78] The level of estrogens may play a more important role than testosterone for the maintenance of bone mass also in aging men,[79,80] with a positive correlation between BMD and serum estradiol concentrations rather than testosterone levels.

As in other tissues, there are most likely both direct and indirect effects of estrogens in maintaining a balanced bone metabolism. The likelihood of important direct effects of estrogens on bone is based on the presence of ERα in the bone-forming osteoblasts[81,82] and in the bone-resorbing osteoclasts.[83] ERβ mRNA has been found in primary rat osteoblasts, in rat osteosarcoma cells,[84] and in immortalized human fetal osteoblasts.[85] Evidence for indirect effects of estrogens on bone metabolism stems from studies in mice, rats, and humans,[86–91] suggesting a coupling and cooperativity between GH and estrogen in bone metabolism. Taken together, these studies indicate that estrogen substitution can increase the circulating levels of GH[87] and the levels of GH receptor on osteoblasts[90] and that there is a mutual dependence of GH and estrogen action on bone growth, mineral density, and maintenance.[86,88,89,91] In addition, estrogens may have indirect effects on osteoclast differentiation, maturation, and activity by inhibition of cytokine expression[92–95] and via stimulation of osteoprotegerin expression from human osteoblasts.[96] The importance of these interactions for the maintenance of bone health needs to be evaluated.

Despite approximately tenfold higher levels of circulating estradiol in ERα-/- mice, there was a significant decrease in the length and size of the femur in females but only slight decrease in males.[64] In contrast, the decrease in BMD and BMC was more pronounced in ERKO males than females.[64] In BERKO mice, the bone phenotype of male mice was unaffected compared to wild-type male mice, while there was a masculinization of the long bones (femur) in the female BERKO mice.[97] Lack of ERβ expression in the female BERKO mice led to increased length of the femur, thicker cortical bone (increased BMC due to increased periosteal circumference), and increased size of the vertebrae, approaching the corresponding characteristics of wild-type male mice. There was no effect on trabecular architecture or BMD in the male or female BERKO mice. Ovariectomy of female mice leads to loss in trabecular BMD to a similar extent in both BERKO and wild-type animals,[97] suggesting an important role for ERα in the maintenance of trabecular BMD and architecture in mice. A further support for the importance of ERα in bone physiology was obtained from examination of a male estrogen-insensitive patient with a nonsense mutation of the ERα gene.[70] Similar to the ERKO mice, he had elevated levels of LH, FSH, and estrogen. Despite the elevated levels of estrogen, he had low BMD and continuous linear growth because of unfused epiphyses, suggesting an important role for ERα in human bone biology. The decrease in length and size of femur in the female ERKO mice may be indicative of an effect of ERβ in the presence of excessive amounts of estradiol or its metabolites. The possible effects of disrupted ERα and ERβ expression in ERKO and BERKO mice, respectively, on GH expression and its consequences for the bone phenotype in these animals are not yet known.

Male and female patients with aromatase-deficiency[63] have increased bone turnover, delayed bone maturation, low BMD, and tall stature due to unfused epiphyses. They have elevated circulating levels of androgens, FSH, and LH but very low or undetectable levels of estrogen. ERT of both female and male aromatase-deficient patients resulted in

growth spurt, closure of the epiphyses, and increased BMD,[63] suggesting a very important role for estrogens not only in females but also in males.

The pubertal growth spurt starts earlier in girls than in boys,[98] beginning at midpubertal stage in boys. The average duration of pubertal growth spurt in girls is shorter than in boys, possibly explained by higher levels of estrogen in prepubertal girls than in prepubertal boys, hypothesized to cause a more rapid skeletal maturation and epiphyseal closure in girls than in boys. Using an ultrasensitive assay for determination of serum estrogen levels, the rise and decline in estrogen levels in boys have been assessed in correlation to age, pubertal growth peak velocity, bone maturity, and epiphyseal closure.[99] In this study, there was a close correlation between the rise in estrogen level and the rise in the level of testosterone, and the rise in estrogen level correlated with the time of peak growth velocity.[99] Following growth spurt in these boys, there was a further increase in estrogen levels that was sustained toward the end of puberty, hypothesized to accelerate epiphyseal fusion.[99]

## 5. Cardiovascular System

Women's risk for the occurrence of CVD clinical events at an early age is less than that for men. The CVD risk increases with age for women, approaching the same incidence rate as for men, starting from the age of 50. (See also ch. 8.) Based on observational epidemiological studies, HRT is described to have a cardiovascular protective effect in postmenopausal women, decreasing the risk of developing atherosclerosis and CVD. (See ch. 8.)[100–102] The cardioprotective effect of estrogens is debatable as no such data from clinical trials are available yet. On the other hand, the outcome of HERS,[103] which did not show any overall cardiovascular benefit in postmenopausal women (treated with oral CEE plus MPA) with established CHD, may be explained on the basis of recent findings, according to which medroxyprogesterone antagonizes positive effects of estrogens on the vasculature. (See ch. 8, sec. 3.2.) The recommendation drawn from HERS was not to initiate hormone treatment for secondary prevention of CHD. Despite an early increase in risk in treated women, fewer CHD events were observed over time in the hormone treatment compared with the placebo group; it was therefore recommended that women with CHD already on HRT may well continue the treatment.

ERα and ERβ are expressed in vascular endothelial cells,[102] smooth muscle cells,[104] and myocardial cells.[105] A number of direct effects of estrogen on vascular tissue have been reported:[101,102,106,107] nongenomic vasodilation as an effect of estrogen on ion-channel function[108] and NO synthesis,[109] long-term effects by modulation of prostaglandin synthase, NO synthase and endothelin gene expression,[105,110] regulation of angiotensin AT1 receptor density on vascular smooth muscle cells,[111] and inhibition of injury induced vascular intimal thickening.[112] Furthermore, reduced heart contractility in ovariectomized female rats normalized following estrogen replacement,[113] an effect, in part, explained by estrogen-mediated changes in expression of contractile proteins.[106,114]

***Besides a higher risk for men to develop atherosclerosis and CVD at an early age compared to women, there are other gender-related cardiovascular differences.***

Besides a higher risk for men to develop atherosclerosis and CVD at an early age compared to women, there are other gender-related cardiovascular differences. Men have a higher prevalence of left ventricular hypertrophy than women,[106,115,116] hypothesized as an effect of the difference in the level of circulating estrogens in men compared to women[106] but possibly also due to gender-specific differences in ER levels and in the induction of endogenous gene expression in cardiac myocytes

in response to estrogen.[106,105] In rats, intimal thickening after vascular injury is significantly greater in males than in females.[107] Male level of intimal thickening occurred in female rats after ovariectomy, an effect that was reversed by estrogen therapy.[112] The primary inhibitory effect of estrogen on intimal thickening was mediated by its direct effect on vascular smooth muscle cells, inhibiting their migration and proliferation.[112] Another gender difference is the rapid response to estrogen after acetylcholine-induced coronary arterial constriction in women and men with coronary artery disease (CAD).[117] In female patients, administration of estrogen reversed the vasoconstriction response to acetylcholine, while there was no response to estrogen in male patients. Coronary blood flow was significantly enhanced in the presence of estrogen in the female patients, but no response to estrogen occurred in the men. A plausible explanation for these differences may be that vascular endothelium in women produces more NO in response to estrogen than in men. The specific role of ERα and ERβ in maintaining normal cardiovascular function and in prevention of the development of atherosclerosis and CVD is still largely unknown.

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However, disruption of the ERα gene, as in ERKO mice, showed a reduced production of NO.[64] ERα also seems involved in neovascularization, as there was no angiogenic response to estrogen in ERKO mice.[64] An increased number of L-type $Ca^{2+}$ channels was reported in ERKO male mice,[64] suggesting an involvement of estrogen and ERα in the regulation of cardiac excitability. In the man bearing an ERα nonsense mutation,[64] there was absence of endothelium-dependent vasodilation of the carotid arteries following ischemic cuff occlusion.[118] However, this lack of ischemic response may relate more to atherosclerosis-induced endothelial dysfunction than to a direct consequence of lack of ERα-mediated responses in the vascular endothelium.[107,119] Sublingual estrogen delivery caused a rapid vasodilator response in the ERα-deficient man,[118] possibly suggesting a role for ERβ in rapid vascular responses to estrogen. In contrast, there was no negative effect of vascular endothelium-dependent vasodilation in ERα-/- mice.[64] Estrogen treatment protects against vascular injury, suppressing smooth muscle cell proliferation and intimal thickening, in ERKO mice.[64] The expression of ERβ but not ERα was dramatically increased in wild-type mice after vascular injury.[102] These data suggest an important role for ERβ in vascular injury response and protection. However, a similar estrogen-dependent vascular injury protection was also seen in BERKO mice, suggesting an ERα and ERβ redundancy in vascular injury protection or that an unknown signaling pathway or a still unidentified ER is involved.[102] In this context, the estrogen resistant man[70] showed intimal thickening of the common carotid arteries[118] despite elevated circulating levels of estrogen.

Part of the beneficial effects of estrogen on cardiovascular function and reactivity relates to liver-specific effects, regulating serum lipid-cholesterol, levels.[101] Estrogens increase the level of apolipoprotein A1 in postmenopausal women.[120] Apolipoprotein(a), the major protein component of the atherogenic lipoprotein (Lp(a)), is down-regulated in the liver by estrogen at the mRNA level resulting in decreased plasma levels of Lp(a).[121] Estrogen also increases the expression of angiotensin in postmenopausal women,[122] regulates the level of HMG CoA reductase at the protein level, and increases LDL receptors on the surface of liver cells.[101] Regulation of the apoE gene by estrogen has been demonstrated in the rat[123] and mouse.[64]

As in skeletal tissue, GH may play an important role for estrogen effects in liver,[91] with hypophysectomy blunting the cholesterol-lowering effect of estrogen in ovariectomized rats.[91] The liver in

female rats has more GH receptors than in male rats,[124] and liver GH receptor expression positively correlates to estrogen status in female and male rats.[125]

So far ERα but not ERβ has been shown to be expressed in liver;[126] thus all effects of estrogen reported on liver-specific gene expression are ERα mediated. Further support for the physiological role of ERα and estrogens in the regulation of liver-specific gene expression and lipid-lipoprotein homeostasis stems from the analysis of the ERα-deficient[70] and the aromatase-deficient patients[63] and from the ERKO mice,[64] demonstrating glucose intolerance and lipid abnormalities as a consequence of estrogen resistance or estrogen insufficiency.

In addition to liver and cardiovascular cells, monocytes-macrophages also are involved in health and disease of the cardiovascular system.[127,128] Several studies, both *in vitro* and *in vivo*, have indicated that growth factors and cytokines that mediate the critical processes of inflammation and wound healing also play a central role in vascular disease and during the initiation and progression of atherosclerosis. The cytokines interleukin-1b (IL–1b) and tumor necrosis factor α (TNFα) have been implicated in the processes of vascular injury and atherogenesis.[129] Both ERα and ERβ are reported to be expressed in monocytes-macrophages.[130] Estradiol has been shown to inhibit LDL oxidation, to inhibit and cholesteryl ester formation and accumulation in macrophages,[131] and to reduce the uptake of acetylated LDL into macrophages, resulting in a reduced rate of foam cell formation.[132] Estrogen down-regulates the expression of TNFα in human macrophages[133] by a mechanism that involves ERβ but not ERα.[134] These results suggest that monocytes-macrophages also are potential targets for the protective effects of estradiol on the cardiovascular system and the development of atherosclerosis.[128]

## 6. Central Nervous System and the Hypothalamo-Pituitary Axis

Estrogens are reported to influence a variety of functions in the CNS, such as learning, memory, awareness, fine motor skills, temperature regulation, mood, and reproductive functions.[135] Estrogens are also linked to symptoms of depression and treatment of depressive illness. (See also ch. 12.)

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Different brain structures and neurotransmitter systems are involved in the different effects of estrogens.[135] The serotonin 5–hydroxytryptamine (5–HT) system, with neurons projecting from the dorsal and medial raphe of the midbrain/brainstem raphe nuclei to multiple forebrain areas such as the hypothalamus, hippocampus, and cortex,[135] is involved in the modulation of reproduction, mood, sleep, and cognition. Serotonin levels and activity in CNS are altered by serum estrogen fluctuation in rodents, and estrogen substitution in ovariectomized rats positively affects the serotonergic system.[135,136] Estrogen has been reported to increase the expression of tryptophan hydroxylase (TPH), the rate-limiting enzyme for serotonin synthesis,[137] and to suppress the expression of the serotonin reuptake transporter (SERT) in raphe nuclei of ovariectomized monkeys.[138] Estrogen reduced the level of the $5–HT_{1A}$ autoreceptor subtype in the dorsal raphe nucleus of spayed monkeys[139] and reduced agonist stimulated $5–HT_{1A}$ receptor inhibition of dorsal raphe neuron firing in rats,[140] suggesting that estrogen may facilitate 5–HT neurotransmission.[139] The level of postsynaptic $5–HT_{1A}$ receptors, mainly localized in the limbic brain areas and the cerebral cortex, is also affected by estrogen.[141] $5–HT_{2A}$ receptors, suggested to be involved in the control of hormone and transmitter release, control of sexual activity, regu-

lation of sleep, motor behavior, and psychiatric disorders such as anxiety and depression,[142] are positively regulated by estrogen in the dorsal raphe, olfactory bulb, and cerebral cortex.[143–145] In male rats, 5–$HT_{1A}$ receptor levels also are regulated by estrogen.[146] ERβ mRNA has been reported within the dorsal raphe of the rat,[147] and an ERα immunoreactive protein has been detected in neurons adjacent to serotonergic cells in rat dorsal raphe.[135] An autoradiographic study in ERα-/- mice indicated an abundant presence of ERβ in mouse dorsal raphe,[148] and no ERα protein has been detected in the macaque raphe,[135] suggesting that ERβ may play a more important role than ERα in mediating estrogen effects on the serotonergic system.

The dopaminergic system, involved in motor function, motivation, reward, cognition, and hypothalamic-pituitary control, is also affected by estrogen.[149,150] Dopamine levels and turnover fluctuate during the estrous cycle,[151] and administration of estrogen, following ovariectomy, potentiates the release of dopamine.[152,153] Estrogen also increases dopamine transporter binding sites in the striatum[154] as well as the densities of dopamine receptors $D_1$ and $D_2$.[155] In the hypothalamus, the dopaminergic tuberoinfundibular neurons inhibit PRL release from the anterior pituitary by release of dopamine into the hypophyseal portal system, an effect that is inhibited by estrogen.[156]

The basal forebrain cholinergic neurons project to the cerebral cortex and hippocampus and are implicated in learning and memory.[135] Long-term ovariectomy results in impaired learning due to decline in high-affinity choline uptake and choline acetyl transferase (ChAT) activity in rats.[135] Estrogen substitution following ovariectomy in rats induced ChAT enzyme levels and increased ChAT activity in the basal forebrain and possibly ChAT activity in projection areas ending in the cerebral cortex and hippocampus.[135] ChAT mRNA levels fluctuate in the basal forebrain cholinergic neurons during the estrous cycle in the rat.[135] The colocalization of ERα with nerve growth factor (NGF) receptors in cholinergic neurons of the rat basal forebrain,[135] and the stimulation of estrogen of both NGF receptor mRNA and ChAT mRNA in the rat basal forebrain,[135] suggest a possible role for ERα in learning and memory functions. However, the predominant expression and localization of ERβ in rat neocortex, hippocampus, and nuclei of the basal forebrain suggest an important role for ERβ in learning and memory.[147,157] This assumption is further supported by the maintained normal memory and learning function in ERKO mice.[64] In a recent study on human brain, the predominant presence of ERβ message in the hippocampal formation, entorhinal cortex, and thalamus suggests a putative role of ERβ in cognition, memory, and motor functions.[158]

Additional transmitter systems shown to be influenced by estrogens are vasopressin and oxytocin,[159,160] somatostatin,[161] galanin,[162] the γ-aminobutyric acid (GABA) system,[163] and the glutamate system.[164,165]

The expression patterns of ERα and ERβ, based on mRNA, autoradiographic, or immunohistochemical studies of rat and mouse brain, indicate a more abundant or distinct presence of the two ER subtypes in certain areas of the brain but also areas where they seem to overlap. ERα seems to be more abundant in the hypothalamus (preoptic, arcuate, periventricular, and ventromedial nuclei) and amygdala (amygdala hippocampal area, medial and cortical nuclei).[147,166] High levels of ERβ mRNA have been found in the medial preoptic, paraventricular and supraoptic nuclei of the rat hypothalamus. In the amygdala, ERβ is primarily expressed in the medial amygdala nucleus. Moderate to high ERβ mRNA levels are found in olfactory bulbs, bed nucleus of the stria terminalis, hippocampus, cerebral cortex, cerebellum, midbrain raphe, and basal forebrain.[135,147,148,157,166–168]

The HPA regulates overall endocrine homeostasis in the body. Estrogen, through effects on the HPA, modulates the expression and secretion of several

hormones from the anterior pituitary gland, such as LH, FSH, GH, and PRL.[64] Both ERα and ERβ are expressed in the pituitary gland, but ERα predominates,[64] in particular in the gonadotrophs and lactotrophs. Both ER subtypes are also expressed in the preoptic area of the hypothalamus and are believed to be involved in regulating the expression of pituitary hormones, but ERβ predominates.[147]

Although serum levels of LH and FSH are directly controlled by hypothalamic GnRH, it is the circulating level of estrogen, other sex steroids, and the inhibin glycoproteins that are the most important physiological determinants of serum gonadotropin levels.[64,169,170] There is a strong inverse correlation between the circulating levels of inhibin and FSH. The main source of inhibin (inhibin A and inhibin B) production in females is the ovary, inhibin B being expressed in the early follicular phase with a peak at the mid-follicular phase and inhibin A being expressed by the dominant follicle and the corpus luteum with a peak in the late follicular phase and in the midluteal phase.[169,170] In men, inhibin B, proposed to be the main inhibin involved in FSH regulation, is primarily produced by the Sertoli cell.[169]

Female and male patients with aromatase-deficiency have elevated levels of LH and FSH, elevated circulating levels of androgens, but very low circulating levels of estradiol and estrone.[63] Therapy with conjugated estrogens in both female and male aromatase-deficient patients resulted in normalization of gonadotropin and testosterone levels.[63] Clinical data on the male patient with the ERα nonsense mutation[70] also showed increased serum LH and FSH levels despite normal levels of testosterone and high estrogen levels. Transdermal ethinyl-estradiol therapy of this man did not lower serum LH or FSH. Estradiol substitution of ovariectomized rats prevented the expected increase in LH but only partially blocked the rise in FSH. In ERα-/- mice, the circulating LH levels, but not FSH, are elevated despite tenfold higher serum levels of estrogen.[64] Taken together, these data indicate that estrogen is more important than testosterone (also in men[171–173]) in regulating circulating gonadotropin levels and that ERα plays a major role in mediating the effect of estrogen in this process. The effect of activin-inhibin feedback regulation of pituitary FSH expression is independent of ERα. Whether ERβ has a role in ovarian activin-inhibin expression and the feedback regulation of gonadotropin expression remains to be investigated.

LH and FSH surge is critical to female ovarian cycle and fertility;[64] elevated estradiol levels in proestrous are required for the preovulatory LH surge from the anterior pitutary, triggered by a discharge of GnRH into the hypophyseal portal system.[174] The anteroventral periventricular nucleus (AVP) of the preoptic region, a sexually dimorphic part of the hypothalamus, is thought to play a critical role in transducing the gonadotropin surge.[64] The AVP is larger in female mice and contains a greater number of dopaminergic neurons than in males.[64] Testosterone exposure of neonatal females reduces the number of dopaminergic neurons and precludes an LH surge. The AVP provides direct projections to a subpopulation of GnRH neurons in the preoptic region that are thought to participate in the initiation of the preovulatory LH surge.[64] Also progesterone and the PR are necessary components of the LH surge.[64,175] Both ERα and ERβ have been shown to trigger PR expression in the preoptic nucleus,[167] suggesting that either of the two ER subtypes or both may participate in triggering the LH surge. Also other neurotransmitter systems in the brain are suggested to contribute to the induction of the LH surge.[64] ERα-containing histaminergic neurons located in the tuberomammillary complex were shown to be involved in the positive feedback effect of estrogen in the induction of the LH surge, mechanistically via histaminergic axo-dendritic and axo-somatic appositions onto GnRH neurons and the histamine H1 receptor.[174]

## 7. Hormone Replacement Therapy: Traditional Alternatives and Future Perspectives

***The most common regimens used to treat symptoms of the menopause and postmenopausal health risks, such as osteoporosis and CVD, are 17β-estradiol, esterified estrogens, or CEEs, each in combination with a progestin.***

The most common regimens used to treat symptoms of the menopause and postmenopausal health risks, such as osteoporosis and CVD, are 17β-estradiol, esterified estrogens, or CEEs, each in combination with a progestin, for example, MPA, to avoid increased risk of endometrial or uterine cancer in women with an intact uterus. Another combination used is estrogen with testosterone, claimed to increase libido and decrease depression. The awareness of undesired effects (e.g., resumption of monthly bleeding, breast tenderness, and headaches) or health risks (breast cancer, endometrial cancer, venous thromboembolism, ovarian cancer, asthma, and gall bladder disease) with existing HRT (first generation HRT) warrants alternatives with improved safety profiles. Recently developed nonsteroidal ER ligands with mixed agonist-antagonist activity, the so-called SERMs (second generation HRT), display a tissue-selective estrogen agonism in for example, bone and liver, but estrogen antagonism in breast and uterine tissue.[176–178] Additional ER ligands with similar mixed agonist-antagonist activity (SERMs) are in development.[177] Although the increased risk of breast cancer and endometrial cancer is obviated by the SERMs, they have not shown the same efficacy as estrogen to prevent bone fractures of the hip, though they have proved efficacious in reducing vertebral fracture risk. Current SERMs increase the incidence of or aggravate hot flushes in postmenopausal women, and the incidence of venous thromboembolism is the same as for first generation HRT. A serious disadvantage for this category of drugs became evident as the SERMs levormeloxifene and idoxifene were withdrawn from further development due to increased incidence of UI and uterine prolapse in postmenopausal women. The discovery of a second ER subtype, ERβ, has revitalized the search for improved drugs for HRT that most likely will better provide the benefits of ERT. Several large pharmaceutical companies are engaged in the development of ERα- and ERβ-selective SERMs (third generation HRT), but as yet there is no information regarding their development. However, synthetic ER subtype-selective ligands have been reported.[179] The most ERα-selective ligand showed 120-fold higher agonist potency for ERα than for ERβ. Another ER subtype-selective ligand, synthesized by the same group, showed full ERα agonism but pure ERβ antagonism.

Current alternatives for women who do not wish to take the HRT cited above are: (1) synthetic progestins, megestrol acetate (a synthetic derivative of androgens), or tibolone (a synthetic steroid with estrogenic, progestational, and androgenic activity) for alleviation of hot flushes; (2) bisphosphonates or calcitonin for prevention of osteoporosis; and (3) statins or antioxidants for prevention of CVD.[176]

## 8. Future Needs

Further characterization of the phenotypes of ERα and ERβ knockout mice will be of continuing importance, not least regarding the effects of ERα and/or ERβ deficiency in aging mice. That ERα/ERβ double knockout mice are viable needs an explanation: the role of redundant systems to secure viability and functionality, the importance of membrane or non-genomic effects of estrogens, and/or the possible existence of a third ER subtype have to be clarified. Other compelling questions to be answered about the biological role of ERα and ERβ stem from the observation that both ERα and ERβ are expressed in normal and malignant breast tissue. Phenotypic characterization of the ERβ-/- mice revealed a role for ERβ as an antiproliferative receptor. In several tissues it operates to oppose the effects of ERα (yin-yang principle). Male BERKO mice develop prostate hyperplasia, which becomes malignant with age, and aging female BERKO mice develop lymphoma. Furthermore, BERKO mice have severely impaired ovarian function related to the dysregulation of AR. Treatment of BERKO females with antiandrogens reversed the phenotype. We have concluded that the major role of ERβ in the ovary is down-regulation of the AR in maturing follicles. In BERKO mice ovaries, AR remains high, for example, the ovary is in a hyperandrogenic state and is similar to ovaries seen in polycystic ovarian disease in humans. There is a need not only to identify genes, which are regulated by ERβ, but also to understand the regulation of the ERβ gene itself. Furthermore, it will be of importance to identify possible mutations in ERβ and to investigate the role mutated ERβ might play in human diseases.

**Priority issues:**

- Understand whether breast tumors arise in cells that already contain one or more of the ERs.
- Investigate the roles of the two ERs in the breast (synergistic or opposing).
- Compare BERKO mice susceptibility to development of breast cancer to that of controls or of ERKO mice.
- Determine whether both ERα- and ERβ-containing stromal cells secrete growth factors in response to estrogens.
- Investigate, if present, the role of mutations in ERβ in human breast cancers.
- Recognize the role of the splice variants of ERβ in the normal breast and in breast malignancy.
- Unravel the mechanism of activation of ER in postmenopausal breast.
- Identify genes that are regulated by ERα and ERβ in normal breast and in breast malignancy.

***Current SERMs increase the incidence of or aggravate hot flushes in postmenopausal women, and the incidence of venous thromboembolism is the same as for first generation HRT.***

**More specifically there is a need to:**

- Understand why epithelial cells in the prostates of ERβ knockout mice are never in G0 and identify the stage in the cell cycle in which they are arrested.
- Identify the genes involved in the change from hyperplasia to malignant phenotype in the prostate.
- Characterize the lymphoma which develops in BERKO females.
- Characterize the role of ERβ in the immune system.
- Investigate the role of ERβ mutations in women with polycystic ovarian syndrome.

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# Chapter 6: The Pharmacologic Modulation of Estrogen Receptor Activity

*Adriana Maggi, Ph.D.* and Rodolfo Paoletti, M.D.†*

***Increased knowledge of the structure of ERs and of the mechanisms of the receptors' synthesis and their interaction with key elements of the transcription apparatus is facilitating the synthesis of new pharmacologically active molecules.***

## Key Points[a]

1. Cell specificity of estrogen action. Increased knowledge of the structure of ERs and of the mechanisms of the receptors' synthesis and their interaction with key elements of the transcription apparatus is facilitating the synthesis of new pharmacologically active molecules.
2. Pharmacologic modulation of ERs. Synthetic ER modulators can be classified as steroidal or nonsteroidal. Novel synthetic steroidal ER agonists hold promise for use in HRT because of agonist activity on the progesterone and androgen receptors. Of particular interest are the nonsteroidal agents that can act as SERMs by behaving as agonists in target tissues, such as bone and liver, and as antagonists or partial agonists in reproductive tissues [A and B].

## 1. Introduction

Natural estrogens modulate the activity of target cells by binding at least two intranuclear receptors. ERα and ERβ belong to a large family of structurally related transcription factors that are well conserved from the evolutionary and functional points of view.[1] The considerable progress made recently in comprehending ER structure (figs. 6–1 and 6–2) and mechanism of action (fig. 6–2) provides a basis for the development of new synthetic ligands aimed at modulating ER functions in an organ-specific fashion.

Transcriptionally inactive ERs reside in the target cell nucleus; they are generally bound to inhibitory proteins. Their activation can occur either by binding of the cognate hormone (ligand-dependent activation) or by posttranslational modifications (ligand-independent activation) that enable them to dissociate from the inhibitory proteins and associate with EREs, which are specific DNA sequences in the promoters of target genes.[2–7] Although currently little is known about ligand-independent activation of ERs, analyses of crystal structures of

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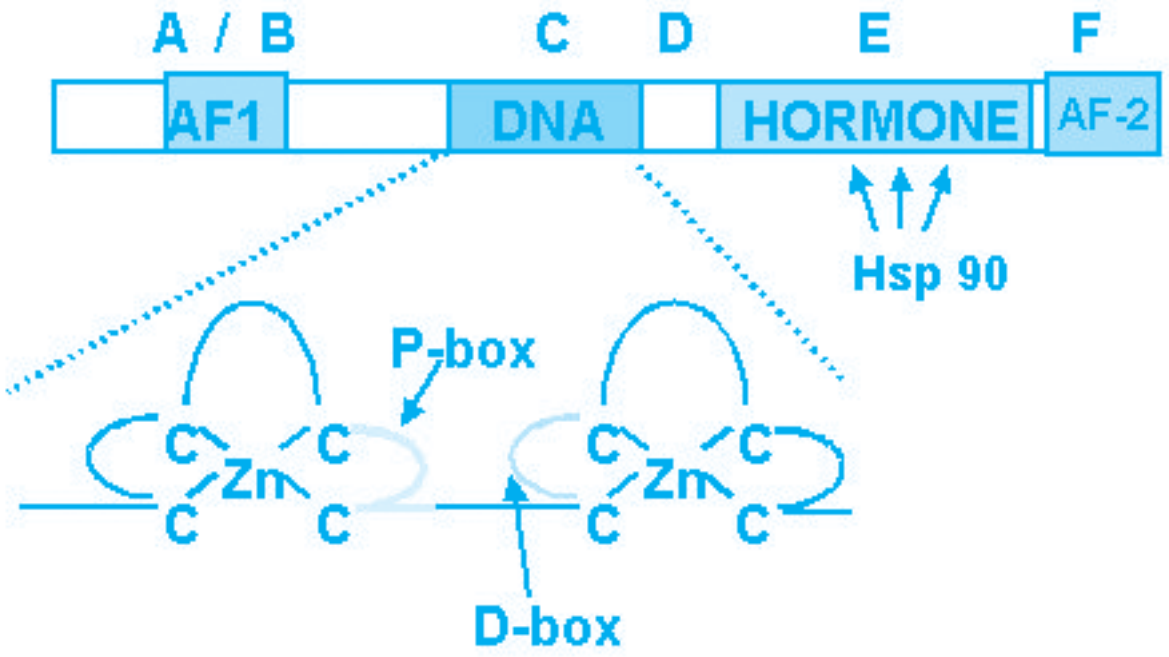
[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1).

## FIGURE 6–1

Structural features of ERs. Mutation studies have identified six functional domains within the ER molecule (see ch. 5 for a more detailed description of ER functional domains): the N-terminal A/B domain, C domain, or DNA binding domain, D domain, the so-called "hinge region," and E/F domain, or ligand-binding domain. Ligand-independent AF-1 is located in the A/B domain, while ligand-dependent AF-2 is harbored by C-terminal E/F domain. C domain mediates the interaction between the receptor and the DNA through "zinc finger" structures.




the hormone-binding domains of ERβ and Erα complexed with agonists and antagonists provide some insight into the intramolecular modifications leading the ligand-receptor complexes to interact with the transcription machinery.[8,9] In addition, several coregulators involved in the generalized and tissue-specific activities of the receptors have been identified.[10–13] ERs may also influence the transcription of genes lacking EREs through binding other transcription factors (e.g., AP1) and thereby hindering these factors' capability to act on their responsive elements.[14,15]

## 2. CELL SPECIFICITY OF ESTROGEN RECEPTOR ACTION

It is now well known that estrogens produce a wide variety of physiologic effects and that ERs are expressed in most mammalian tissues. To design drugs able to mimic estrogen activity in only selected target tissues, it is mandatory to understand how the same hormone can exert so many different effects in the various cells targeted. One hypothesis is that the genes regulated by the hormone are different in each type of target cell. Because the hormone-receptor complex acts through the binding of the same EREs in all the cells, the question arises as to the factors determining the specificity of estrogen action. A number of

factors listed below may contribute, although, in spite of very active research in the field, more studies are needed to clarify which of the mechanisms predominate in the various targets.

**Developmental Cues:** During the process of cell differentiation, fragments of the genome are modified enzymatically or are bound by specific proteins and become inaccessible to transcription factors. The process will undoubtedly involve some of the ER-inducible promoters, which will become insensitive to the hormone activity.

**Complexity of the Target Promoters:** In complex promoters, in which different responsive elements control the transcriptional activity of a single gene, the activity of estrogens will be influenced by the presence of the other factors involved in gene transcription control.

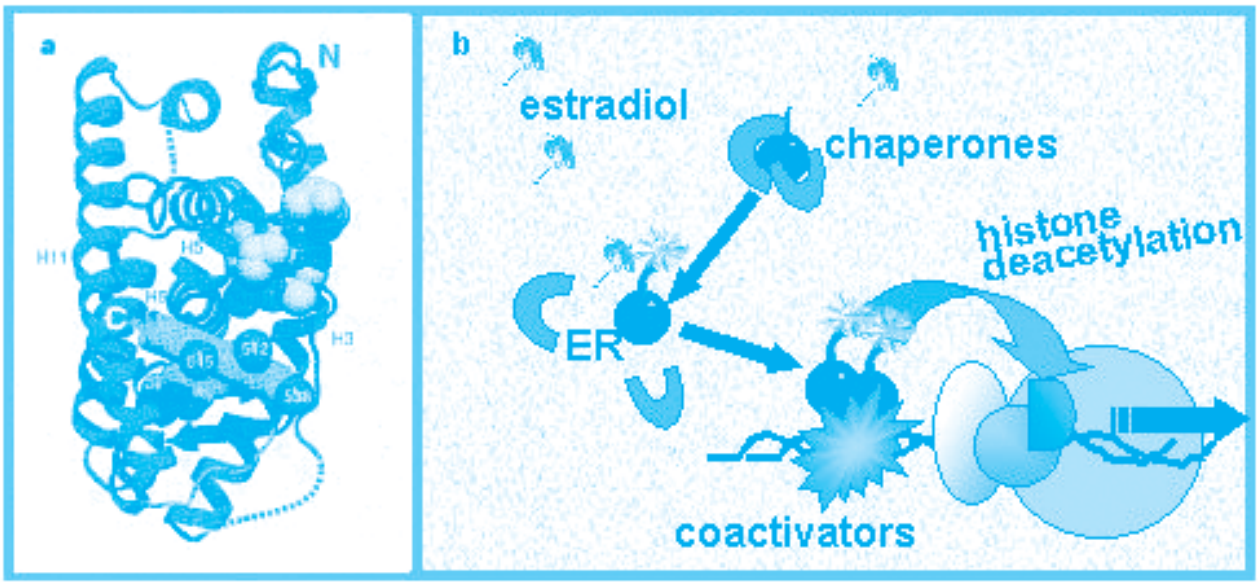
**Tissue-specific Transcription Elements:** As mentioned above, an ER must interact with transcription factors to initiate the transcription of target genes. The factors are in part ubiquitous and in part cell-specific. Therefore, the abundance of these cell-specific proteins will contribute to affect estradiol-ER action on individual promoters.

**Receptor Dosage:** Like other membrane receptors, ERs can be up- or down-regulated. It is most likely that higher concentrations of the receptor protein will allow the hormone to stimulate most of the target promoters, whereas lower concentrations will allow generation of subgroups of transcripts, for example, from genes whose promoters possess multiple EREs.

**Ligand Characteristics:** ERs bind estradiol and some of its metabolites. Depending on the ligand

## FIGURE 6–2

Panel a. Graphic of the three-dimensional structure of the ER hormone-binding domain. The binding of the agonist induces a series of conformational changes that expose sites of the receptor capable of interaction with co-activators. The binding of antagonists induces a very different conformation of the receptor, mainly in the displacement of helix 12 (solid cylinder), and prevents the exposure of the domains involved in co-activator recruitment. Panel b. Mechanism of ligand-dependent activation of ERs. On binding to the receptor (ER), estradiol induces release of inhibitory proteins, which allow the receptor to dimerize and associate with the responsive elements in the promoters of target genes. Once bound to the target DNA, the receptor initiates a series of protein-protein interactions that result in the activation of the transcriptional apparatus.



bound, the conformation of the receptor differs, thus changing its functional activity.

***To design drugs able to mimic estrogen activity in only selected target tissues, it is mandatory to understand how the same hormone can exert so many different effects in the various cells targeted.***

**Receptor Subtype:** The type of ER expressed in a single cell type may also be important for the selectivity of estrogen action. In addition to the different effects exerted by ERα and ERβ homodimers, it is possible that ER heterodimers act differently and that the two receptors exert mutual control. That has been reported to occur with other members of the intracellular receptor superfamily.[16]

**Influence of Other Members of the Nuclear Receptor Superfamily:** Orphan receptors highly homologous to ERα—for example, ER-related receptors α, β, and χ may interfere with ER activities, also by heterodimerization.

## 3. Pharmacologic Modulation of Estrogen Receptors

Pharmacologic treatment of endocrine dysfunction involves the control of (1) endocrine signaling, by acting on the synthesis, storage, or release, or intracellular transport and metabolism, of the specific hormone; (2) sensitivity of a single target tissue to the hormone, by blocking or enhancing synthesis of the receptor of interest; or (3) activity of the receptor, by the use of specific ligands with agonist or antagonist activity. The synthetic compounds generated and in use to date for ER modulation belong to the third category, with the exception of progestins. In several organs, progestins antagonize the activity of estrogens by a dual mechanism: down-regulation of the synthesis of new ERs and control of the transcription of genes that interfere with estrogen action. Therefore, progestins are administered in combination with estrogens to limit the undesired side effects of estrogens on uterine cells.

The ligands for the ER can be grouped as ER agonists, ER antagonists and SERMs. Subgroups are based on chemical structure, categorized as steroidal and nonsteroidal compounds.

### 3.1 Estrogen Receptor Agonists

Known agonists of the ER consist of both steroidal and nonsteroidal molecules, with the latter including examples of different chemical structures.

#### *3.1.1 Steroidal Agonists*

Natural human estrogens are the follicular hormone 17β-estradiol and its main metabolites, estrone, estriol, and 2-hydroxyestradiol—together with their sulfated and glucuronidated counterparts. A more extended definition of natural estrogens includes the mare equilin and equilenin. Critical structural characteristics of this class of compounds include (1) a phenol at the C–3 position of the aromatic A ring, (2) a relatively flat and rigid hydrocarbon core, and (3) a ketone or alcohol function at the C–17 position. A detailed pharmacophore model suggests the important contribution of the two hydroxyl groups of 17β-estradiol to receptor binding, with C–3 hydroxy acting as the major contributor to the binding free energy. The model is supported by recent X-crystallography data.[8,9]

***In replacement therapy, natural steroids are currently preferred over synthetic molecules.***

When natural estrogens are administered orally, they undergo rapid catabolism in the intestinal mucosa and liver; shortly after estradiol ingestion, there are high concentrations of the metabolites, predominantly estrone, in the systemic circulation. Peak concentrations are observed at 1 to 4 hours after ingestion; subsequently, concentrations rapidly decline. For this reason, major efforts have been made, particularly

in the past, to synthesize steroid analogues of estrogens with longer half-lives. All the synthetic molecules developed are far more potent than the natural estrogens and have, when administered orally, much longer half-lives. Some, like DES are no longer used in clinical practice. The finding of a high incidence of clear cell adenocarcinoma of the vagina in daughters born to DES-treated mothers led to the hypothesis that the compound was a carcinogen. However, further studies did not show a significant increase in breast cancer in the DES-treated mothers, and studies of male offspring showed genital abnormalities, suggesting that DES should be considered more as teratogenic than cancerogenic. Other synthetic estrogens, such as ethinyl estradiol, have been and are largely used in oral contraception. Ethinyl estradiol is obtained by the addition of an ethinyl radical in position C–17 and is much more resistant than natural estrogens to liver metabolism. Orally administered ethinyl estradiol has a half-life of about 48 hours.

In replacement therapy, natural steroids are currently preferred over synthetic molecules. In the United States, the most commonly used natural estrogens are CEEs, extracted from the urine of pregnant mares. CEEs are mainly composed of estrone and estrone sulfate; other components include the ring-B unsaturated sulphoconjugated estrogens equilin, equilenin, and their 17α-derivatives. The metabolites account for a great part of the estrogenic effects of CEEs. In addition, equilin can be stored in adipose tissue and released for several weeks after withdrawal of the treatment. 17β-estradiol is also used in HRT, particularly in Europe. Preparations of estradiol valerate or micronized estradiol were shown to have half-lives compatible with therapeutic effects when administered orally.[17] To avoid the intensive first-pass metabolism, nonoral routes of administration of 17β-estradiol have been studied. Several parenteral delivery systems are available: 17β-estradiol can be administered through injections, vaginal rings, percutaneous gels, or transdermal therapeutic systems (TTS). Of particular interest are the TTS that allow the rate-controlled delivery of estrogen. The hormone is suspended in an ethanol solution or, in second-generation TTS, in a matrix, which ensures the programmed release of the hormone for several consecutive days.

More recently, novel synthetic molecules such as (7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)en-20-yn-3-one (tibolone) have raised considerable interest because they combine with the estrogenic activity progestogenic and androgenic properties that relieve climacteric symptoms without stimulation of the endometrium.[18,19]

***Observational epidemiologic studies indicate that women who ingest phytoestrogens, particularly in soy products, in large amounts seem to have lower rates of CVD, breast cancer, and uterine cancer as well as fewer climacteric symptoms than women consuming typical western diets.***

#### *3.1.2 Nonsteroidal Agonists*

Pioneering studies published more than 60 years ago showed the effects of subcutaneous administration of nonsteroidal compounds on the onset of estrus in mammals and on uterine growth. They enabled the identification of several nonsteroidal molecules with estrogenic activity. The studies were also instrumental in the subsequent development of antiestrogens and of partial agonists-antagonists, including SERMs.

The major categories of the nonsteroidal agonists are (1) 1,2-diarylethanes and ethylenes; (2) flavones, isoflavones, coumestans, and lignans; (3) macrolactones; (4) alkylphenols and arylphenols; and (5) nonaromatic estrogens.

**1,2-Diarylethanes and Ethylenes:** DES and hexestrol (fig. 6–3) represent a milestone in the identification of orally active nonsteroidal agents

with extremely potent estrogenic activity. The medical uses of compounds with 1,2-diarylethylene and 1,2-diaryl ethane include maintenance of pregnancy, HRT, suppression of lactation, postcoital contraception, and cancer treatment, as has been reviewed.[20]

**Flavones, Isoflavones, Coumestans, and Lignans:** The best studied plant-derived estrogens, or phytoestrogens, belong to these classes of chemicals with estrogenic activity. A significant source of isoflavones is soybeans. The most abundant and active components of isoflavones are genistein (fig. 6–3) and daidzein, which appear to have selective estrogenic actions. In some tissues, they provoke proestrogenic responses; in others, they inhibit estrogenic effects. This finding is perhaps explained by different affinities for the two described ERs. Indeed, genistein has a thirtyfold higher affinity for ERβ than for ERα.[21,22] The estrogenic activity of flavones and isoflavones is dependent on ER binding affinity, which is determined by the presence of the aromatic ring as well as hydroxyl groups at specific sites.

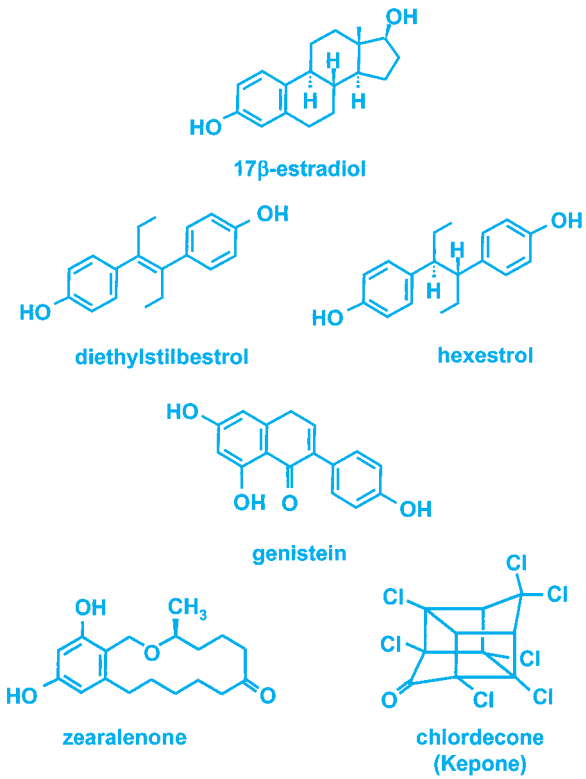
Compared with estradiol, genistein and daidzein bind to ERs with significantly less affinity.[23] Nevertheless, in the quantities that can be consumed in the diet, isoflavones can have biologic effects. Soybean isoflavones do not have feminizing effects in male primates as reflected by unchanged weights of the reproductive organs in the animals,[24] although prenatal exposure of rats resulted in diminished weights of ovaries and uteri.[25] Observational epidemiologic studies indicate that women who ingest phytoestrogens, particularly in soy products, in large amounts seem to have (1) lower rates of CVD, breast cancer, and uterine cancer and (2) fewer climacteric symptoms than women consuming typical western diets.[26] (See ch. 3, 8, and 10.) Preclinical and clinical studies have shown that isoflavones can improve plasma lipid profiles as well as the ability to inhibit oxidation of low-density lipoproteins.[26] Isoflavones have been shown to normalize vascular reactivity in estrogen-deprived primates.[27] Antineoplastic activity of the compounds has been postulated on the basis of their inhibitory activity on angiogenesis.[28] In addition to climacteric symptoms, bone density appears to be favorably influenced by phytoestrogens.[26] (See also ch. 9.)

Other known phytoestrogens are coumestans (e.g., coumestrol), found in alfalfa sprouts, and lignans (e.g., enterolactone), found in cereals and oil seeds such as flaxseed.

**Macrolactones:** Macrolactones were first identified when hyperestrogenicity was seen to develop in swine fed mold-infected corn. Katzenellenbogen and colleagues extensively studied these mycotoxins, exemplified by zearalenone (fig. 6–3), which was shown to bind ERs with high affinity and induce uterotropic responses in rats.[29] Zearalenone has been used to relieve the incidence and severity of hot flushes in women.[30]

## FIGURE 6–3

### Structural Characteristics of Estrogen Receptor Agonists



**Alkylphenols and Arylphenols:** Alkylphenols are used in the synthesis of detergents and as antioxidants. The detergents are not estrogenic; upon degradation during sewage treatment, however, they can release estrogenic compounds, such as para-octyl phenol and para-nonyl phenol, which have been shown to possess uterotropic activity in vivo and in vitro.[31] The structural requirements of alkylphenols indicate that both the position (para > meta > ortho) and the branching (tertiary > secondary) of the alkyl group dramatically affect estrogenicity.[32] In addition to alkyl substitution at the para position of the halogenated or the hydroxy-substituted aromatic ring, aryl substituents have estrogenic activity. Compounds in the class include bisphenol A; polychlorinated biphenyls; diphenylmethanes, such as DDT (dichlorodiphenyltrichloroethane); and tricyclic aromatic hydrocarbons, such as dioxin.[33] Many of these compounds are used in the manufacture of plastics, and their estrogenic activity was discovered by accident because they are released by polystyrene and polycarbonate test tubes used in laboratory experiments. Bisphenol A was found to contaminate the content of canned food because tin cans are lined with polycarbonate. Bisphenol A is also used in dental sealants and composites.

**Nonaromatic Estrogens:** Interest in nonaromatic estrogens has increased because xenoestrogens of this class can derive from commercial sources, such as pesticides. Most of the agents are halogenated carbocycles, such as hexachlorocyclohexane, chlordecone (Kepone) (fig. 6–3), chlorobornane (Toxaphene), dieldren, and endosulfan. Studies with hexachlorocyclohexane showed it to have estrogen agonist activity in human breast cancer cell lines. It and others of the class have not been shown to bind to ERs. Therefore, the origin of the estrogen activity of the compounds is not clear; it is believed to occur through nonclassic pathways.[34]

### 3.2 Estrogen Receptor Antagonists

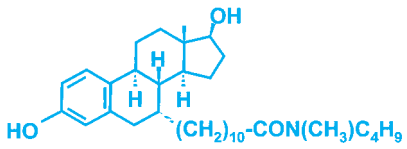
Antiestrogens can be grouped according to basic structure as steroidal or nonsteroidal.

#### *3.2.1 Steroidal Antagonists*

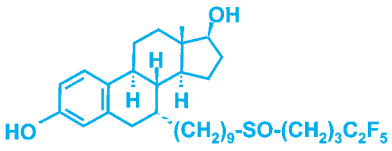
The difficulty in modifying the basic steroid structure discouraged research into steroidal antagonists of ERs until Raynaud et al. demonstrated that the 7α-estradiol derivatives with a long, unbranched alkyl chain retained high affinity for ERs.[35] The compound ICI 164,384 was developed and shown to act as a pure ER antagonist, stimulating further research. The most active compounds that emerged from the studies are ICI 164,384 and ICI 182,780 (fig. 6–4a). Both avidly bind to ERs and retain a pure antiestrogen activity in all tissues studied to date.

## FIGURE 6–4a

## Structural Characteristics of Estrogen Receptor Antagonists




ICI 164,384




ICI 182,780

#### *3.2.2 Nonsteroidal Antagonists*

For the rational design of nonsteroidal antiestrogens, essentially two basic structures were systematically altered: the triphenylethylene and stilbene structures. The first nonsteroidal antiestrogen discovered was ethamoxytriphetol (MER–25) (fig. 6–4b).

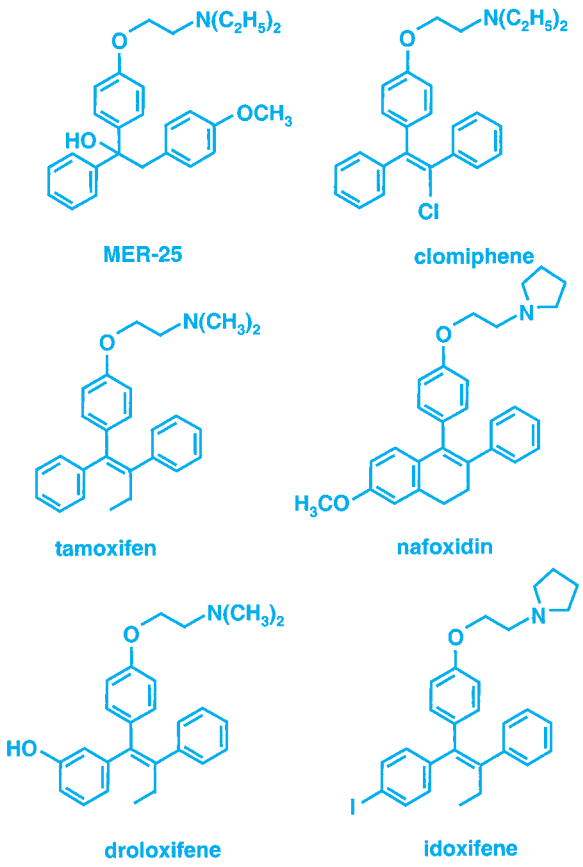
Its potency as an antiestrogen was rather low, and serious side effects in the CNS were found during clinical development.[36] The antagonist activity of the molecule may be due to the hydrophilic hydroxy group in the center of the molecule, which most likely interferes with the receptor binding. Clomiphene (fig. 6–4b), the second ER antagonist developed, lacks the central hydroxy group, and a double bond with a chloro substituent improves its lipophilicity. Clomiphene is used as a gonad-stimulating agent in subfertile women. With the identification of the ER antagonist activity of nafoxidin (fig. 6–4b), it became evident that a certain steric arrangement at the double bond favors the antiestrogenic activity. The most prominent among the group of drugs is tamoxifen, which was developed by ICI and is marketed as a citrate salt. The activity of tamoxifen in postmenopausal patients with hormone-dependent breast cancer has been demonstrated in many clinical studies, and the agent has become a treatment of choice for the malignancy. Tamoxifen is used in patients with advanced disease, as well as in the adjuvant setting after surgical removal of the primary tumor.

***The activity of tamoxifen in postmenopausal patients with hormone-dependent breast cancer has been demonstrated in many clinical studies, and the agent has become a treatment of choice for the malignancy.***

Other triphenylethylene derivatives were synthesized with the objective of obtaining an antiestrogen that would have a lower rate of metabolism and a different pharmacodynamic profile compared with tamoxifen and would not present its cis/trans isomerization. The knowledge that 4-hydroxytamoxifene is more potent in vitro than the parent drug but is more readily catabolized provided the basis for the development of the 3-hydroxy derivative droloxifene and of the iodo derivative idoxifene (fig. 6–4b). Droloxifene and idoxifene were

**FIGURE 6–4b**

**Structural Characteristics of Estrogen Receptor Antagonists**




shown to have minimal uterotropic activity, to reduce plasma cholesterol concentrations, to stimulate osteoclast apoptosis, and to block gene expression in endometrial cells.[37] Despite the fact that the basic side chain is one of tamoxifen's most important structural elements, only a very limited number of variations of that part of the molecule have been synthesized. Interestingly, when the 2-(dimethylamino)ethoxy fragment was replaced by acrylic acid, the agonist activity was lost in the uterus but was retained in bone and the cardiovascular system.[38]

Studies carried out principally at Eli Lilly and Company demonstrated that the geminal arrangement of the two phenyl rings of tamoxifen is not

essential and can be replaced by structures in which all three phenyl groups are located at different atom groups. Several compounds were generated (fig. 6–4c), among them LY 117,018, the first to undergo detailed study of its endocrine activities.[39] A series of modifications of LY 117,018 led to the synthesis of keoxifene (LY 156,758), which is now known as raloxifene.[40] In raloxifene, the presence of two free hydroxy groups in the benzothiophene and phenyl rings gives rise to an ER-binding affinity higher than in compounds lacking those polar functions.

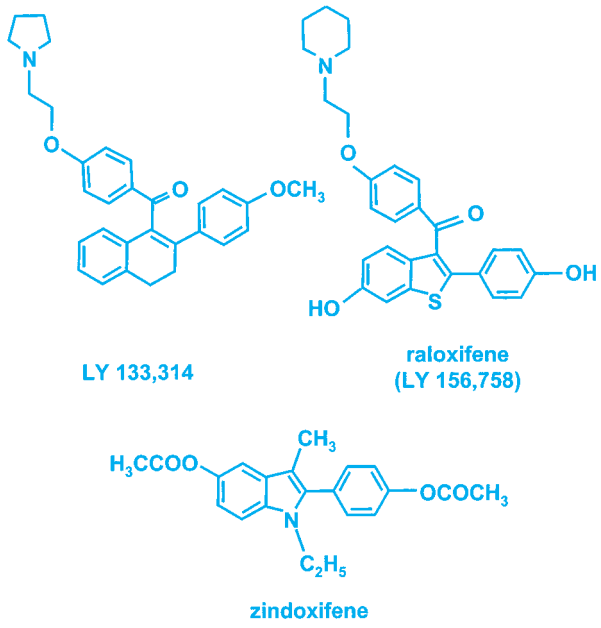
Another basic structure that has been utilized for the rational design of antiestrogen drugs is 2-phenylindole. Zindoxifene (fig. 6–4c) belongs to the compounds synthesized with this structure. Its endocrine profile is that of an antiestrogen with partial agonist activity. The preclinical and clinical data thus far obtained suggest that zindoxifene is a new lead structure of interest for the design of drugs acting through ERs.

### *3.2.3 Estrogen Receptor Subtype–Specific Antagonists*

The substantial structural homology between ERα and ERβ has raised the question of whether the two receptors are, indeed, responsible for different physiologic responses. Localization studies performed in mature and developing mammals suggest different roles for the two receptors. In fact, ERα and ERβ are often differentially expressed in developing and mature tissues (e.g., mammary gland and brain) and seldom colocalize in a given cell type.[41] Ablation of one or the other of the two receptors in gene knockout experiments further supports the hypothesis of a different effect of the two receptors. ERα activity seems to predominate in the uterus and breast, whereas ERβ may have significant roles in the CNS, cardiovascular system, immune system, urogenital tract, kidney, and lung. (See also ch. 5.) ERβ appears to be the only form expressed in the embryonic CNS.[42–44] On the other hand, the two receptors can co-localize; it is possible that they form heterodimers, the transcriptional activity of which may significantly differ from the homodimers.[45,46] Finally, in vitro studies evaluating the response of reporter genes or more physiologic parameters of pharmacologic activation of the two receptors have demonstrated significant differences between ERα and ERβ activities. In spite of the remarkable similarity in their response to synthetic ligands, the two receptors seem to activate distinct target genes, with divergent consequences for cell physiology.[47,48] The differential activity can be attributed to the significant structural diversity of the A/B region carrying the ligand-independent, N-terminal activation function AF–1. This hypothesis is supported by studies with a chimera receptor in which the A/B domain of ERα was substituted to the same domain of ERβ.[49] Thus, because of the potential physiologic differences in the activities of the two receptors, differences in ligand interaction or activity could translate into important differences in their biological and pharmacological profiles.

**FIGURE 6–4c**

**Structural Characteristics of Estrogen Receptor Antagonists**



The observation that the degree of homology of the two hormone-binding domains of ERα and ERβ is approximately 56 percent suggests the possibility of developing ligands with different agonist or antagonist characteristics with regard to the two receptor subtypes. Recently, novel compounds with pronounced subtype-selective differences in binding affinity and transcriptional potency or efficacy were identified.[50] An aryl-substituted pyrazole was shown to be an ERα potency-selective agonist: in fact, it showed a higher binding affinity for ERα than for ERβ and, in transactivation assays, a potency of ERα of about two orders of magnitude higher than ERβ.

Another compound, a tetrahydrochrysene (THC), was shown to have a fourfold preferential binding affinity for ERβ; it was an agonist for ERα and a complete antagonist for ERβ. Interestingly, the antagonist activity appeared to be associated with the R,R-enantiomer (R,R-THC); the S,S-THC was an agonist for both ERα and ERβ but had a twentyfold lower affinity for ERβ than R,R-THC.

#### *3.2.4 Molecular Mechanisms of Antiestrogen Action*

The molecular mechanisms of antiestrogen blockade of ER activities have been the object of several studies addressing all the steps necessary for ER transcriptional activation.

**Receptor Binding:** Generally, the affinity of antagonists for ERs is similar to or even higher than the affinity of estradiol. It was initially proposed that the binding of an antagonist, in particular the binding of pure antagonists,[51] prevents the dimerization and limits the affinity of the complex for DNA. Those studies were highly controversial, and the mechanism cannot be extended to tamoxifen, which was clearly shown to allow the formation of ER dimers.[52]

**DNA Binding:** Most in vitro studies have shown that DNA binding activity of the ER complexed with agonists and antagonists is very similar, even though the DNA binding of antagonist-ER complex seems to be slower than that of agonist-ER complex. Dissociation of the former complex is much slower than dissociation of the latter.

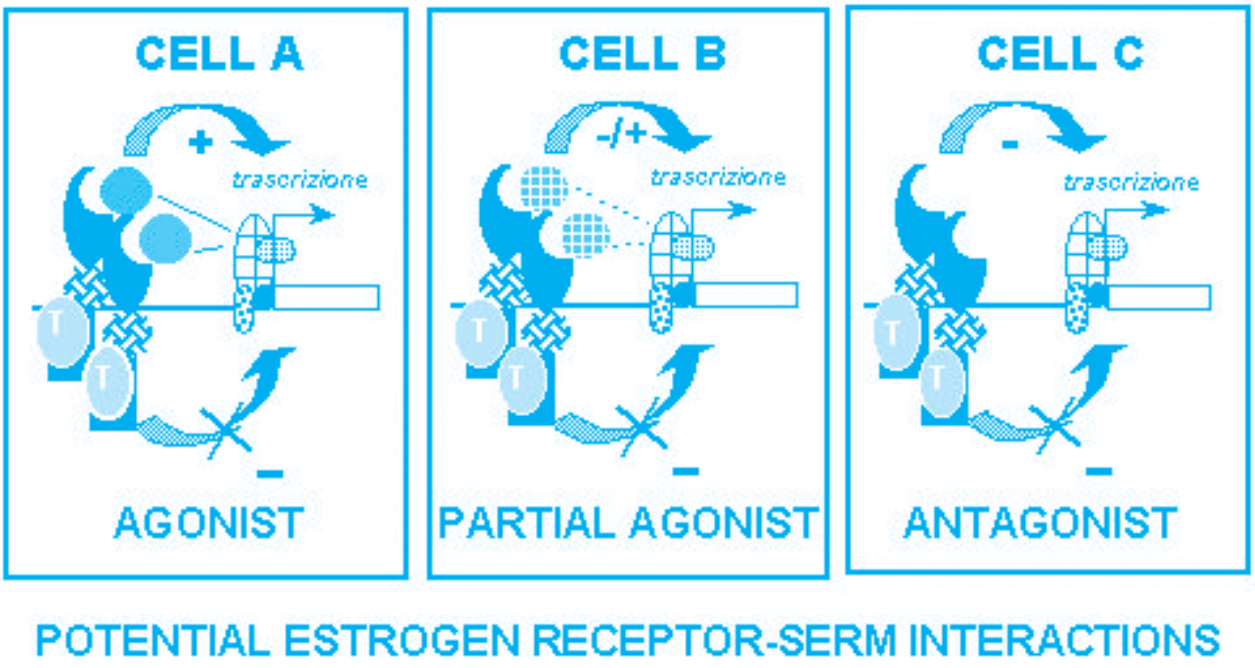
**Protein-Protein Interaction:** The availability of crystals of the ERα and ERβ hormone-binding peptides bound to 4OH-tamoxifen and raloxifene provides important new information about the mechanism of these agents' activity. Studies show that the additional side chain of the antagonists protrudes from the ligand-binding cavity, so that helix 12 is translocated to a position in which the co-activator binding side is obscured. As a consequence, the antagonist-ER complex can still dimerize and bind to DNA, but this event cannot be followed by the series of protein-protein interactions indispensable for AF–2-dependent transcription initiation, mediated through ligand-dependent, C-terminal activation function.

Those findings underline the importance of protein-protein interactions (ER with co-activators or co-repressors) in the mechanism of action of ER antagonists. Furthermore, they provide an explanation for the mixed agonist-antagonist activity reported for both raloxifene and tamoxifen bound to ERα. (See fig. 6–5.) In fact, the binding of this antagonist prevents interactions of AF–2, but not AF–1, with the transcription machinery. Therefore, the receptor, once bound to the ERE, may still attract transcription factors with the AF–1 region and allow the transcription of selected genes. Deletion and mutation studies have demonstrated that the full transcriptional activation of ERα is observed when both AF–1 and AF–2 are present and activated.[53] When access to AF–2 is prevented by the presence of an antagonist, the activity of the receptor is limited to those cells and those promoters that contain factors that activate AF–1. (See also ch. 5 for mechanisms of differential actions of antagonists on ER subtypes α and β.)

**Receptor Turnover:** ER antagonists may affect the kinetics of ER degradation. This represents another potential mechanism of action of antago-

## FIGURE 6–5

Mechanism of action of SERMs in different cell settings. Binding with a SERM results in blockage of activity of the AF–2 region of the ER; the AF–1 region, however, is free to interact with other proteins, which allows the interaction of the DNA-bound ER with other elements of the transcription apparatus. Thus, depending on the proteins expressed in the host cell, the SERM-bound receptor will be able to act as a full agonist (cell A) or a partial agonist (cell B). In cells that lack proteins able to interact with the AF–1 region of the receptor, the SERM will completely prevent the activation by estrogens and, therefore, will be a complete antagonist (cell C).




nists; it has been shown to be of importance for pure ER antagonists, such as ICI 164,884 and ICI 182,780, but not for nonsteroidal antagonists.[54]

### 3.3 Selective Estrogen Receptor Modulators (SERMs)

A SERM is defined as a compound that has estrogen agonism in one or more of desired target tissues, such as bone and liver, and antagonism and/or minimal agonism in reproductive tissues such as breast and uterus.[55]

The path leading to SERM development began with the synthesis of the first nonsteroidal estrogen antagonist, MER–25, which was shown to inhibit the action of estradiol in the endometrium without itself causing endometrial stimulation. Later, the nonsteroidal triphenylethylene compounds clomiphene citrate and tamoxifen were reported to be capable of inducing ovulation by blocking the negative feedback of estradiol on the HPA[56,57] and to block the development of dimethylbenzanthracene-induced mammary tumors in rats[58] (tamoxifen). The results clearly demonstrated the antiestrogenic activity of the molecules and stimulated interest in their development for antineoplastic activity. In the 1980s, two seminal studies, by Beall et al.[59] and Jordan et al.,[60] demonstrated that clomiphene and tamoxifen had a more varied portfolio of action in that the agents were able to decrease bone loss in ovariectomized rats. The

findings were remarkable because a pure antiestrogen would have been expected to promote rather than inhibit bone loss. Because clomiphene is a racemic mixture of enclomiphene and zuclomiphene, primacy in the SERM field must be accorded to tamoxifen. However, the discovery that tamoxifen was, in some patients, capable of endometrial stimulation leading to hyperplasia or neoplasia[61] precluded its development as a bone antiresorptive agent that would be free of uterine bleeding and, it was hoped, breast safe.

The concept of selective ER modulation has been demonstrated subsequently for a number of compounds, including raloxifene, droloxifene, GW5638, idoxifene, and FC–1271. Toremifene and idoxifene are molecules similar to tamoxifen; despite their potential as SERMs, they have been targeted for the treatment of advanced breast cancer. Droloxifene is known to have efficacy as a breast cancer drug but is also a SERM at bone sites.[62] Raloxifene was developed because it held promise for multiple applications. It is used in the prevention of bone loss and fracture in postmenopausal women and is being tested against tamoxifen in the Study of Tamoxifen and Raloxifene (STAR) for the prevention of breast cancer in high-risk postmenopausal women.[63] Additionally, raloxifene reduces circulating cholesterol concentrations[64] and may be efficacious to reduce risk for endometrial cancer.[55] The main drawback of the drug is that it does not reduce the occurrence of hot flushes, which could hinder compliance. Similar pharmacologic profiles are shared by idoxifene and FC–1271, which were shown to have beneficial effects on bone metabolism in rat models and to act like estrogens in bone and on circulating lipoprotein concentrations, with little estrogenic activity in the uterus.[37,65] A number of SERMs are in preclinical or clinical development (table 6–1).

The molecular mechanisms of the different effects of SERMs in different organs are summarized above (“Molecular Mechanisms of Antiestrogen Action”) and in figure 6–5.

The challenge for the future in the development of ligands for the ERs will be to refine the target specificity of SERMs and, it is hoped, amplify their scope of action. For instance, a SERM with a profile similar to idoxifene or raloxifene in the peripheral organs and CNS might protect against Alzheimer’s disease and hot flushes, while helping prevent osteoporosis, CAD, and breast and endometrial cancers.

## 4. Future Needs

The availability of drugs selective for ERα and ERβ will constitute a major milestone toward the development of drugs with specificity of action. On the other hand, the acquired knowledge of the molecular mechanisms of estradiol activity in different cells might suggest novel paths to be followed for the development of molecules active through the ERs. For example, ER turnover is differentially regulated in various organs (e.g., following gonadectomy, ERα mRNA is increased in the uterus but significantly decreased in the liver[66]). Drugs aimed at modulating the synthesis of ERs in specific organs may enable fine tuning of the activity of the hormone. Antisense oligonucleotides have been able to block ER synthesis in cells in culture. The development of such molecules as drugs might allow their future clinical use.[67] Alternatively, novel preparations of estradiol in which its bioavailability is modified might have pharmacologic profiles of interest. For instance, a formulation allowing a very rapid intraplasmic release of estradiol and its rapid clearance (e.g., transnasal administration of appropriately modified estrogens) could have a quite different profile of action compared with estradiol administered orally or transdermally. Such a drug could rapidly activate the receptors but, because of its rapid clearance from the blood, might have little effect on ER down-regulation or might affect it differently in the various targets.

## TABLE 6–1

## Selective Estrogen Receptor Modulators Under Development

| Drug | Pharmaceutical Company | Phase of Development | Therapeutic Class |
|---|---|---|---|
| SERM 339 | Aventis | Phase IIa | |
| HM 144 | Hormos Medical | Preclinical | Anti-Alzheimer |
| LY 139,478 | Eli Lilly and Company | Preclinical | Bone calcium regulation |
| LY 326,391 | Eli Lilly and Company | Preclinical | Cytostatic, bone calcium regulation |
| ERA 932 | Ligand Pharmaceuticals | Phase I | Cytostatic |
| NNC 450,320 | Novo Nordisk | Preclinical | Bone calcium regulation |
| NNC 450,781 | Novo Nordisk | Preclinical | Bone calcium regulation |
| M.D.L 101,986 | Aventis Pharma | Preclinical | Cytostatic, bone calcium regulation |
| Fc1271A | Hormos Medical | Phase II | Other drugs for the musculoskeletal system |
| Arzoxifene | Eli Lilly and Company | Phase II | Cytostatic |
| Research program SERMs | Signal Pharmaceutical | Preclinical | Cytostatic, bone calcium regulation |
| Lasozifene | Pfizer | Phase II | Bone calcium regulation |
| Research Program SERMs | Ligand Pharmaceuticals /Pfizer | Preclinical | Cytostatic, bone calcium regulation, anti-Alzheimer |
| SR 1,634 | SRI International | Preclinical | Cytostatic |

Recently, the use of phage display has allowed the identification of peptides that interact specifically with estradiol- or tamoxifen-activated ERα. Some peptides were shown to regulate ER transcriptional activities.[68] Such studies demonstrate that ER activity can be regulated even by targeting sites that are outside the ligand-binding pocket of the protein. This is not surprising within the current view of ER interactions with other proteins relevant in transcription. Such results have pharmacologic implications of interest because they provide new targets for drug activities and more opportunities for the development of drugs that will modulate the activity of ERs in selected cells or even at specific genes. Finally, increased knowledge of the physiologic relevance of unliganded activation of ERs might lead to the development of pharmacologic compounds that will activate ERs through membrane receptors.

These and other molecular developments will in the near future represent starting points for the preclinical and clinical development of estrogen compounds, of both natural and synthetic origins, with selective spectrums of action, as the following points summarize:

- Developing drugs with receptor specificity (ERα or ERβ)
- Modulating the activity of the hormone interfering with the synthesis of ERs
- Attaining different profiles of action for exogenous estradiol through use of different formulations
- Obtaining higher specificity of action by identification of new target molecules involved in gene transcription
- Increasing knowledge of the mechanisms involved in ER activation through membrane receptors to develop new pharmacologic compounds acting along these pathways

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# Chapter 7: Sexuality

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***Declining sexual function is common with aging. There may be an additional decrement associated with the menopausal transition.***

## Key Points[a]

1. Declining sexual function is common with aging. There may be an additional decrement associated with the menopausal transition.
2. The causes of decreased sexual activity are multiple and include physiologic, psychologic, and social factors.
3. Definitions and Classification of Female Sexual Dysfunction, given by the consensus panel of the Sexual Function Health Council of the American Foundation for Urologic Disease, provide a standardized system for clinical diagnosis and treatment and are recommended for use by health care professionals [D].
4. Sexual interest, behavior, and activity should be routinely assessed at office visits on a regular basis, and a plan should be developed to address the woman's concerns.
5. Hormonal and behavioral therapy have had variable success in the treatment of sexual dysfunction but should be considered in patients who desire treatment for their dysfunction [B].

## 1. Introduction

"Sex is a biologic expression of love and part of a universal human behavior with roots stretching back to the beginning of humankind."

*Won-whe Kim, M.D., Ph.D.*

As women live longer, are healthier and more educated, have more leisure time, and are more aware of their own sexuality, they become inquisitive and sometimes apprehensive about changes in sexual function after menopause. Sarrel and Whitehead,

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.)

in their survey of postmenopausal women, found a high prevalence of sexual problems, corroborating these changes in sexual function after menopause.[1] When women experience changes in their sexual function, they frequently turn to their health care provider for help with their problems.

***The prevalence of female sexual disorders, in both premenopausal and postmenopausal women, ranges from 25 to 63 percent.***

The prevalence of female sexual disorders, in both premenopausal and postmenopausal women, ranges from 25 to 63 percent.[2–4] The recently published U.S. National Health and Social Life Survey included survey data from 1,749 women between the ages of 18–59 years (table 7–1).[5] Sexual dysfunction was more prevalent in women (43 percent) than men (31 percent). One-third of women lacked sexual interest, and almost one-fourth stated that they were unable to experience orgasm in menopause. According to the survey, 20 percent of those women reported lubrication difficulties, and another 20 percent reported that sex provided them little pleasure. Relevant to this survey, sexual dysfunction appeared to be more common in menopausal women than in premenopausal women. Similarly, more than 86 percent of postmenopausal women in Sarrel and Whitehead's survey reported a variety of psychosexual problems.[1] Due to the high prevalence of sexual dysfunction and the importance that patients attach to sexual function, it is essential to identify and address these problems in our patients. Ultimately, it will assist them in improving their quality of life and interpersonal relationships.

Much attention has been given to male sexual dysfunction, and only recently has attention shifted to better understand and identify female sexual dysfunction as a research priority. Clinicians receive little or no training in the diagnosis or treatment of sexual dysfunction and lack information on its causes and ways to prevent the changes that may occur. The clinician's individual clinical impressions and previous experience are frequently used as the basis for clinical practice and are conveyed to the patient as truth, without evidence to support those views. Regrettably, most practitioners' clinical experience is not representative of most women's experience in the menopause. This is in part because those presenting for treatment are only a small proportion of women troubled. Those who choose to identify themselves to the clinician as having a problem represent only a fraction of women with problems.[6,7] Armed with the appropriate facts, the clinician will be rewarded because all patients appreciate clinician awareness and competency in this field.

Because of these barriers, many studies in this review have methodologic weaknesses, including sample bias, low measurement sensitivity, and lack of detail on sexual preference. Population-based surveys suggest a link between menopause and changes in sexuality. Yet, relatively few studies of the menopausal transition in middle-aged women have inquired about sexual functioning. Of those, only a minority have used a validated questionnaire to assess the different aspects of sexual functioning. In addition, cross-sectional studies are unable to distinguish between effects of social change on different age groups and aging, and some improperly infer causation from associations. (See also ch. 3, sec. 3.)

Not insignificant is the controversy surrounding the study of sexual relationships. Kim noted that in some ethnic groups it is almost impossible to get an accurate answer from women about their sexual activities (Kim WW, personal communication). He accurately commented that there are very few norms set biologically or statistically, and, as a consequence, analyses done with questionnaires and interviews might not be reliable. Some interviewees are not sincere in answering the questions, and some give false information, as they feel shy about presenting their thoughts and feelings frankly. He emphasized that in most Asian countries,

## TABLE 7–1

## Prevalence of Female Sexual Disorders (Percent of Women)

| | Lacked Interest in Sex (n = 1,486) | Unable to Achieve Orgasm (n = 177) | Experienced Pain During Sex (n = 1,479) |
|---|---|---|---|
| **Age (years)** | | | |
| 18–29 | 32 | 26 | 21 |
| 30–39 | 32 | 28 | 15 |
| 40–49 | 30 | 22 | 13 |
| 50–59 | 27 | 23 | 8 |
| **Marital Status** | | | |
| Currently married | 29 | 22 | 14 |
| Never married | 35 | 30 | 17 |
| Divorced, separated, widowed | 34 | 32 | 16 |
| **Race** | | | |
| Caucasian | 29 | 24 | 16 |
| Black | 44 | 32 | 13 |
| Hispanic | 30 | 22 | 14 |
| Other | 42 | 34 | 19 |

where over half the world's population lives, the situation is even more complicated. Women are raised under the influence of Confucian ideology from early childhood and are taught that they should not even be allowed to express their desire to have sex. All the myths and misconceptions concerning female sexuality, especially in old women, remain. They believe, "It is natural to be away from sex when you are old" or "Remarriage after the death of your spouse should never be thought of."

***Population-based surveys suggest a link between menopause and changes in sexuality.***

Other methodological problems limit study in this field. Until recently, there were no objective, standardized definitions of both the physiologic and psychologic basis of female sexual dysfunction and menopause. On the other hand there is still no consensus on an age cohort that covers the menopausal transition. Should it be 45–55 years of age, or should it be defined by shorter intervals? There are differences between naturally and iatrogenically induced menopausal women and these distinctions are often not made in discussions of sexual dysfunction. Furthermore, the differences between those who choose to take exogenous hormones and those who wish to make the menopausal transition without pharmacotherapies are not well defined. Therefore, how we approach these women differently is confusing. Objective measures of hormonal change are not defined or standardized; instead, the absence of uterine bleeding repeatedly defines menopause. (See ch. 2 for definitions.) Questionnaires are not designed to reflect how women experience, problems and data analysis techniques have to be more appropriate. (See ch. 3 and 4 for biases in women sampling.)[8] The studies reviewed in this chapter represent the available current evidence and must be used as a basis for best practice.

This chapter is designed to provide the best answers to the following questions based on the current evidence in the literature:

- Do changes in sexual behavior, interest, or response, occur with age or menopause, or both?
- If changes occur, what are they, and what causes them?
- How do we define the changes?
- Do we treat the changes, and if so, what therapies have proven efficacy?

## 2. Influence of Age on Sexuality

The most frequent measures of change in sexual function used in the literature are coital and orgasmic frequency. To understand the changes of the menopausal transition, we must first review the changes leading up to the years most commonly used to define menopause.

The Kinsey studies conducted in the 1950s were the earliest to examine the relationship between sexuality and age. In 1953, in a cross-sectional descriptive analysis, Kinsey et al. described the aging patterns of sexual activity in unmarried men and women.[9] The frequency of orgasm reported by women remained relatively constant at 0.5 episodes per week from puberty through age 55. Men reported a constant decline from 2.3 episodes per week at age 15 to 1 episode per week at age 50. Married women and men showed similar declines in frequency, with women having lower levels of activity than men at all ages. The authors surmised that the married woman's decline might be a result of her husband's and not her own aging. Women also indicated that their sexual activity reflected whether or not they had a partner and, if they did, their partner's preferences. Their report lacks indication of a decline in a woman's sexual function secondary to age, and it was unable to determine whether a decline in function with age was due to physiologic, psychologic, or social factors.

A legitimate question to ask is whether this information obtained from two generations past applies today. The answer awaits further study. There have clearly been changes in sexual mores over the years. Nowadays, the orgasmic frequency of women may be much higher than 0.5 episodes per week. Many women experience orgasm in different ways than is classically described, and this may explain the relatively low frequency of orgasm reported in the Kinsey studies. Moreover, many women get sexual satisfaction without achieving orgasm, especially those who value intimacy and the relationship with their partner. This is often not accounted for in research studies.

Some of the earliest studies of sexuality attempted to define the factors that influenced sexual activity. In 1960, Newman and Nichols reported cross-sectional data on 250 men and women between the ages of 60 and 93.[10] In the 100 persons in the single, divorced, or widowed group, only 7 percent were sexually active. In the remaining 150 persons in the married group, 54 percent were sexually active, suggesting that a socially permitted and legally approved partner significantly influenced the continuance of sexual activity. There was a gradual decline in activity through adulthood, although some level of activity persisted into late adulthood.

In 1972, Pfeiffer et al. attempted to report the various sexual behaviors in middle-aged and older both women and men.[11] Using a subsample from a larger longitudinal study on the determinants of adaptation in middle life (the Duke study), they showed a pattern of declining sexual activity with age in both sexes. The frequency of intercourse was lower for women than for men at all ages; however, 98 percent of the men versus 71 percent of the women were married. Both women and men attributed the choice of discontinuing sexual intercourse to the man. Only 7 percent of women reported no sexual interest. Of those who did note a decline, the sharpest increases were noted between ages 45 and 50 and between ages 51 and 55. These findings contradicted earlier work.

In 1981, George and Weiler reported on 502 married men and women 46–71 who were followed from the original Duke cohort at 2-year intervals for 4 years.[12] Of those who attended all interviews and remained married (278), 20 percent of the total group reported a decrease in sexual activity while 5 percent reported an increase. Only a small portion of the sample (n = 57) were women aged 46–55 at the beginning of study. Despite the overall decrease, the authors concluded that sexual activity remained more stable over time than was previously suggested. One limitation of the Duke Study was that it obtained its sample from enrollees of an insurance company and was therefore a biased sample of middle, and upper-class healthy, employed people 55 years and older.

As evidenced by the above reports, there had been only small, descriptive reports up to the late 1970s. This led Hallstrom to recruit 800 perimenopausal Swedish women aged 46, 50, and 54 years and a premenopausal group, 38 years of age to attempt to better define changes in sexual functioning which may be related to the menopausal transition.[13] All of the women had intact uteri and ovaries, and none were using oral contraceptives (OCs). All were cohabiting with a man. Factors assessed were sexual interest, orgasm with coitus, change in sexual interest, change in capacity for orgasm, and mean frequency of coitus—all stratified by age cohort. There was a striking decline in sexual interest, capacity for orgasm and coital frequency from age 38 to 54. Not all women reported a decrease, but the majority of the menopausal women did. The Gothenburg Women Study refuted a century-old belief that sexual interest abruptly increases during the climacteric. Although a small group reported increases in sexual interest or capacity for orgasm, the numbers were small and decreased with age.

The Danish study of Koster and Garde involved a general population sample of 474 women, all born in 1936, who were subsequently examined at the ages of 40, 45, and 51.[14] Personal interviews were conducted in 1976 and 1981, and questionnaires were mailed for the last followup. Of the 51-year-old women, 59 percent reported no change in sexual desire over the study period of 11 years, 30 percent reported decreased desire, and 11 percent reported an increase. However, this was based on recall from 11 years earlier. Decrease in sexual desire correlated significantly with the woman's subjective assessment of being climacteric.

One of the more recent investigations was by Hallstrom and Samuelsson, who utilized the women in the original Swedish cross-sectional study for a prospective study on sexual desire.[15] The study surveyed 497 married or cohabiting women, on two occasions, 6 years apart, about their sexual desire. They found significantly decreased sexual desire between ages 46 and 60. After the age of 50 years, none reported a strong sexual desire; 27 percent reported a decrease, and 10 percent reported an increase in desire between the interviews.

To assess what changes women complained of, Osborn et al. surveyed 436 women with a male sexual partner (94 percent married) and found 33 percent to have at least one operationally defined sexual dysfunction. (See sec. 6).[16] The most frequent dysfunctions were reduced sexual interest (17 percent), vaginal dryness (17 percent), and infrequent orgasm (16 percent). Dyspareunia was described by 8 percent. Significant factors were assessed, with age emerging as the most important determinant of operationally defined dysfunction. One or more dysfunctions occurred in 49 percent of women aged 50 and older and in 21 percent of women younger than age 50.

In 1997, Barlow et al. reported on their study of 2,045 women between the ages of 55 and 85 years.[17] Their aim was to describe urogenital aging and its associated problems in older British women. The survey reported 73 percent of the women were not sexually active, with the lack of a partner being a major reason. There was decreasing sexual activity with increasing age; however, women aged 65–74 had a frequency of activity similar to the younger women studied. Dyspareunia and/or vaginal dryness were described as a severe problem by 12 percent, among which 33 percent did not seek professional advice and 36 percent used "over-the-counter" remedies. HRT was of short duration and declined with age.

### 2.1 Influence of Menopausal Status and Ethnicity on Sexuality

Sarrel and Whitehead were among the earliest to associate a decline in sexual activity with menopause. They interviewed 185 women attending a menopause clinic to define what issues, concerns, and dysfunctions were present.[1] More than 86 percent reported a sexual problem. Most women (121/185) reported developing their sexual problem immediately preceding and following the transition through menopause. Problems they identified included disorders of sexual desire, sexual response, and sexual behavior. Newman and Nichols also showed a decline in sexual interest with age, with an implied association with the menopause transition.[10] In contrast, Pfeiffer et al. reported that, in comparison to age, menopausal status made a small contribution.[11]

In 1996, Myers performed a meta-analysis of sexuality and menopause.[18] Empirical studies performed from 1972 to 1992 that assessed sexuality and perimenopausal and postmenopausal women were collected and reviewed. A blinded review of the methodologies was performed. The findings of the analysis of viable studies indicated that hormones, both exogenous and endogenous, had some importance to perimenopausal and postmenopausal sexuality, suggesting an influence of sex hormones on menopausal sexuality.

It makes sense intuitively that there are ethnic variations in sexual function at menopause; however, few reports address this important issue. The most common complaints of naturally postmenopausal Thai women are loss of libido, orgasmic dysfunction, and dyspareunia.[19] Menopausal status appeared to impact sexual function, as both sexual desire and activity decreased after menopause. Only 14 percent occasionally reached an orgasm, while the other 86 percent never had orgasm after menopause.

Although many studies suggest some relationship, albeit ill-defined, between sexuality and menopause, Cawood and Bancroft did not concur. They recruited 141 women into a survey study of the determinants of sexuality and well-being in the menopause.[20] They found no relationship between menopausal status and interest or frequency of sexual activity and no support for the direct role of estrogens or androgens in the sexuality of women between the ages of 40 and 60. Only 54 women in their study were menopausal. Testing for hormone levels did not significantly predict measures of sexuality, while other aspects of the sexual relationship that were predictive were sexual attitudes and measures of well-being. They also identified vaginal lubrication as an important factor in the sexuality of women of this age group.

### 2.2 Summary

It is difficult, if not impossible, to separate the effect of aging effects on sexual function from that of menopause. Also, the menopausal transition is a time of psychosocial as well as biological change. It appears that there is a decline in sexual function as women age, but whether these changes are due to aging, the hormonal changes of menopause, psychosocial factors or health status remains uncertain. The most frequent complaints of women were reduced sexual interest, vaginal dryness, infrequent orgasm and dyspareunia.

## 3. Causes of Decreased Sexual Interest

Controversy exists over whether a reduced level of sexual interest is the cause of, or is caused by, infrequent or decreasing sexual activity in women or a decline in estrogen and/or androgen levels. Adaptation theory postulates a declining interest of the husband induces a similar response in the woman. Seemingly, the most common cause of declining sexual drive in men is age. However, the Gothenburg Study[15] showed no difference between the husbands of women with declining sexual interest and those with no change. In fact, a higher percentage of the women with declining interest reported that their partners' sexual interest was stronger. The same group admitted to submitting to their husbands' desire for intercourse without having desire themselves.

***The most frequent complaints of women were reduced sexual interest, vaginal dryness, infrequent orgasm, and dyspareunia.***

Zumoff et al. observed that endogenous androgens may play an important role in psychosexual functioning in the menopausal transition, during which testosterone levels are approximately 50 percent of the levels between 20 and 30 years of age.[21] Two studies have shown a correlation between endogenous androgen levels and optimal sexual function. McCoy et al.[22] evaluated 16 perimenopausal women who recorded their menstrual and sexual activity daily. Estradiol and testosterone levels showed significant declines during the menopausal transition; however, testosterone showed the most consistent association with coital frequency. Floter et al.[23] used the McCoy questionnaire to correlate the total score (for sexual enjoyment, orgasm, frequency, and vaginal state) with levels of testosterone, dehydroepiandrosterone sulfate, androstenedione, and the ratio of testosterone to SHBG (an indicator of free testosterone).[23] Androstenedione correlated with increased sexual functioning of perimenopausal women.

Many studies of sexual interest in premenopausal women suggest a cause-effect relationship between hormone levels and sexual function. Schiavi found a relationship between circulatory androgens and sexual desire and arousability in a large group of reproductive-aged women with regular menstrual cycles.[24] A higher sex drive at midcycle, during the testosterone peak, has been reported; however, it is difficult to relate these changes in sexuality to a single factor.[25]

## 4. Changes In Sexual Behavior, Interest, and Response

The cross-sectional baseline study of the Melbourne Women's Midlife Health Project surveyed 1,879 women by telephone with three aims: to describe women's subjective assessment of the changes that they experienced in sexual interest and reasons for those changes; to relate changes in interest, coital frequency, and dyspareunia with menopause; and to attempt to identify those variables that are associated with change in sexual behavior.[26] The majority reported no change in interest (62.3 percent), while a large number (31.1 percent) reported a decline in interest associated with menopause rather than age. Only 6.6 percent of women reported an increase in sexual interest. Natural menopause was associated with decreased interest and likelihood of intercourse and an increase in dyspareunia. Hysterectomy, with or without oophorectomy, had little influence on sexual activity.

Subsequently, 354 of these women participated in a longitudinal study and reported menopausal status significantly affected vaginal dryness and dyspareunia.[27] There was also an effect on sexual responsivity mediated through symptoms and well-being. Feelings for partner, sexual responsivity, frequency of sexual activities, and libido all significantly decreased with time, while vaginal dryness/dyspareunia and partner problems increased.

Another common condition that impacts sexual functioning is urinary and fecal incontinence. In a report by Hilton, 46 percent of women reporting UI felt that it had a negative impact on their sexual functioning.[28]

## 5. Anatomic and Physiologic Changes Associated with Aging

Masters and Johnson described how anatomic and physiologic changes associated with aging could negatively affect sexual response.[29] It may take a longer time to reach the excitement phase because of a reduction in the blood flow to the vagina, a reduction in engorgement of the genital organs, including the clitoris, as well as decreased amount of vaginal lubrication and a delay in time to lubrication. These factors may cause dyspareunia. The plateau phase may be prolonged as a result of reduced uterine elevation, decreased nipple erection, and vasocongestion of the breasts. Although orgasmic capacity is retained, there is a reduction in the number and intensity of vaginal contractions.

## 6. Defining Sexual Dysfunction

Classically, the definitions of female sexual dysfunction have been modeled on the human sexual response cycle first described by Masters and Johnson[29,30] and later enriched by Kaplan.[31] Their work formed the basis for the diagnostic systems of both the International Statistical Classification of Diseases and Related Health Problems (ICD–10)[32] and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV).[33] Recently, the Sexual Function Health Council of the American Foundation for Urologic Disease convened a consensus panel to reevaluate and better define and classify female sexual dysfunction.[34] Retaining the categories of both systems, several changes were made in the definitions and classifications; the new format is shown

below. One of the major changes in the classification schema was to add the criterion of personal distress to the diagnosis.

### 1999 Consensus Classification System

#### *Sexual Desire Disorders*

##### *Hypoactive Sexual Desire Disorder*

Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress. This allows for trigger of sexual desire to be secondary to the partner's initiative. If the choice is made to not be sexual, there is no disorder present.

##### *Sexual Aversion Disorder*

Sexual aversion disorder (SAD) is the persistent or recurrent phobic aversion and avoidance of sexual contact with a sexual partner, which causes personal distress. Because often this disorder is secondary to sexual or gynecologic trauma, some experts believe that it belongs in the category of phobias.

#### *Sexual Arousal Disorders*

A sexual arousal disorder is a persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement or genital (lubrication/swelling) or other somatic responses. Goldstein and Berman theorize that the etiology in some women experiencing difficulties with vaginal engorgement or clitoral erectile insufficiency may be secondary to atherosclerosis.[35]

##### *Orgasmic Disorder*

Orgasmic disorder is a persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress. This disorder occurs in 20–30 percent of women, not infrequently with vaginal intercourse.

#### *Sexual Pain Disorders*

##### *Dyspareunia*

Dyspareunia is a recurrent or persistent genital pain associated with sexual intercourse. The prevalence of this disorder has been reported to affect between 10–15 percent of women.[36] Consideration should be given to physical causes such as endometriosis, episiotomy scarring, or skin sensitivity.

##### *Vaginismus*

Vaginismus is a recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina, that interferes with vaginal penetration, which causes personal distress. Vaginismus occurs in 12–17 percent of all women in reports from the United States. However, in Asia, it is very rare to see it (Kim WW, personal communication).

##### *Other Sexual Pain Disorders*

Other sexual pain disorders are recurrent or persistent genital pain induced by noncoital sexual stimulation.

Each of the categories above has the following subtypes on the basis of the medical history, physical examination, and laboratory tests:

a) Lifelong versus acquired.

b) Generalized versus situational.

c) Etiologic origin (organic, psychogenic, mixed, unknown).

Health care professionals and the lay public are encouraged to implement this new classification system in the conduct of future research, the clinical diagnosis and treatment of women with sexual dysfunction, and the education of women with these problems.

## 7. Assessing Sexual Activity

Clinicians should routinely ask their patients about their sexual functioning. Many elderly couples wonder if it is still possible or safe to have coitus after the menopause or how long they can enjoy sex without harming their health. Sexual history questions particularly pertinent to postmenopausal patients include the following:

- Are you satisfied with your sexual life?
- Do you have any questions about sex?
- Has there been a change in your sex drive, lubrication, or orgasm?
- Do you have any sexual problems? Would you like help with the problem or problems?
- Can you describe when the problem started, and how often it occurs?
- Have you tried anything to correct the problem? Has it worked?
- Does your partner have any sexual problems?

It is important to be alert to the possible effects of aging, illness, or medical or surgical treatment on libido and sexual responsiveness. Sexual dysfunctions may have a negative influence on a woman's self image, her physiologic response, or her partner's response. One of the most controversial issues is whether hysterectomy impacts sexual function. If done for symptoms, such as pain or bleeding, a hysterectomy can result in improved sexual functioning.[37] Alternatively, some women view it as causing a loss of their female identity that negatively impacts sexual functioning.[38,39] Possible medical causes of sexual problems include the following:

**Illnesses:** Any physical or emotional chronic disease—physical or emotional, including liver, renal, cardiac, anemia, hypertension, stroke, cancer, neurologic disease, colostomy, neostomy, bladder surgery, incontinence, herpes virus or HIV infection, venereal warts, and cystitis—may cause sexual dysfunction.

**Medications:** Hypoglycemic agents, antihypertensive drugs, vasodilator and other cardiac drugs, antineoplastic drugs, major or minor tranquilizers (depending on dose), diuretics, and antihistamines may cause sexual problems. (See table 7–2.) Some studies suggest antidepressants (including SSRIs) may reduce desire and delay orgasm.[40] Decreased libido occurs in 20 percent of patients on tricyclic antidepressants, and 30 percent have impaired orgasm.

**Treatments:** Major surgery (hysterectomy, mastectomy, coronary artery bypass, organ transplant), dialysis, radiotherapy, and chemotherapy may cause sexual dysfunction.

## 8. Treatment For Sexual Dysfunction

Sexual function for any person at any age involves sexual thoughts, desires, feelings of arousal, potential for orgasm, and physical and mental relaxation. The treatment of sexual dysfunction is dependent adequate research showing efficacy of the treatment over another medication, a placebo or another treatment. Compared to with treatments for other mental health diagnoses, treatment for sexual dysfunction has lagged behind. The causes are multiple and include such issues as a lack of a standardized approach to therapy, the lack of control groups, and the dominance of the techniques described by Masters and Johnson.[30] However, one of the most probable causes for the lack of treatment options for sexual dysfunction has been the lack of research funding to study these disorders.

Behavioral and medical treatments for sexual dysfunction are reviewed below, and where evidence exists, recommendations are made as appropriate.

### 8.1 Behavioral Therapy for Sexual Dysfunction

A literature review of the application and outcome of sex therapy and other treatments for sexual dysfunction showed the format of effective conjoint sex therapy may be of significant benefit to couples with sexual dysfunction.[41] Sarwer and Durlak con-

## TABLE 7–2

**Medications Associated With Adverse Effects on Female Sexual Function and Response**

Antihypertensive drugs
Antidepressants and anxiolytics (especially SSRIs)
Anti-inflammatory drugs
Antiparkinsonian drugs
Antiseizure drugs
Beta-blockers
Bromocriptine (painful clitoral tumescence)
Cimetidine
Digoxin
Diuretics
Gemfibrozil
Gonadotropin-releasing agents
Methyldopa
Psychoactive drugs
Sleeping pills
Tranquilizers

**Abusive Drugs Associated with Abnormal Sexual Response**

Alcohol
Narcotics
Nicotine

ducted a field trial of behavioral sex therapy for 365 married couples presenting with a range of sexual dysfunctions at an outpatient sexual dysfunction clinic of a large medical center.[42] The number of sensate focus exercises completed in the last week of treatment was the strongest predictor of successful treatment. The results of this study confirmed that behavioral sex therapy is effective in the treatment of married couples with sexual dysfunction.

### *8.1.1 Anorgasmia*

The approach to treatment of primary anorgasmia utilizes the techniques of sensate focus, desensitization, and/or directed masturbation exercises. The primary elements of sensate focus developed by Masters and Johnson are physical caresses coupled with nonsexual progressing to sexual touching exercises.[30] The success rate was 84 percent in just over 1 year and 82 percent at 5 years. Desensitization is used when anxiety plays a major role in the dysfunction; however, it alone does not improve orgasmic capacity.[43] Directed masturbation exercises have had varying success in the treatment of primary anorgasmia.

Kilmann et al. investigated the differential effectiveness of various treatments for 55 couples where the woman reported secondary orgasmic dysfunction.[44] Compared with women in the control group, a significantly greater number of treated women reached or exceeded the project's 50-percent criterion for coital orgasmic functioning. However, these differences were not significant at the followup visit.

None of these studies evaluated the effects of treatment of individuals without partners and of, combining sex therapy with marital therapy and with physical methods of treatment. Thus, no evidence-based recommendations can be made.

A thorough review of behavioral therapies for sexual dysfunction is beyond the scope of this review but is available.[45]

## 9. The Influence of Endogenous Hormones and Exogenous Hormone Therapy for Sexual Behavior, Interest, and Response

### 9.1 Endogenous Hormones

The influence of the sex hormones, including estrogens, androgens, and progestogens, in the menopause remains debatable.

***Although estrogen and estrogen/progestin replacement therapy have been shown to be an effective treatment for vaginal atrophy, increasing vaginal lubrication, they have not been shown to consistently increase sexual desire or activity.***

Two studies have shown the importance of adequate estrogen levels in maintaining genital health and vaginal lubrication and preventing insertional dyspareunia. Semmens and Wagner reported on 14 women between the ages of 51 and 70 years who had decreased vaginal pH, vaginal fluid, and vaginal blood flow, all of which improved with HRT.[46] Sarrel showed a correlation between serum estradiol levels (concentrations) and sexual dysfunction.[47] At a level of less than 50 pg/mL, women reported vaginal dryness, increased frequency and intensity of dyspareunia, pain with penetration and deep insertion, and burning, all of which were significantly bothersome.

At the cellular level, Ginkel et al. compared the vaginal pH and microbial environment in women before and after starting HRT.[48] With HRT, the vaginal pH became more acidic, there was an increase in superficial cells, and most importantly, there was a significant decrease in the number of anaerobes and an increase in Lactobacillus species in the vagina.

Similarly, in an interview survey of 52 perimenopausal women with adequate records, Cutler et. al. reported women with estradiol levels below 35 pg/mL described reduced coital frequency compared with those with levels greater than 35 pg/mL.[49] Women with higher estradiol levels had no complaints related to sexual desire, response, or satisfaction.

Additionally, in observational study, 59 healthy, postmenopausal women between 60 and 70 years of age were evaluated for sexual function.[50] Two-thirds were sexually active. The sexually active group reported higher levels of sexual desire, greater sexual satisfaction, more comfort in expressing sexual preferences, and greater premenopausal sexual satisfaction than women who were not sexually active. On pelvic examination, the sexually active group had less genital atrophy than the abstinent group. Of the hormones studied, higher serum levels of free testosterone were associated with reports of increased sexual desire.

### 9.2 Estrogen/Hormone Replacement Therapy

Although estrogen and estrogen/progestin replacement therapy have been shown to be an effective treatment for vaginal atrophy, increasing vaginal lubrication, they have not been shown to consistently increase sexual desire or activity.

In the 1970s, three double-blind studies on the effects of HRT on sexual response reported conflicting results. Campbell found vaginal dryness was significantly decreased with estrogen treatment compared with placebo, but participants noted no change in masturbation, orgasm, and frequency of coitus or coital satisfaction.[51] Previous reports by Utian[52] and Coope et al.[53] failed to show improve-

ment in sexual desire in surgically and naturally menopausal women with CEEs.

Fedor-Freybergh showed significant benefit of ERT on libido, sexual activity, satisfaction, pleasurable experience, sexual fantasies, and capacity for orgasm.[54] This was corroborated in a randomized, double-blind, placebo-controlled, crossover trial of estrogen and progestin, alone and in combination, which found beneficial effects of estrogen alone or combined with the progestin on sexual desire, enjoyment, orgasmic frequency, and vaginal lubrication.[55] There were no differences between groups in coital frequency.

In a more recent study of estrogen transdermal replacement therapy in postmenopausal women, there was an improvement in patient satisfaction with frequency of sexual activity, sexual fantasies, degree of enjoyment, vaginal lubrication, and lack of pain during intercourse, without impacting frequency of orgasm or sexual arousal.[56]

### 9.3 The Role of Androgens in Sexual Function and Estrogen/Androgen CoTherapy for HRT

The role of sex steroids, including androgens, in sexual function remains controversial. As previously discussed, sexual desire can be influenced by many factors. In addition, the decline in serum testosterone is not unique to the menopause. In a study of 33 healthy volunteers, 24-hour serum levels of testosterone decreased steadily between ages 20 and 50.[21]

Ovarian and adrenal changes associated with the menopause lead to a decline in all androgen concentrations, with androstenedione production decreased more substantially than testosterone production.[57] Postmenopausal women obtain most of their circulating estrogen from peripheral aromatization of these androgens. SHBG is an important determinant of sex steroid activity, since the unbound steroid fraction is the biologically active component. SHBG is increased by estrogens, decreasing biologically available androgen. SHBG is decreased by androgen, increasing biologically available androgen.[58] Applying the evidence from animal studies, this may influence sexual desire at the level of the CNS.[59,60]

Geist and Salmon, although not the first, were among the early investigators to supplement ERT with androgens.[61] They studied the effects of testosterone propionate administered twice weekly at a dose of 25 mg, starting on the 12th day of the menstrual cycles for its effects on menopausal symptoms. Maintenance doses of 10 mg of either testosterone propionate or methyltestosterone monthly thereafter were also studied. They found that menopausal symptom relief was particularly helpful in women on estrogen alone with menorrhagia and in those who only had partial symptom relief with estrogen.

Shortly thereafter, Greenblatt reported on the use of androgens for hot-flush relief and an added benefit of improving libido.[62] Again in 1950, Greenblatt and colleagues studied the safety and efficacy of multiple estrogen-androgen formulations in a prospective, double-blind, placebo-controlled, crossover study.[63] They reported improved well-being and libido, with better relief of hot flushes and other menopausal symptoms than either HRT or placebo. Additionally, those on estrogen-androgen reported less breast tenderness, pelvic congestion, and nausea. In 1950, Glass reinforced the benefit of testosterone on women's sexual response.[64] He reported that combination therapy with estrogen and androgen produced a "smoother transition" and "provides reassurance to the menopausal woman that she is not failing in her psychosexual life."

Sherwin and Gelfand published a case series of surgically menopausal women and confirmed earlier studies showing the role of androgens in the maintenance of sexual functioning.[65] Sexual arousal, desire, and fantasies increased in women with estrogen-androgen replacement therapy as opposed to estrogen alone. They also noted that the rates of coitus and orgasm were higher in the

estrogen-androgen group during the first two post injection weeks. Additionally, they performed a crossover study of 53 surgically menopausal women and showed that the major impact of androgen in women was on sexual motivation, not increased sexual activity. Although there has been concern about the potential of negative impact of androgens on lipids and heart disease, research has not confirmed any increase in risk secondary to the addition of androgens in HRT.[66,67]

***Although there has been concern about the potential of negative impact of androgens on lipids and heart disease, research has not confirmed any increase in risk secondary to the addition of androgens in HRT.***

Sarrel et al. reported in 1998 on 20 postmenopausal women unhappy with their estrogen/hormone replacement therapy regimen who were randomized to receive either esterified estrogens or esterified estrogens with androgen for 8 weeks.[68] They described significantly improved sexual sensation and desire after 4-8 weeks of double-blind treatment with estrogen and androgen. They showed increased SHBG in the estrogen-only group with decreased free androgens and showed the reverse in the estrogen-androgen group. This led to the explanation that improvement in sexual sensation and desire may be related to the increased availability of endogenous or exogenous androgens.

In a pilot case series of 17 nonresponders to oral ERT, estradiol-testosterone combination implants appeared to significantly improve libido, enjoyment of sex, the ability to climax, and the initiation of sex, as examined by an analog scale, in a majority of women.[69]

### 9.4 Other Agents

Newer hormonal agents in research trials have indicated a possible benefit in reducing vaginal dryness, which may impact sexual function. Tibolone, a preparation with weak estrogen, progestin, and androgen activity not yet released for use, was studied in 437 women with postmenopausal complaints; they showed improvement of vaginal dryness, similar to 17β-estradiol/norethisterone acetate, with fewer bleeding problems.[70] In an RCT of tibolone versus 17β-estradiol, sexual frequency, satisfaction, and enjoyment were significantly improved over estradiol alone.[71]

Bupropion is an antianxiety medication which appeared to increase libido and orgasm in combination with sertraline.[72] It may be used as an antidote in women who have sexual dysfunction while on SSRIs.[73,74] A dose of 150 mg of trazodone daily has been reported to increase sex drive in a woman postmastectomy with low sex drive.[75] A recent small study of oral phentolamine in six postmenopausal women with female sexual arousal disorder showed self-reported improvement of vaginal lubrication and pleasurable vaginal sensations and deserves future study.[76]

Although there has been much interest in the use of sildenafil (Viagra®) in the sexual dysfunction of women, the only published study on the efficacy of this agent for female sexual arousal disorder was not shown to improve sexual response in women receiving estrogen.

Herbal remedies for sexual dysfunction lack rigorous study. A few small trials have assessed efficacy. A drug-monitoring study investigated 12 weeks of treatment with St. John's Wort extract, one tablet three times daily (900 mg Hypericum, Kira), in 111 women from a general medical practice in Germany. Patients were between 43 and 65 years of age, and had climacteric symptoms characteristic of the premenopausal and menopausal state. The Menopause Rating Scale,[78] a self-designed questionnaire for assessing sexuality, evaluated

treatment efficacy. Sexual well-being improved after treatment with St. John's Wort extract.[79] Although there are anecdotal reports of other herbal agents, no clinical trials have been performed to date. Of interest, clinicians in Asia do not expect herbal remedies to be effective in treating a woman's sexual dysfunction, since after thousands of years of use of oriental medicine, they still could not find appropriate therapy, even for men (Kim WW, personal communication).

## 10. Conclusions

Multiple population-based studies imply a decrease in female sexual functioning associated with the midlife years, and there is growing evidence that this reflects hormonal changes of the menopausal transition rather than increasing age. Hormonal change is only one aspect of the many factors that impact sexual functioning. These include presence of a sexual partner, partner's age and health, length of the relationship, feelings towards the partner, level of past sexual functioning, social class, educational level, experience of physical or psychological ill health, stressors, employment, personality factors, and negative attitudes towards the menopause.

Changes in sexual behavior, interest, and response should be assessed in the office on a regular basis and a plan developed with the woman to address her needs. Therapeutic options include the use of estrogen and estrogen-androgen replacement therapy.

## 11. Future Needs

As life expectancy continues to increase, the challenge for the future will be to improve the quality of aging years. Sexual health and well-being is an important part of that quality of life. Future needs are to:

- Improve understanding of the natural hormonal changes that occur with aging and menopause.
- Understand the role of endogenous estrogens and androgens in the sexuality of women.
- Develop standardized methods to measure libido in women.
- Better define the determinants of sexual health, including sexual desire and arousal, in menopausal women.
- Increase understanding of the effect of medications on female sexuality in the menopause.
- Understand the role of therapeutic hormonal and nonhormonal agents in the treatment of sexual dysfunction.
- Improve the transmission of information about sexual health to postmenopausal women.

***Changes in sexual behavior, interest, and response should be assessed in the office on a regular basis and a plan developed with the woman to address her needs. Therapeutic options include the use of estrogen and estrogen-androgen replacement therapy.***

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# Chapter 8: Cardiovascular and Pulmonary Disease

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## Key Points[a]

1. CVD is the commonest cause of morbidity and mortality in women [C].
2. The risk factors contributing to CVD are generally the same in women and men, with the possible exception of hormonal effects [C].
3. Evidence-based medicine has demonstrated that beta-blockers, aspirin, statins, and ACE inhibitors can reduce the risk of cardiovascular events in women. The main causes, prevention, and treatment of CVD in women are similar to those in men [A].
4. Although the use of HRT has been associated with a lower risk of CVD in epidemiological studies, this has not been borne out in clinical trials to date [C].
5. Until the long-term benefit of HRT is proven, attention should focus on identifying and treating the same risk factors in women as in men [A].

***CVD is the commonest cause of morbidity and mortality in women.***

## 1. Introduction

CVD afflicts more women than any other disease. It is by far the commonest cause of morbidity and mortality in women, and there is a steep increase in the incidence of CVD with age, especially after menopause. Ovarian hormones are thought to be protective of the cardiovascular system; 17β-estradiol and progesterone. Hormones that are effective for the short-term treatment of symptoms of perimenopause may not necessarily be the best choices for preventing CVD. HRT is not a single entity but encompasses a diverse number of agents, which may have differing effects on the cardiovascular system. It is therefore important, from a public health standpoint, to perform studies using different

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgment. (See also table 1–1.)

routes of administration and different doses and combination of hormones to arrive at firm conclusions about the role of HRT in the prevention of CHD in postmenopausal women. CHD prevention is conventionally divided into primary and secondary prevention. Primary prevention addresses interventions in the absence of clinically recognized disease, although atherosclerosis may be present. In secondary prevention, a cardiovascular event has already been documented. In this chapter we have made no distinction between primary and secondary prevention of CHD, since therapies that work for secondary prevention usually work for primary prevention and vice versa.

***HRT is not a single entity but encompasses a diverse number of agents, which may have differing effects on the cardiovascular system.***

Although HRT has been the focus of much attention in menopausal women, the approach to the prevention of CVD should be multifaceted. There is increasing information on the beneficial effects of lifestyle changes (e.g., nutrition and exercise), which can contribute greatly to the reduction in risk of CVD. One of the problems in CVD research in women is that some of the major pharmacologic studies have been conducted in men or have included only a small proportion of women. Nonetheless, a number of drug interventions, including beta-blockers, aspirin, statins, and ACE inhibitors, have been shown to decrease events associated with CHD in women as well as in men. Future studies have to include adequate numbers of women in order to make valid assessments of treatment effects in women.

This chapter identifies important areas of CVD that have been studied and reported in women and that provide a basis for future research in this area of women's health. Only with large, well-conducted clinical trials can important and accurate information be accrued on CVD in postmenopausal women.

## 2. Risk Factors for Coronary Heart Disease in Women

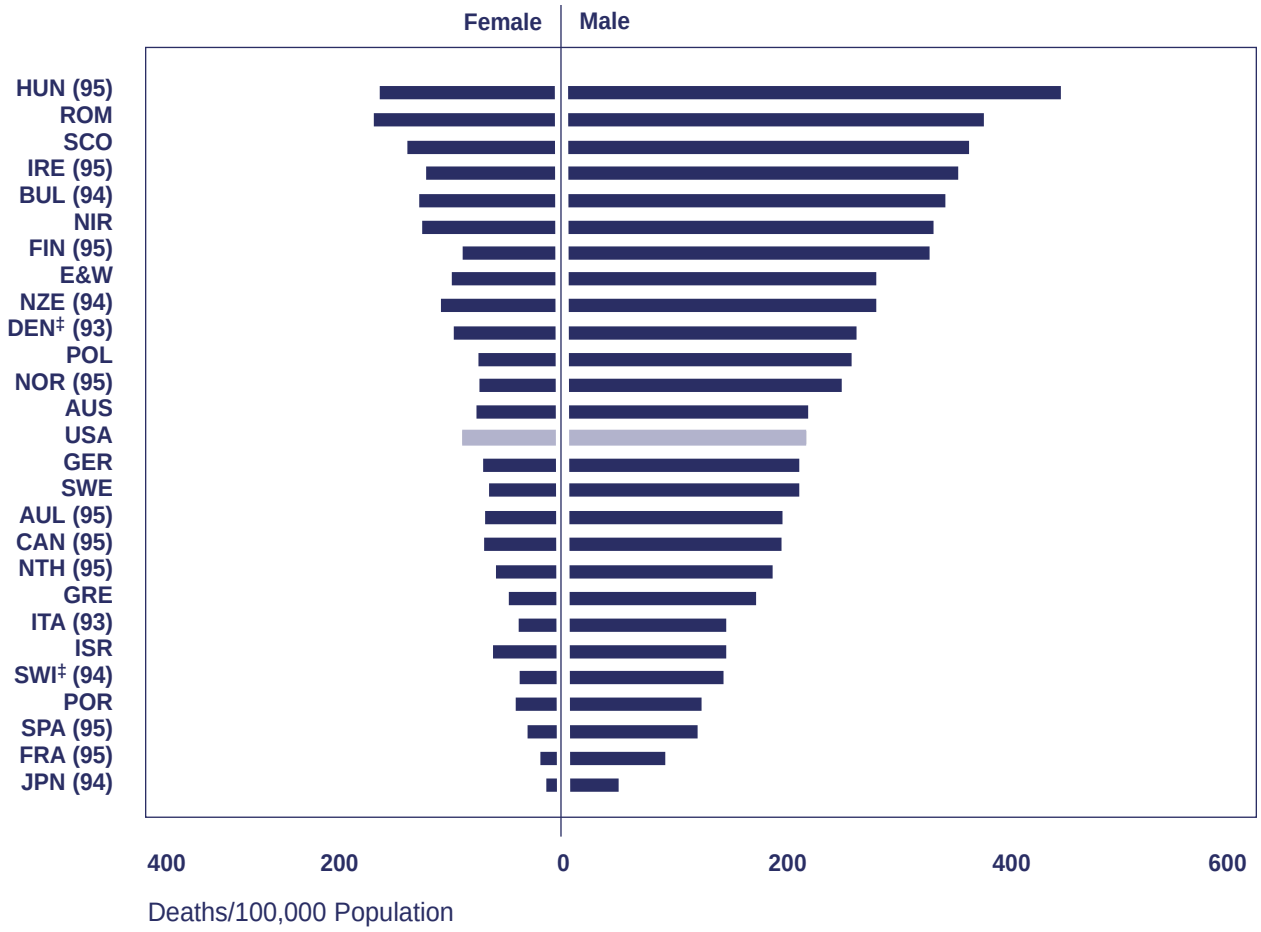
The term "risk factor" is used to describe characteristics found in healthy individuals that have been observed in epidemiological studies to be related to the subsequent occurrence of CHD. The risk factors for CHD are multifactorial, and many of these are similar in women and men.

- Age
- History of CHD, stroke, or peripheral vascular disease
- Family history of premature CHD
- Dyslipidemia
- Cigarette smoking
- Hypertension
- Diabetes mellitus
- Obesity (especially central)
- Lifestyle—diet, physical activity, psychosocial factors, alcohol
- Homocysteine and C-reactive protein (CRP)

Some risk factors are modifiable, such as smoking habit, alcohol intake, lifestyle, and biochemical and physiological characteristics. Other personal characteristics, such as age, gender, and family history of early onset of CHD, are nonmodifiable. Countries with high rates of heart disease in men also have higher rates in women; and conversely, low rates in men correspond to low rates in women (fig. 8–1). In developed countries, death rates for CHD in women aged 35–74 are decreasing (fig. 8–2); in contrast, rates are static or increasing in developing and eastern European countries. Women appear to be protected from CHD especially at younger ages, and it has been postulated that sex-specific hormones may be implicated.[2] Data from the Framingham Heart Study[3] reveal that the risk of CHD in an asymptomatic woman who has both elevated systolic blood pressure and smokes cigarettes is significantly less than the risk

## FIGURE 8–1

### Age-Adjusted Death Rates* for Coronary Heart Disease by Country and Sex, Aged 35–74, 1996†




* Age adjusted to European Standard.

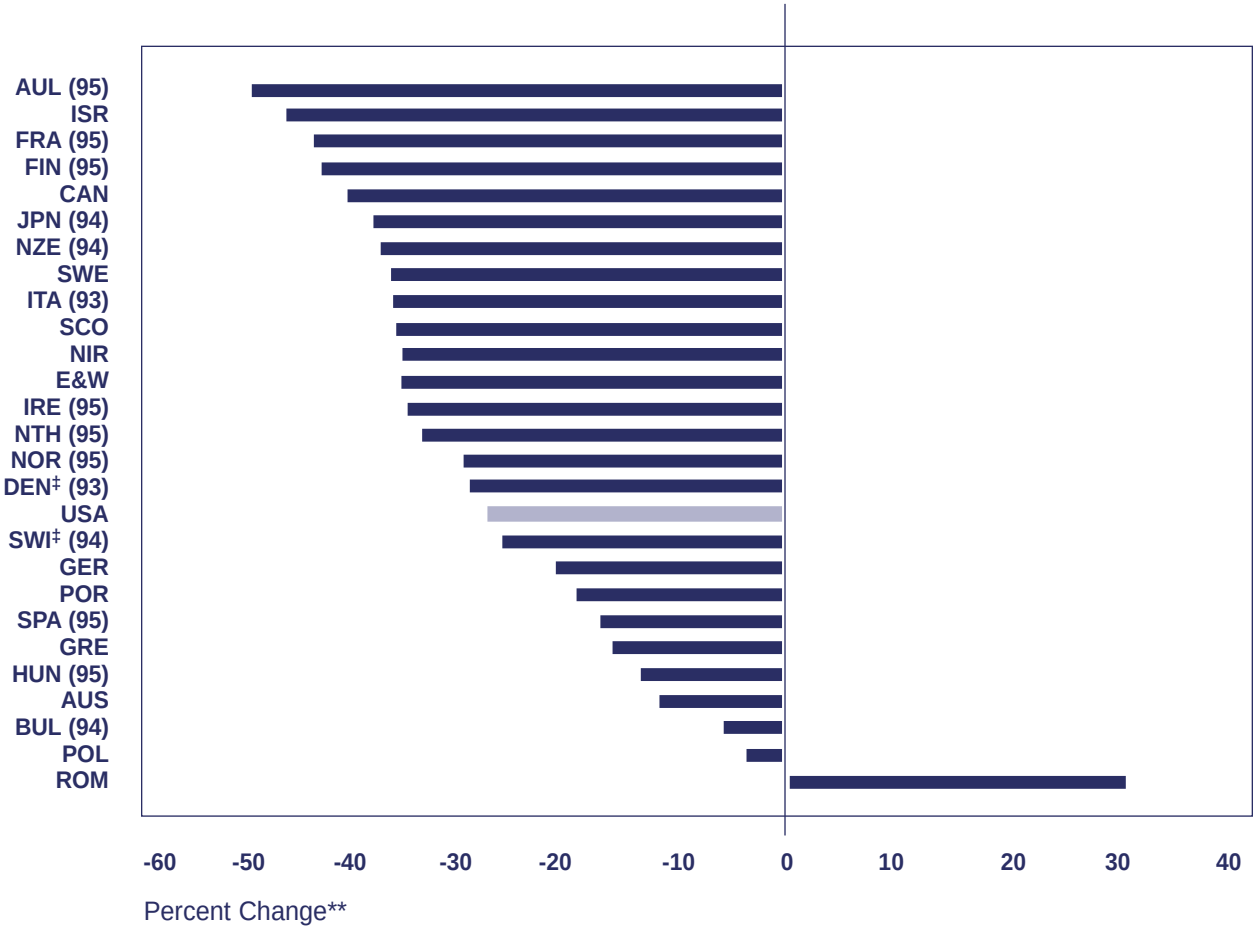
† Data for 1996 unless otherwise noted in parentheses.

‡ Eighth revisions of the ICD.

in a man of the same age. This applies to women and men at younger ages (age 50) but the differences between women and men no longer apply at older age (beyond the age of 80).[4] Established major modifiable risk factors for CHD in women, based on prospective studies, include raised total cholesterol (or LDL cholesterol), low high density lipoprotein (HDL) cholesterol, high blood pressure, cigarette smoking, diabetes, obesity, and physical inactivity. High triglycerides, raised Lp(a), and raised fibrinogen levels are also considered to be major risk factors by some authorities. The modifiable risk factors shown to be of cardiovascular benefit in randomized trials include

## FIGURE 8–2

### Change in Age-Adjusted Death Rates* for Coronary Heart Disease in Females by Country, Aged 35–74, 1986–1996†




* Age adjusted to European Standard.

** Based on a log linear regression of the actual rates.

† Data for 1996 unless otherwise noted in parentheses.

‡ Eighth revisions of the ICD.

reduction of blood pressure and blood cholesterol. Many studies have not included sufficient numbers of women to detect gender-specific differences. Factors such as homocysteine have clearly been identified as a risk factor in men,[5] and recent data suggest that higher homocysteine levels are observed among both male and female children with a positive family history of CHD:[6] in menopausal women increasing levels of homocysteine are associated with an increased risk of CVD.[7] More data are required before conclusions can be made about this and other postulated "new" risk factors, such as CRP levels.

### 2.1 Dyslipidemia

There is a strong graded positive association between plasma total cholesterol (or LDL cholesterol) and risk of CHD events in middle-aged (< 65 years) and older (> 65 years) women, but the strength of the association diminishes with age.[8] Although the general level of CHD risk is lower in women than in men, the association with total cholesterol remains powerful. Treatment of elevated total and LDL cholesterol in women has been shown to reduce CHD risk.[9] A low level of HDL cholesterol is a risk factor for CHD in both younger and older women.[10] Hypertriglyceridemia may be a more reliable risk factor for CHD in menopausal women than in men.[11,12] Lp(a) is associated with an increased risk of CHD[13,14] and is probably a determinant of CHD in both premenopausal and postmenopausal women.[15]

### 2.2 Cigarette Smoking

There is overwhelming evidence for an adverse effect of smoking on the risk of CHD and other vascular disease in women and men. The adverse effect of smoking cigarettes is dependent on both the daily amount smoked and the duration of cigarette smoking. However, the evidence derives from multiple observational studies rather than clinical trials.[16,17] The detrimental effects of cigarette smoking on CHD may be even more pronounced in women. In Europe, the impact of cigarette smoking on the risk of CHD is smaller in Mediterranean populations than in the northern European population.[18] Dietary factors probably explain this difference in the effects of cigarette smoking.

### 2.3 Hypertension

There is a strong association between high levels of blood pressure, both systolic and diastolic, and the risk of CHD in both women and men.[19] Isolated systolic hypertension is particularly important in older women as it affects up to a one-third of women older than 65 years and is associated with a significant increase in risk of CHD and stroke.[20] Treatment of older women in the Systolic Hypertension in the Elderly Program (SHEP) trial demonstrated a 25 percent reduction in CHD and a 36 percent reduction in stroke in both women and men combined,[21] as well as decreased late occurrence of heart failure.[22] In a meta-analysis of the trials, the greatest benefit of control of blood pressure of the trials is in subjects at high combined overall risk. Following a MI for example, elevated blood pressure is associated with an increased risk of reinfarction and death.[23]

### 2.4 Diabetes Mellitus

Diabetes mellitus is an important risk factor for CVD in women.[24] It negates the female sex-related differences in CHD prevalence, and diabetic women have as high a risk of MI as nondiabetic women with a previous MI.[25,26] Data from the Framingham Study show that for subjects aged 50–59 years, diabetes mellitus was a greater risk factor in women compared to men.[27] Even when corrections are made for other established risk factors, diabetes is associated with more than double the risk of CHD compared with women without diabetes.[26] Elderly women have a relatively high incidence of diabetes, contributing to a higher CVD risk. There are many reasons why a diabetic woman is at excess risk. She has dyslipidemia with lower HDL cholesterol, elevated triglyceride levels, and more atherogenic (oxidized) LDL.[28] Treatment of elevated LDL in diabetics reduces CHD risk.[29–31] Other factors include abnormalities of coagulation and fibrinolysis as well as abnormalities of platelet function. Endothelial cell dysfunction has also been shown in diabetics.[28]

***There is overwhelming evidence for an adverse effect of smoking on the risk of CHD and other vascular disease in women and men.***

### 2.5 Obesity

In the Third National Health and Nutrition Examination Survey (NHANES III), 55 percent of the adult female American population was classi-

fied as overweight or obese.[32] The cardiovascular health burden of obesity includes a strong predisposition to both type 2 diabetes and to hypertension. The prevalence of these conditions in the presence of obesity is increased by twelvefold and fivefold respectively, in women younger than 55 years.[32] Although there remains no causal evidence for the relationship between a sedentary lifestyle and obesity, the association between the two factors is strong.[33] In a female twin study, twins discordant for intensity of physical activity displayed significant differences in total and central body fat.[34] In that study, physical activity was the strongest predictor of total body fat, even after accounting for age, diet, smoking, and HRT. In an 18-month randomized behavioral study of sedentary obese women, there was a dose response effect of exercise duration on weight loss.[35] Women who were given access to home exercise equipment showed the greatest weight loss and maintained significantly greater exercise duration at the completion of the trial. HRT decreased central abdominal fat in a small prospective study of obese women with type 2 diabetes.[36]

***Diabetes mellitus is an important risk factor for CVD in women.***

Obesity in women is a complex metabolic disorder with strong genetic components. The peroxisome proliferator-activated receptors (PPARs) consist of three receptors α, β, and γ. PPAR-γ is expressed in adipose tissue. It has recently been shown that two polymorphisms in the PPAR-γ gene are associated with severe overweight among obese women.[37] The exact mechanisms by which the PPAR-γ variant affects adipose tissue mass are not known. Changes in the activity or structure of the PPAR gene in vivo may result in changes in expression of target genes in differentiating cells. Alterations in adipocyte differentiation may then lead to obesity.

### 2.6 Lifestyle

A number of lifestyle factors (other than cigarette smoking) have been implicated in CHD. These include diet, physical activity, psychosocial factors, and excessive alcohol intake. There appears to be a synergistic effect of lifestyle readjustments, such as the combination of diet, exercise and abstinence from smoking, in the primary prevention of CHD in women.[38]

#### *2.6.1 Diet*

***The use of alcohol has a U-shaped relationship with regard to the risk of CHD.***

Diet is an important determinant of CHD risk both in women and in men. Epidemiological studies show that diets low in saturated fat and high in fruits, vegetables, whole grains, and fiber are associated with a reduction in the risk of CHD. Consistent with early metabolic feeding studies, recent epidemiological studies suggest that replacing saturated and trans-unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats may be more effective in preventing CHD in women than in reducing total fat intake.[39] Clinical trials have shown reductions in CHD events or angiographic outcomes for a variety of dietary interventions: very low fat diets,[40] diets low in saturated fat and high in polyunsaturated fat,[41–42] a Mediterranean diet high in oleic acid and ω-3 fatty acids,[43] and diets rich in antioxidant fruits, vegetables, and legumes.[44] The effect of food supplements such as vitamins B6, B12, and folate, as well as flavonoids and soy isoflavones, require further investigation in clinical trials before firm conclusions can be made about their potential to favorably affect cardiovascular outcomes in healthy women and those with established CHD.

#### *2.6.2 Physical Activity*

Diet alone failed to lower LDL cholesterol levels in women with high-risk lipoprotein levels who did not engage in aerobic exercise. A combination of the NHLBI's National Cholesterol Education Program (NCEP) Step II Diet plus exercise beneficially reduced LDL cholesterol compared with the

diet alone.[45] The Lifestyle Heart Trial showed that intensive lifestyle changes in both women and men with severe CHD resulted in regression of coronary atherosclerosis at both 1 and 5 years. The benefit was greater at 5 years.[40] In a cohort of women after coronary bypass surgery, depressed women (comprising 23 percent of the entire cohort) not only improved their mental health in response to a formal rehabilitation program but also lost more weight and increased their HDL levels to a greater degree than the nondepressed patients.[46] This study confirms that the benefits of an exercise program extend beyond weight reduction and fitness to include psychosocial and even risk factor modification. In a recent report from the Nurses' Health Study, brisk walking, as compared with vigorous walking, was associated with a similar and substantial reduction in the incidence of coronary events among women aged 40–60 years.[47]

#### *2.6.3 Psychosocial Factors*

Psychosocial factors, such as anger and hostility, are positive predictive factors for an increase in intimal medial thickness of the carotid arteries over a 10-year period; this may be predictive of early atheroma development.[48] In a Swedish study, lack of social support contributed to the severity of CAD in women, independent of standard risk factors.[49,50] Hostile attributes, fasting insulin level, and weight gain in mid-life, may contribute to the development of visceral adipose tissue in healthy menopausal women, which may then lead to the increase in risk of CHD. Socioeconomic status had an independent association with factor VII level, suggesting an increase in thrombotic tendency.[51]

#### *2.6.4 Alcohol Intake*

The use of alcohol has a U-shaped relationship with regard to the risk of CHD. Nondrinkers have a higher risk than moderate drinkers (10–30 g ethanol daily), but the risk increases with increasing alcohol consumption.[52] Importantly, alcohol intake in women may also be related to an increase in blood pressure and risk of breast cancer.[53]

### 2.7 Homocysteine and C-Reactive Protein

Increasing levels of homocysteine are associated with an increased risk of CVD in postmenopausal women.[7] Homocysteine has been shown to damage vascular endothelial cells, which may contribute to a consequent increase in the tendency to thrombosis. One study[54] demonstrated low plasma homocysteine levels in premenopausal women compared with high values in postmenopausal women, suggesting a close relationship between homocysteine metabolism and estrogen status. Several other studies demonstrated that HRT decreases homocysteine levels in postmenopausal women.[55–59] In some reports, this effect was found especially in women with initially elevated pre-treatment homocysteine values. Although recent data on vitamin B administration (as a potent homocysteine lowering drug) are promising, randomized clinical trials are needed to investigate whether decreasing plasma homocysteine levels by any means will result in a reduction of CVD risk in women.

With the recognition that atherosclerosis is an inflammatory process, several plasma markers of inflammation have been evaluated as potential tools for prediction of the risk of CHD. CRP appears to be a potent predictor of the risk of coronary events in postmenopausal women.[60] Adding CRP to lipid screening may provide an improved method of identifying women at risk for coronary events. A guide to risk reduction for women is given in the American Heart Association (AHA)/ American College of Cardiology (ACC) Scientific Statement: "Consensus Panel Statement. Guide to Preventive Cardiology for Women" (table 8–1).[61]

***Changes in vascular function directly attributable to menopause are difficult to identify.***

### 2.8 Gender Differences in Atherosclerotic Plaque

Endothelial erosion and plaque rupture are regarded as sequelae of an inflammatory process involving activated macrophages and their response to oxidized LDL within the intima of the vessel wall.

## TABLE 8–1

## Guide to Risk Reduction for Women

| Lifestyle Factors | Goal(s) | Screening | Recommendations |
|---|---|---|---|
| Cigarette Smoking | 1. Complete cessation.<br>2. Avoid passive cigarette smoke. | 1. Ask about current smoking status and exposure to others' cigarette smoke as part of routine evaluation.<br>2. Assess total exposure to cigarette smoke (pack-years) and prior attempts at quitting.<br>3. Evaluate readiness to stop smoking. | 1. At each visit, strongly encourage patient and family to stop smoking. If complete cessation is not achievable, a reduction in intake is beneficial as a step toward cessation.<br>2. Reinforce nonsmoking status.<br>3. Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with behavioral therapy or a formal cessation program. |
| Physical Activity | 1. Accumulate ≥ 30 min of moderate-intensity physical activity on most, or preferably all, days of the week.<br>2. Women who have had recent cardiovascular events or procedures should participate in cardiac rehabilitation, a physician-guided home exercise program, or a comprehensive secondary prevention program. | 1. Ask about physical activity (household work as well as occupational and leisure-time physical activity) as part of routine evaluation.<br>2. In women with symptoms that suggest CVD or in previously sedentary women > 50 years old with ≥ 2 risk factors for CVD, consider a stress test* to establish the safety of exercise and to guide the exercise prescription. | 1. Encourage a minimum of 30 min of moderate-intensity dynamic exercise (e.g., brisk walking) daily. This may be performed in intermittent or shorter bouts (≥ 10 min) of activity throughout the day.<br>2. Women who already meet minimum standard may be encouraged to become more physically active or to include more vigorous activities.<br>3. Incorporate physical activity in daily activities (e.g., using stairs).<br>4. Muscle strengthening and stretching exercises should be recommended as part of an overall activity program.<br>5. Recommend medically supervised programs for women who have had a recent MI or revascularization procedure. |

**TABLE 8–1 *(continued)***

| Lifestyle Factors | Goal(s) | Screening | Recommendations |
|---|---|---|---|
| Nutrition | 1. AHA Step I Diet in healthy women (≤ 30% fat, 8–10% saturated fat, and < 300 mg/d cholesterol).<br>2. AHA Step II Diet in women with CVD or if a further reduction in cholesterol is needed (≤ 30% fat, < 7% saturated fat, and < 200 mg/d cholesterol).<br>3. Limit sodium chloride (salt) intake to 6 mg/d. Women with high blood pressure may require further restriction.<br>4. Attain total dietary fiber intake of 25–30 mg/d from foods.<br>5. Consume ≥ 5 servings of fruits and vegetables per day. | 1. Assess nutritional habits as part of a routine evaluation in all women.<br>2. Consider formal dietary assessment in women with hyperlipidemia, diabetes, obesity, and hypertension. | 1. Encourage a well-balanced and diversified diet that is low in saturated fat and high in fiber.<br>2. Use skim milk instead of milk with a higher fat content.<br>3. Diets rich in antioxidant nutrients (e.g., vitamin C, E, and beta-carotene) and folate are preferred over nutritional supplements. Note: Daily supplements of 0.4 mg of folic acid are recommended for women of child-bearing age to help prevent neural tube defects.<br>4. Limit alcohol intake to ≤ 1 glass of alcohol per day (1 glass = 4 oz wine, 12 oz beer, or $1^1/_2$ oz 80-proof spirits). Pregnant women should abstain from drinking alcohol. |
| Weight Management | 1. Achieve and maintain desirable weight.<br>2. Attain target BMI (weight in kilograms divided by height in meters squared) between 18.5 and 24.9 $kg/m^2$ (BMI of 25 $kg/m^2$ = 110% of desirable body weight).<br>3. Achieve desirable waist circumference of < 88 cm (< 35 inches) in women with a BMI of 25–34.9 $kg/m^2$. | 1. Measure patient's weight and height, calculate BMI, and measure waist circumference as a part of a periodic evaluation. **Note:** BMI and waist circumference are used for diagnosis, and measurement of height and weight are used for followup. | 1. Encourage gradual and sustained weight loss in persons whose weight exceeds the ideal weight for their height.<br>2. Formal nutritional counseling is encouraged for women with hypertension, hyperlipidemia, or elevated glucose levels associated with overweight.<br>3. The recommended weight gain during pregnancy is 25–35 lb if the patient's prepregnancy weight is normal. Adjust for multiple gestation and prepregnancy weight (e.g., overweight women should gain 15–25 lb, obese women, < 15 lb) |

**LV:** Left Ventricular
**SBP:** Systolic Blood Pressure
**TC:** Total Cholesterol
**TG:** Triglycerides

*The choice of test modality should be based on the resting ECG, physical ability to exercise, and local expertise and technology.

†The ACC and the AHA recommend cholesterol screening guidelines as outlined by the NCEP (measure total and HDL cholesterol at least once every 5 years in all adults ≥ 20 years old. The consensus panel recognizes that some organizations use other guidelines, such as the U.S. Preventive Services Task Force, which recommends that cholesterol screening in women without risk factors begin at age 45 years.

Modified from Mosca L, Grundy SM, Judelson D, et al., 1999. [61]

**TABLE 8–1 *(continued)***

<table>
<tr><th>Lifestyle Factors</th><th>Goal(s)</th><th>Screening</th><th>Recommendations</th></tr>
<tr><td>Psychosocial Factors</td><td>1. Adapt positively to stressful situations.<br>2. Improve quality of life.<br>3. Maintain or establish social connections.</td><td>1. Assess presence of stressful situations and response to stress as part of a routine evaluation.<br>2. Evaluate for depression, especially in women with recent cardiovascular events.<br>3. Assess social support system and evaluate for social isolation.</td><td>1. Encourage positive coping mechanisms for stress (e.g., substitute physical activity for overeating or excessive smoking in response to stress).<br>2. Encourage adequate rest and relief for women who are caretakers of others.<br>3. Consider treatment of depression and anxiety when appropriate.<br>4. Encourage participation in social activities or volunteer work for socially isolated women.</td></tr>
<tr><td>Blood Pressure</td><td>1. Achieve and maintain blood pressure < 140/90 mmHg and lower if tolerated (optimal < 120/80 mmHg).<br>2. In pregnant women with hypertension, the goal of treatment is to minimize short-term risk of elevated blood pressure in the mother while avoiding therapy that may compromise the well-being of the fetus.</td><td>1. Measure blood pressure as part of a routine evaluation.<br>2. Followup is based on initial measurement as follows:<br><table><tr><th>SBP, mmHg</th><th>DBP, mmHg</th><th>Followup</th></tr><tr><td>< 130</td><td>< 85</td><td>Recheck in 2 yr</td></tr><tr><td>130–139</td><td>85–89</td><td>Recheck in 1 yr</td></tr><tr><td>140–159</td><td>90–99</td><td>Confirm in 2 mo</td></tr><tr><td>160–179</td><td>100–109</td><td>Evaluate in 1 mo</td></tr><tr><td>≥ 180</td><td>≥ 110</td><td>Evaluate in 1 wk</td></tr></table>(Followup screening may be modified on the basis of prior history, symptoms, presence of other risk factors, and end organ damage.)<br>3. In pregnant women with hypertension, evaluate for preeclampsia.</td><td>1. Promote the lifestyle behaviors described above (weight control, physical activity, moderation in alcohol intake) and moderate sodium restriction.<br>2. If blood pressure remains ≥ 140/90 mmHg after 3 months of lifestyle modification or if initial level is > 160 mmHg systolic or 100 mmHg diastolic, then initiate and individualize pharmacotherapy based on the patient's characteristics.<br>3. In pregnant women with hypertension, reduction of diastolic pressure to 90–100 mmHg is recommended.</td></tr>
</table>

**TABLE 8–1 *(continued)***

| Lifestyle Factors | Goal(s) | Screening | Recommendations |
|---|---|---|---|
| Lipids, lipoproteins | **Primary goal:**<br>*Women without CVD*<br>Lower risk (< 2 risk factors)LDL goal < 160 mg/dL (optimal < 130 mg/dL)<br>Higher risk (≥ 2 risk factors)LDL goal < 130 mg/dL<br><br>*Women with CVD*LDL ≤ 100 mg/dL<br><br>**Secondary goals:**<br>HDL > 35 mg/dL<br>Triglycerides < 200 mg/dL<br><br>Note: In women, the optimal level of triglycerides may be lower (≤ 150 mg/dL) and the HDL higher (≥ 45 mg/dL). | *Women without CVD**<br>Measure nonfasting total and HDL cholesterol, and assess nonlipid risk factors. Followup is based on the following initial measurements: TC < 200, HDL > 45, followup in 5 years; TC < 200, HDL < 45, followup with fasting lipoprotein analysis. TC 200–239, HDL ≥ 45, and < 2 risk factors, followup in 1–2 years. TC 200–239, HDL < 45 or ≥ 2 risk factors, followup with fasting lipoprotein analysis. TC ≥ 240, followup with fasting lipoprotein analysis. (All cholesterol values in mg/dL)<br><br>*Women with CVD*<br>Fasting lipoprotein analysis (may take 4–6 wks to stabilize after cardiovascular event or bypass surgery). | 1. Promote lifestyle approach in all women (diet, weight management, smoking avoidance, and exercise as described above). Rule out other secondary causes of dyslipidemia.<br>2. Suggested drug therapy for high LDL levels (defined as (a) ≥ 220 mg/dL in low-risk, premenopausal women, (b) ≥ 190 mg/dL in postmenopausal women with < 2 risk factors, and (c) ≥ 160 mg/dL with ≥ 2risk factors) is based on triglyceride level as follows:<br>*TG < 200 mg/dL*<br>Statin, Resin, Niacin<br>Note: ERT is an option for postmenopausal women, but treatment should be individualized and considered with other health risks.<br>*TG 200–400 mg/dL*<br>Statin, Niacin<br>*TG > 400 mg/dL*<br>Consider monotherapy with statin, niacin, fibrate, or a combination of the above. |
| Diabetes | For patients with diabetes:<br>1. Maintain blood glucose:<br>Preprandial = 80–120 mg/dL<br>Bedtime = 100–140 mg/dL.<br>2. Maintain Hb $A1_C$ < 7%.<br>3. Maintain LDL < 130 mg/dL (< 100 mg/dL if established CVD).<br>Note: Many authorities believe that LDL should be < 100 mg/dL in all patients with diabetes.<br>4. Maintain triglycerides < 150 mg/dL.<br>5. Control blood pressure. | 1. Monitor glucose and hemoglobin $A1_C$ as part of a routine periodic evaluation in women with diabetes.<br>2. Screen for diabetes (fasting glucose > 125 mg/dL or > 200 mg/dL 2 h after 75 g glucose) as part of a periodic examination in women with risk factors for diabetes, such as obesity. | 1. Encourage adoption of the American Diabetes Association Diet (< 30% fat, < 10% saturated fat, 6–8% polyunsaturated fat, cholesterol < 300 mg/d).<br>2. A low-calorie diet may be recommended for weight loss.<br>3. Encourage regular physical activity.<br>4. Pharmacotherapy with oral agents or insulin should be used when indicated. |

**TABLE 8–1** ***(continued)***

| Pharmacological Interventions | Goal(s) | Screening | Recommendations |
|---|---|---|---|
| HRT | 1. Initiate or continue therapy in women for whom the potential benefits may exceed the potential risks of therapy. (Short-term therapy is indicated for treatment of menopausal symptoms.)<br>2. Minimize risk of adverse side effects through careful patient selection and appropriate choice of therapy. | 1. Review the menstrual status of women > 40 years old.<br>2. If menopausal status is unclear, measure FSH level. | 1. Counsel all women about the potential benefits and risks of HRT, beginning at age 40 or as requested.<br>2. Individualize decision based on prior history and risk factors for CVD as well as risks for thromboembolic disease, gallbladder disease, osteoporosis, breast cancer, and other health risks.<br>3. Combination therapy with a progestin is usually indicated in a woman with an intact uterus and prescribed estrogen. The choice of agent should be made on an individual basis. |
| OCs | 1. Minimize the risk of adverse cardiovascular effects while preventing pregnancy.<br>2. Use the lowest effective dose of estrogen/progestin. | Determine contraindications and cardiovascular risk factor status of women who are considering the use of OCs. | 1. Use of OCs is relatively contraindicated in women ≥ 35 years old who smoke.<br>2. Women with a family history of premature heart disease should have lipid analysis before taking OCs.<br>3. Women with significant risk factors for diabetes should have glucose testing before taking OCs.<br>4. If a woman develops hypertension while using OCs, she should be advised to stop taking them. |

**TABLE 8–1 *(continued)***

| Pharmacological Interventions | Goal(s) | Screening | Recommendations |
|---|---|---|---|
| Antiplatelet agents/anticoagulants | Prevent clinical thrombotic and embolic events, DBP, in women with established CVD. | 1. Determine if contraindications to therapy exist at the time of the initial cardiovascular event.<br>2. Evaluate ongoing compliance, risk, and side effects as part of a routine followup evaluation. | 1. If there are no other contraindications, women with atherosclerotic CVD should use aspirin 80–325 mg/d.<br>2. Other antiplatelet agents, such as newer thiopyridine derivatives, may be used to prevent vascular events in women who cannot take aspirin. |
| β-blockers | Reduce the reinfarction rate, incidence of sudden death, and overall mortality in women after MI. | 1. Determine if contraindications to therapy exist at the time of the initial cardiovascular event.<br>2. Evaluate ongoing compliance, risk, and side effects as part of a routine followup evaluation. | Start within hours of hospitalization in women with an evolving MI without contraindications. If not started acutely, treatment should begin within a few days of the event and should continue indefinitely. |
| ACE inhibitors | Reduce morbidity and mortality among MI survivors and patients with LV dysfunction. | 1. Determine if contraindications to therapy exist at the time of the initial cardiovascular event.<br>2. Evaluate ongoing compliance, risk, and side effects as part of a routine followup evaluation. | 1. Start early during hospitalization for MI unless hypotension or other contraindications exist. Continue indefinitely for all with LV dysfunction (ejection fraction ≤ 40%) or symptoms of congestive heart failure; otherwise, ACE inhibitors may be stopped at 6 wks.<br>2. Discontinue ACE inhibitors if a woman becomes pregnant. |

Interesting differences in atherosclerotic plaque morphology between men and women have been reported. In a study of 113 cases of sudden death due to MI in men, 59 men had culprit thrombotic lesions, 69 percent of the lesions were due to atherosclerotic plaque rupture, and 31 percent were due to endothelial erosion.[62] This is in marked contrast to a study in women, which showed that 69 percent of the thrombi were associated with endothelial erosion.[63] These eroded plaques were characterized by smooth muscle cells and proteoglycans rather than lipid-laden macrophages. These data suggest that gender may influence plaque morphology, which may allow the development of gender-specific therapy in the future.

## 3. Menopause and Vascular Function

Changes in vascular function directly attributable to menopause are difficult to identify. Most studies have found little change in blood pressure associated with the menopause.[64–66] Healthy cohort studies suggest a change in endothelial function at approximately the appropriate age for the menopause to have an effect.[67,68] This is supported by a study which suggests that menopause is associated with an impairment in endothelial function, even in hypertensive women.[69] Whether these changes are due entirely to menopause or aging is not definite, as there have been no longitudinal studies to examine this question in detail. A recent review discusses menopause and vascular and ventricular function in depth.[70]

***Extensive concordant physiological evidence supporting an important role of HRT in the modulation of vascular function.***

### 3.1 Hormone Replacement Therapy and Cardiovascular Function

There is extensive concordant physiological evidence supporting an important role of HRT in the modulation of vascular function. This is particularly true in acute and chronic arterial endothelium-dependent effects, both in the periphery and in the coronary arteries. Apart from effects on responsiveness, arterial structural remodeling changes due to estrogen are suggested by animal models but have not been universally supported by large human cross-sectional studies. Clinical studies of aortic compliance have also led to inconsistent results. Studies of ventricular function are still limited and do not allow definitive conclusions. A consistent problem is the lack of prospective studies. Interpretation of studies which suggested a positive effect of HRT is limited by relatively small numbers and nonrandomized or unblinded designs.

### 3.2 Hormones and the Vessel Wall

A range of alternate mechanisms explaining the nonlipid-related cardiovascular benefit attributable to HRT have been proposed, particularly effects of hormones on the arterial wall. These actions are varied and include induction of endothelial prostacyclin,[71] improvement or restoration of endothelial function,[72,73] NO release,[74,75] attenuation of endothelin effect[76] and production,[77] calcium blockade,[78,79] direct effects on vascular depolarization[80] and smooth muscle relaxation,[81] and modulation of autonomic function.[82] Early reports of increases in renin or renin substrate may have been related to the higher estrogen doses used previously,[83] as recent work suggests that ERT is associated with decreased plasma renin substrate.[84]

A common endpoint of many estrogen actions, suggesting a beneficial effect, involves arterial vasodilatation. Systemic vasodilatation due to HRT has been associated with increased cardiac output and diminished systemic vascular resistance, both in experimental animals and in humans.[85,86] Coronary vascular reactivity has also been used as a surrogate marker for beneficial cardiovascular effect. Numerous studies have shown improvement in coronary diameter in response to estrogen,[87–89] particularly in the presence of atherosclerotic dis-

ease. Clinical studies have also shown decreases in exercise induced myocardial ischemia which may be due either to improved hemodynamics or direct coronary vasomotion.[90,91]

It has been suggested that the mechanism of estrogen action may vary according to the concentration of estrogen, with low concentrations relying on induction of NO release from the endothelium and higher concentrations being associated with smooth muscle relaxation and, therefore, endothelium-independent mechanisms.[92] A number of studies have confirmed improved endothelial function in postmenopausal women receiving HRT, both estrogen alone[72] and estrogen in combination with progesterone.[93]

The mechanisms by which estrogen alters vascular function have received extensive study, and the molecular mechanisms of its actions have recently been reviewed. (See also ch. 5.)[94] ERα is found on vascular smooth muscle cells[95] as well as endothelial cells.[96] Estrogen has also recently been shown to have nongenomic activity via ERα on the cell surface,[97] helping to explain acute vascular effects of estrogen found in numerous studies. The acute rapid ER-dependent but nongenomic actions result from activation of the MAPK cellular signaling pathway in a number of different cells.[98] The other known ER, ERβ, has been suggested to explain estrogenic action on both vascular smooth muscle and endothelial cell activity in ERα-deficient mice.[99]

Apart from estrogen, other sex hormones have significant vascular effects. Because estrogen is prescribed in combination with a progestin in women with an intact uterus, recent work has examined the modulating effect that this might have on cardiovascular function. Importantly, while the beneficial fibrinolytic[100] and lipid effects[101] of estrogen do not appear to be impaired with concurrent medroxyprogesterone use, experimental[102] and clinical studies[103] show how beneficial vascular effects of estrogen can be reversed by MPA. If further substantiated, these findings could be important in understanding results of some recently published studies, such as the HERS,[101] the first large trial conducted in postmenopausal women with CHD. (See sec. 4.2 below.) The effects of ERA[104] also showed no benefit either from estrogen or estrogen plus progestin in an angiographic study.

### 3.3 Selective Estrogen Receptor Modulators

***SERMs have been developed to avoid the potential harmful effects of estrogen on a number of tissues, including the breast and uterus.***

SERMs have been developed to avoid the potential harmful effects of estrogen on a number of tissues, including the breast and uterus. They appear to share the beneficial effects of estrogen on bone and lipids but are not associated with an increased risk of breast or uterine carcinoma, with the exception of tamoxifen, which increases endometrial cancer risk in women aged 50 years or older.[105] The possibility of a beneficial effect of SERMs on the cardiovascular system is intriguing. SERMs, such as raloxifene, have effects on both ERα and ERβ, which may be important in its vascular actions.[106] It is possible that SERMs may significantly contribute to the improvement of women's health in this century.[107] Evidence is emerging that the newer SERMs may have effects on cardiovascular and other systems which may contribute to improvement in vascular health and function. Research over the next 5 to 10 years may provide definitive data as to whether the newer SERMs will provide cardioprotection in postmenopausal women.

#### *3.3.1 Effects of SERMs on the Vasculature*

SERMs may have beneficial effects on the cardiovascular system in a way similar to estrogen. Randomized studies with cardiovascular endpoints are in progress.

#### *3.3.2 Effects of SERMs on Serum Lipids and Myocardial Infarction*

Studies investigating the effects of SERMs on serum lipids and lipoproteins have demonstrated

similar effects in both patients with breast cancer and healthy women. The SERMs tamoxifen and raloxifene reduce total cholesterol, LDL cholesterol, and Lp(a).[108–110] These changes in lipid profile may be clinically favorable with regard to the incidence of CVD.[10,111] Data from randomized breast cancer clinical trials suggested that tamoxifen may be of benefit in protecting women from MI. Three adjuvant trials show a reduction of cardiac morbidity in patients with low risk of death from breast cancer when treated with tamoxifen,[112–114] although none of them had been designed for this purpose. The results of a cardiovascular endpoint study—RUTH (Raloxifene Use for The Heart)—will test whether raloxifene HCl (60 mg/day), compared with placebo, will reduce the combined endpoint of non-fatal MI, CHD death, and hospitalized unstable angina other than MI (primary outcome) in postmenopausal women at high risk of cardiac events.[115] A co-primary endpoint of invasive breast cancer incidence has been added to the primary endpoint.

#### *3.3.3 SERMs and Vascular Reactivity*

***The PEPI trial confirmed that there was no effect of any hormone regimen on blood pressure in normotensive postmenopausal women.***

There are few data on the effect of SERMs on the vasculature in humans. One report has shown a beneficial effect of droloxifene on brachial flow-mediated dilatation. Two conflicting reports have been published regarding the effect of raloxifene on atherosclerosis, one showing no effect in ovariectomized cynomolgus monkeys,[116] the other showing beneficial effects in sexually mature female rabbits.[117] The effects of raloxifene on coronary artery vasoreactivity in vitro showed significant dose-dependent relaxation of coronary arterial rings with endothelium by an endothelium- and NO mediated effect.[118]

### 3.4 Phytoestrogens

It has been suggested that phytoestrogens represent a "natural SERM." Genistein has approximately only 4 percent of estrogen's affinity for ERα, but more than 80 percent of estrogen's affinity for ERβ.[106] This marked difference may contribute to the conflicting findings on controlling menopausal symptoms.[119,120] The ERβ activity appears to be sufficient in in vitro studies to inhibit smooth muscle cell proliferation and migration compared with 17β-estradiol.[121] At least one study has shown that supplemental isoflavones may improve arterial stiffness in postmenopausal women.[122] A number of phytoestrogens, including genistein and daidzein, have calcium antagonistic properties in experimental coronary studies.[123]

***Cross-sectional data show that as women age they gain body weight, their blood pressure rises, and their levels of serum LDL increase.***

### 3.5 Hormone Replacement Therapy and Hypertension

Because hypertension is so prevalent in menopausal women and even low-dose contraceptive pills continue to be associated with excess hypertension,[124] there has been controversy over whether HRT may be beneficial or detrimental.[125] While most studies do not show an increase in blood pressure in response to HRT,[101,125,126] occasional patients have idiosyncratic increases in blood pressure in response to estrogen.[127,128] This may be related to excessive renin activation in these subjects.[127] Most case reports date from an era of higher estrogen dose, and it may be that current regimens would not incite such a response. A recent study using a current HRT regimen found, in general, a decrease in plasma renin substrate associated with treatment.[84] It has also been recognized that the type and dose of supplemental estrogen may be important in determining blood pressure response.[129] A well conducted crossover study of two doses of

estrogen found a small, but significant, decrease in systolic and diastolic blood pressure largely due to a prominent fall in peripheral resistance.[130] Results from the PEPI trial confirmed that there was no effect of any hormone regimen on blood pressure in normotensive postmenopausal women.[126]

## 4. The Menopause and Coronary Risk Factors

Cross-sectional data show that as women age they gain body weight, their blood pressure rises, and their levels of serum LDL increase,[131] with little change in triglycerides and a slight reduction in HDL cholesterol.[64] Other blood factors such as serum fibrinogen and plasminogen activator inhibitor (PAI), which are powerful predictors of CHD in women and men are significantly increased in older women.[132] Abnormal glucose metabolism is more common in older women, with some reports showing approximately 30-percent reduction in insulin sensitivity.[133] Older postmenopausal women are more likely to have endothelial dysfunction,[69] which contributes to an impairment of vascular function and may synergize with the adversely altered lipid metabolism and decreased fibrinolytic tendency. These factors may collectively contribute to the increased incidence of CHD in older women.

It is not clear whether the adverse changes in risk factors are an age effect or are due to lowered estrogen levels as women go through the menopause. Cohort studies following women as they approach and pass through the menopause have yielded conflicting results, especially in regard to HDL cholesterol. Some concluded that the menopause is not associated with change in HDL cholesterol, while others concluded that the menopause is associated with a decline in HDL levels.[134,135] The most recent of these studies found an unexplained rise in HDL cholesterol prior to the FMP, followed by a decline thereafter; thus, there was no net effect.[136] The levels of HDL cholesterol 3 years before the menopause were identical to those 3 years after menopause. All other changes in the risk factors measured, including body weight, blood pressure, LDL cholesterol, and triglycerides, were related either to increasing age or to a simultaneous change in one of the other risk factors (in particular, increases in body weight).

### 4.1 The Effect of Hormone Replacement Therapy on Risk Factors

#### *4.1.1 Lipids*

Many studies have shown that that HRT lowers total cholesterol irrespective of the type or route of administration.[137,138] The LDL cholesterol-lowering activity of estrogen occurs by an up regulation of apolipoprotein-B–100 receptors. HDL cholesterol increases, particularly the $HDL_2$ subfraction, by an inhibition of hepatic lipase activity.[139] Although transdermal estrogen has a similar effect on LDL cholesterol, it has a less-marked effect on HDL cholesterol levels because of a lack of the first-pass liver effect.[140] Oral estrogen decreases LDL cholesterol by about 10–15 percent, increases HDL cholesterol by 10–15 percent, increases triglycerides by 20–25 percent, and decreases Lp(a) by about 20 percent.[126] The type and route of administration of estrogen are more important for its effects on plasma triglycerides than they are for its effects on cholesterol. While CEEs result in a 25-percent increase in triglycerides,[126] transdermal estrogen either has no effect or decreases triglycerides.[140]

***Observational studies comparing current hormone users with non-users have shown consistent reductions in CHD risk of 35–50 percent.***

Progestogens have differing effects on lipids and lipoproteins, dependent on the androgenicity of the particular agent. Testosterone-derived progestins reverse the HDL-increasing effect of estrogen[140] because of an increase in hepatic lipase activity. The less androgenic C–21 progestins do not impair the estrogen-induced increase in HDL cholesterol to any great degree. Androgenic progestins result in

a lowering of triglycerides,[140] and the more androgenic steroids lower Lp(a) by approximately 20 percent.[141,142] This effect could prove beneficial as Lp(a) may be an independent risk factor for CHD in women.[15] Recent evidence from HERS suggests that Lp(a) is an independent risk factor for recurrent CHD events.[14] In the placebo arm of the study, women in the second, third, and fourth quartiles of Lp(a) levels had increased relative hazards compared with the lowest quartile. Treatment with HRT significantly reduced Lp(a) levels compared with placebo. In a randomized subgroup comparison, women with higher baseline Lp(a) levels had a less adverse-trend during the first year and more benefit thereafter.

#### *4.1.2 Inflammatory Factors*

Two studies of oral CEEs plus or minus MPA or progesterone have shown rapid increases in the concentration of the inflammatory factor CRP and a reduction in the concentration of soluble E-selectin.[143] In a cross-sectional study, CRP levels were increased in postmenopausal women taking HRT,[144] and in postmenopausal women exposed to short-term HRT of either oral estrogen or estrogen sequentially combined with a progestin.[145] In another prospective randomized controlled study of oral 17β-estradiol combined with 5 or 10 mg of dydrogesterone, there was a 15-percent decrease in plasma levels of endothelin-1, a 21-percent decrease in soluble thrombomodulin, and a 14-percent decrease in von Willebrand factor.[146] These changes were observed at 3 months and sustained after 15 months. It is possible that the increase in CRP is due to first pass effect on hepatic synthesis of the protein, while the decrease in markers of endothelial function and other inflammatory markers is due to direct vascular effects. It is unclear whether estrogen increases or decreases vascular inflammation or whether different forms, doses, and routes of administration have different effects on vessel physiology. One potential mechanism by which there may be an early adverse effect (such as that found in the HERS trial) followed by a later favorable effect is through effects on matrix metalloproteinases (MMP).[147] Preliminary reports indicate that MMP–9 is increased markedly by estrogen and may play a role in the destabilization of vulnerable plaques, thus precipitating a clinical event. However, over the long term, MMP–9 may help keep vessels compliant as it may play a role in removing excess connective tissue. Monocyte activation is associated with atheromatous plaque disruption and acute coronary syndromes (ACS). Increased serum concentration of neopterin, a pterydine derivative secreted by macrophages after stimulation by interferon-gamma, has been observed in patients with ACS as compared with control subjects and patients with stable angina pectoris.[148] Women with unstable angina have significantly higher neopterin concentrations than women with chronic stable angina. Neopterin concentrations may be a marker of risk in women with CHD.[149] HRT has also been shown to significantly reduce the levels of the cell adhesion molecules E-selectin, intracellular adhesion molecule 1 (ICAM–1) and vascular cell adhesion molecule–1 (VCAM–1) with similar magnitude of reduction from placebo values in women on CEE alone compared with women on combination HRT.[150]

***Standard prevention therapies, including lipid lowering, are as effective in women as in men.***

#### *4.1.3 The Effect of Hormone Replacement Therapy Combined With Other Lipid-Lowering Agents*

A number of studies have recently reported the effects of a combination of statin and HRT on serum lipid levels in menopausal women.[151–154] One study also assessed the vascular effects of this combination in hypercholesterolemic postmenopausal women.[155] The studies investigated the effect of differing doses of CEEs, either alone or combined with MPA, and compared the lipid-lowering effects to simvastatin or pravastatin.

Overall, these studies show that oral CEEs plus MPA in combination with a statin is complementary, in that the statins are better at lowering LDL cholesterol levels, the hormones are better at raising HDL cholesterol levels, and the effects on triglycerides cancel each other: thus the combination yields the most optimal lipid profile. The combination is only modestly additive, that is, hormones add little to the LDL-lowering effect of statins, and statins add only modestly to the HDL-raising effect of hormones. Hormones reduce Lp(a) levels, while statins do not. No studies have yet been published comparing other types and routes of administration of HRT combined with a statin.

In one study,[155] 28 women were randomized to continuous equine estrogen (0.625 mg daily), simvastatin 10 mg, and their combination daily for 6 weeks. As shown in the previous studies, all therapies lowered total and LDL cholesterol levels from baseline, with a greater effect on LDL cholesterol from simvastatin and from the combination of HRT and simvastatin. This study also assessed the vascular effects of this therapy; flow mediated dilatation of the brachial artery improved on CEE, simvastatin, and continuous equine estrogen combined with simvastatin, and this was similar among the therapies. Only therapies including CEE lowered levels of PAI–1 and the cell adhesion molecule E-selectin. Only therapies including estrogen improved markers of fibrinolysis and vascular inflammation. Thus, it may be that such a combination will be synergistic in vascular protection.

#### *4.1.4 Coagulation Factors*

The effects on coagulation factors are complicated, diverse, and contradictory. For example, lowering of fibrinogen and PAI–I could be counterbalanced by increases in factor VII and decreases in antithrombin III. In general, it appears that estrogen is procoagulant but, at the same time, profibrinolytic.[156] The net effect is likely to be procoagulant, as evidenced by the observational studies and the HERS clinical trial (see elsewhere). However, the net effect of estrogen on coagulation can depend on the form of estrogen used and on the dose, route, and duration of therapy. There may be critical differences between oral and transdermal delivery of estrogen. In contrast to oral administration, transdermal estrogen does not result in any measurable perturbation of coagulation factors.[156]

### 4.2 Hormone Use and Prevention of CHD Risk

Observational studies comparing current hormone users with non-users have shown consistent reductions in CHD risk of 35–50 percent. In the Nurses' Health Study, the risk reduction was seen at the most commonly used dose of CEEs (0.625 mg/day).[157] There appeared to be a similar risk reduction at the lower dose of 0.3 mg/day, but this was not statistically significant. At higher doses, there was no apparent benefit. The findings from these observational studies have been important in promoting the belief that HRT prevents CHD. However, the findings have to be viewed with caution because several sources of potential bias could result in an overestimation of potential benefits and an underestimation of risks.[158,159] These biases include that women who elect to take hormones are healthier, and those that remain on hormones for many years are by definition good compliers and are under medical surveillance. (See also ch. 4 for biases in sampling.) Thus, they would be taking other steps to improve their health, and early detection and treatment of risk factors would also reduce disease risk. Furthermore, women who stop therapy often do so because of the development of a health condition; thus those who remain on therapy are the healthy survivors. These biases

***Women are approximately half as likely as men to receive known beneficial therapies, such as beta-blocking agents, aspirin, thrombolysis, acute cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), or bypass surgery.***

may account for a substantial proportion (or all) of the apparent CHD risk reduction.

The information on the effects of hormones on lipids and markers of vascular function must be seen in the light of one very important fact: no clinical trial has yet shown a beneficial effect on any CVD. To the contrary, all the evidence to date suggests a harmful effect, at least in the first years of taking HRT. With the exception of the pooled data from a number of small short-term studies,[160] the clinical trials have all been in the area of secondary prevention. In men with CHD given higher doses of estrogen, the trials were stopped early for safety reasons after there was a higher rate of cardiovascular events in the treatment group than in the control group.[161] In HERS, women assigned to daily oral CEE plus MPA also experienced a higher rate of CHD events versus placebo in the first year, with no difference in the second year and with a trend toward decreased risk in the treatment group in the final 2 years. Over the entire 4.1-year study period, there was no difference between the groups. A reanalysis of the Nurses' Health Study observational data for women with prior heart disease disclosed a similar pattern of early risk followed by apparent benefit. The first placebo-controlled angiographic trial of estrogen or estrogen plus progestin also failed to show benefit in women with CHD.[104] Transdermal estrogen and progestin also failed to show benefit in a preliminary report of a randomized trial in women with CHD.[162] No clinical trial data on the role of HRT in primary prevention are available yet, but at least two large studies testing both estrogen and estrogen plus progestin are being conducted.[163] (WHI and the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)). The first of these, the large WHI trial of HRT in the United States, includes women predominantly without prior CVD and has arms testing daily CEE alone and CEEs with MPA versus placebo. All WHI participants were informed of an increased risk associated with active treatment for each of heart attacks, strokes, and blood clots in the legs and lungs during the first 2 years after enrollment.[164] The vast majority (> 90 percent) of participants did not have prior CVD, and the subgroup with prior disease did not account alone for the findings. Over time, the differences between the active treatment and placebo groups seemed to become smaller. The trial is continuing (estimated followup of 9 years) in order to assess long-term benefits and risk of HRT. There is a need for a clinical trial of transdermal estrogen, which may have less thrombotic potential than oral estrogen.

***Gender remains a significant independent predictor of death after adjusting for other risk factors, such as older age, diabetes, and hypertension following PTCA.***

#### 4.3 Statin Use in Women and Reduction of CHD

Since evidence for a protective effect of estrogen is currently lacking, it is encouraging that the standard prevention therapies, including lipid lowering, are as effective in women as in men. This is not surprising since the RRs associated with blood lipids are the same in middle-aged women as in men.[8] One difference worth noting is that a combination of metabolic risk factors may occur more frequently in women and may account for a higher proportion of the CHD burden than in men.[165] For lipid lowering, the pooled data from the major statin trials show that women had a 29-percent (CI 13–42 percent) risk reduction, similar to the 31 percent (CI 26–35 percent) found in men.[9] From these data it has been calculated that 31 women and 27 men have to be treated to prevent 1 major coronary event. A gender bias does exist even in the statin trials that have been reported.[166] In the secondary prevention trials conducted, 31,683 patients were randomized with a combined mean age of 58.1 years, and only 23 percent of the trial population were women. The figures are even worse for primary prevention: in the four primary prevention trials published, only 10 percent of the study population, out of a total of 14,557 subjects,

were women. It can be concluded that extrapolation of evidence from these trials to older people and women requires further evaluation.

### 4.4 Other Prevention Therapies in Women

Similar to the lipid-lowering trials, CHD prevention through treatment of hypertension is as effective in women as in men, and ACE inhibitors are as effective in preventing CHD in women as in men.[167–169] In the recently published Heart Outcomes Prevention Evaluation (HOPE) study, 2,480 women were enrolled as a part of larger study to determine the effect of the ACE inhibitor ramipril (10 mg once daily orally) versus placebo.[169] The study investigated the effect of this therapy over a 5-year period on the risk of the composite endpoint: MI, stroke, or death from cardiovascular causes. The study participants were patients at high risk for cardiovascular events with a mean age of 66 years an without left ventricular dysfunction or heart failure. Ramipril decreased the risk of the primary outcome significantly in women as well as men. There was also a significant decrease in secondary outcomes, such as revascularization and hospitalizations for heart failure. The novelty of this study is that ramipril significantly reduced the rates of the primary endpoint in a broad range of high-risk patients who were not known to have low ejection fraction or heart failure. In particular, this beneficial effect was shown in women with diabetes mellitus. The trialists that estimated the treatment of 1,000 patients with ramipril for 4 years prevented about 150 events in approximately 70 patients. Aspirin and beta-blockers are also effective for secondary prevention in women.[170,171] Thus, although efforts to prevent CHD in women are successful using the same approaches as in men, more data are still required.

## 5. Myocardial Infarction: Prognosis

Initial evaluation suggests that gender affects the course of acute MI in the general population. However, after adjustment for baseline differences, the gender disparities in the outcomes become more uncertain. In a study of 204 consecutive cases (99 men and 105 women) older than 75 years of age and admitted with the first acute MI, elderly women experienced a more complicated hospital course than men. The higher mortality risk (40 percent versus 23 percent) seemed to be related more to the impact of cardiovascular risk factors on left ventricular function than to gender itself.[172] The Framingham Heart Study confirmed a greater 1-year mortality in women compared with men (44 percent versus 27 percent).[173] Early hospital mortality is also greater in women than in men (16 percent versus 11 percent).[174,175] The larger placebo-controlled trials, such as the International Studies of Infarct Survival-1 and -4 (ISIS–1 and ISIS–4), both suggested an increased short and long-term mortality in women.[176,177] More recent data from the National Registry of Myocardial Infarction (NRMI) suggest that, after MI, younger women (but not older women) have higher rates of death during hospitalization than do men of the same age.[178] Data from the Swedish National Acute Myocardial Infarction Register confirms this observation.[179] Much of the excess mortality seen in young women in this study was associated with diabetes mellitus. Some other reasons for these observations is that women are approximately half as likely as men to receive known beneficial therapies, such as beta-blocking agents, aspirin, thrombolysis, acute cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), or bypass surgery; however, age probably still plays a major role in these differences.[171] Sex differences in the presentation and outcome of patients with ACS have been reported in the Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) cohort.[180] In this study, which enrolled 3,662 women, women had more complications than men during hospitalization, had a higher mortality rate at 30 days (6 percent versus 4 percent, $p < 0.001$), but had similar rates of reinfarction. It is of interest that among patients with unstable angina, female sex was

associated with an independent protective effect. It was concluded from this study that some of the differences observed may reflect pathophysiologic and anatomical differences between men and women.

## 6. Percutaneous Transluminal Coronary Angioplasty

Most reports suggest that gender remains a significant independent predictor of death after adjusting for other risk factors, such as older age, diabetes, and hypertension, following percutaneous revascularization. Early studies suggested that women had a greater risk than men of procedural and postprocedural complications, including death and MI following PTCA.[181] Women have been found to suffer more acute vessel closure than men,[182] possibly related to their smaller vessel diameter. When acute closure does occur, women are more likely to die as a consequence of this.[183] An important contributor to higher procedure-related mortality in women is the greater age and coronary risk factor profile in women.[181,184] Nonetheless, analysis of the 1993–94 NHLBI registry has shown that despite their greater risk profile, both clinical success and mortality have improved twofold to threefold in women undergoing PTCA.[185] Many of the reported studies show that sex-related differences in mortality rate after intervention antedate the use of stents, platelet inhibitors, and other recent advances in coronary intervention.[186] In particular, intracoronary stent implantation (with optimal expansion) and ticlopidine have greatly reduced the incidence of acute vessel closure and significantly reduced the combined incidence of death, MI, and urgent revascularization after coronary intervention.[187] More recently, coronary artery stenting has become a very important catheter-based intervention for patients with CHD.[188] One-year outcomes of women with CHD undergoing coronary artery stenting are similar to those of men.[189] There is, however, a sex difference in the prognostic value of baseline characteristics, the strongest being diabetes in women. Other efforts at treatment synergy between intracoronary stenting and platelet IIb-IIIa inhibition are encouraging, showing an improvement in clinical outcomes of primary angioplasty in acute MI in both men and women.[190] The combination of abciximab and stenting was more favorable than balloon angioplasty, with improved angiographic and clinical results at 30 days. Analysis of the Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) data shows that diabetic women treated with a combination of coronary stenting and abciximab resulted in a significant reduction in 1-year rate of death, MI and target vessel revascularization compared with stent-placebo or balloon-abciximab therapy.[191] These recent advances in techniques may have changed the impact of acute vessel closure as a cause of death in women. The risk of acute complications was documented only in women undergoing PTCA for stable angina pectoris and not ACS. Long-term outcome is similar in the two sexes once the initial PTCA had been successfully performed.[192] Data from the Primary Angioplasty in Myocardial Infarction (PAMI) trial suggest that the two most powerful determinants of freedom from death, reinfarction, and recurrent ischemia are young age and treatment by primary angioplasty.[193] This initial benefit of primary angioplasty is maintained over a 2-year followup.[194] Recent reports from this database would suggest that coronary stenting provides even greater benefit than balloon angioplasty in the acute MI setting.[195] Recent data provide evidence that in primary PTCA for acute MI, gender is not an independent predictor of 30-day and 7-month survival after control for baseline characteristics. However, mortality was much higher in women both at 30-day followup (10 percent versus 0.9 percent) and during a mean 7-month followup (15 percent versus 4.4 percent). Women

***Despite a similar prevalence of heart failure in women compared with men, women have largely been excluded from clinical trials of heart failure.***

also experienced more unfavorable cardiovascular events, such as recurrent unstable angina or acute MI, and target vessel revascularization than men.[196]

### 6.1 Hormone Replacement Therapy and PTCA

Some studies have reported a benefit of outcome of PTCA in postmenopausal women if they were already receiving HRT. In a study of 428 patients, postmenopausal women divided into two groups based on ERT at the time of the procedure, there appeared to be protection against clinical coronary events in those women taking HRT.[197] This benefit appeared to be independent of age, smoking, presence of diabetes mellitus, or the number of diseased coronary vessels. HRT did not, however, reduce the repeat revascularization procedures, suggesting no effect on restenosis.[197] One study suggested a decrease in restenosis in women using estrogen, which was particularly apparent in women undergoing atherectomy, an effect which could relate to this procedure.[198] An improved long-term outcome after PTCA in women on HRT was also reported by another group.[199] In this observational study women taking ERT prior to intracoronary stenting had a significantly reduced target lesion revascularization requirement after a three year follow up when compared to women not taking estrogen prior to the procedure. This adds support to the notion that women should continue ERT after intervention if they are taking it prior to the intervention. Overall, HRT appears to be beneficial in women who continue to take it after percutaneous revascularization procedures; however, these conclusions are based on observation and could be confounded by a number of variables.

## 7. Coronary Artery Bypass Graft Surgery

Women undergoing coronary artery bypass graft (CABG) surgery are, on the whole, older than males and more frequently have associated risk factors, such as diabetes and hypertension. They are also more likely to present with unstable angina consequently, resulting in urgent/emergency surgery. It is not surprising, therefore, that women show higher rates of mortality[200] and recurrent angina.[201] Adverse operative and long-term mortality was shown in a large study, the National Cardiac Surgery Database of the Society of Thoracic Surgeons (STS), which compared outcomes in more than 97,000 women with those in 250,000 men.[202] In the Bypass Angioplasty Revascularization Investigation (BARI) study, a stable population of 489 women with symptomatic multivessel CHD was randomized to CABG surgery or PTCA.[203] Although the age-adjusted mortality rate suggested that women and men undergoing these procedures should have a similar 5-year mortality, when these were adjusted for multiple risk factors, female sex was an independent predictor of improved 5-year survival after surgery. This was a study of stable patients and patients, requiring urgent CABG surgery were excluded, which may have contributed to the more favorable result.[203]

***Women undergoing CABG surgery show higher rates of mortality and recurrent angina.***

Effective secondary prevention programs do not appear to be effectively instituted in women following CABG surgery. After CABG surgery, women continued to have high cholesterol levels, putting them at higher risk for future events.[204] This is particularly important since in women aggressive cholesterol lowering in women delays saphenous vein graft atherosclerosis and should be recommended to all women undergoing this procedure.[205] This obviously may contribute to poorer postsurgical survival.

### 7.1 Quality of Life After CABG Surgery

Women generally report a worse quality of life after CABG surgery than men. In a study of 212 women who underwent CABG surgery in 1988–1991, quality of life was assessed.[206] Women were older than men with more concomitant dis-

eases preoperatively. Quality of life was improved on all postoperative occasions for both sexes. Improvement in the physical activity score was greater in males, although this was not significant. It appears that the quality of life is significantly improved after CABG surgery in both sexes, and there appears to be a complex association between improvement in various aspects of quality of life and gender.[205] Women's patterns of exercise following cardiac rehabilitation are well below the recommended guidelines for exercise after cardiac events.[207] In 40 women who had MI or CABG surgery, exercise frequency and duration intensity were measured. In a 3-month study, only 50 percent of the women were still exercising regularly, suggesting that there is considerable room for improvement in establishing exercise regimens after MI or CABG surgery. Women are less likely to be referred to rehabilitation.

***Despite similar stroke rates, women are more likely than men to die of stroke, and this is possibly related to the age at which stroke presents. About 16 percent of women die of stroke compared with only 8 percent of men.***

## 8. Heart Failure

Despite a similar prevalence of heart failure in women compared with men,[208] women have largely been excluded from clinical trials of heart failure. As discussed earlier, women tend to be older at presentation with cardiac disease and may fall outside recruitment guidelines. Secondly, women are more likely than men to have diastolic heart failure and may be excluded when systolic ejection fraction is an entry criterion.

Two large studies have reported improved survival in women with heart failure.[209,210] Of the randomized trials with beta-blockers in heart failure, the U.S. Carvedilol Heart Failure Study group found a statistically significant reduction in the number of deaths in both women and men with heart failure.[211] Other large beta-blocker trials have not been able to discern a sex-specific mortality difference.[212–214] In the trials of ACE inhibitors in heart failure, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS-I) did not show a reduction in mortality in women.[215,216] However, most trials contain such small numbers of women that they are unable to discern a specific mortality benefit for women. A meta-analysis of ACE inhibitor trials has shown a similar survival benefit for both women and men.[217] In the Acute Infarction Ramipril Efficacy (AIRE) study of ramipril in patients with post-MI left ventricular dysfunction, there was a significant mortality benefit in both sexes.[218] Three other studies of ACE inhibitors in patients with left ventricular dysfunction after MI did not show a significant mortality benefit for women. Again, this may be due to the relatively small numbers of women included in these trials.[219–221]

## 9. Stroke

Despite similar stroke rates,[222] women are more likely than men to die of stroke, and this is possibly related to the age at which stroke presents. About 16 percent of women die of stroke compared with only 8 percent of men.[222] Age is an important predictor of survival in stroke victims, and as the incidence of stroke is increased in older women, this contributes to the adverse mortality. The main risk factors for stroke are fairly consistent and nongender dependent. Hypertension probably is the most important, with diabetes mellitus, cigarette smoking, CHD, atrial fibrillation, and transient ischemic attacks comprising the major other risk factors.[223] Hypertension is a major risk factor for stroke, with about a 45-percent increase in stroke risk for every 8 mmHg increase in diastolic blood pressure.[19] Unlike many cardiovascular trials, hypertension treatment has been definitively shown to substantially reduce the morbidity and mortality in women following stroke. Studies such as the Swedish Trial in Old Patients (STOP) and

SHEP have shown that drug treatment reduces the incidence of stroke in hypertensive women.[167,168] Current smoking is associated with an increased risk of stroke, and in the Nurses' Health Study this increased the RR for ischemic stroke by 2.5.[224,225] Diabetes mellitus doubles the risk of ischemic stroke, and also increases the mortality associated with stroke. Cardiovascular conditions such as abnormal left ventricular (LV) wall motion, increased LV mass, carotid artery stenoses, and atrial fibrillation are significantly associated with an increased risk of stroke. Although elevated blood cholesterol is not a powerful risk factor for stroke, lowering of LDL cholesterol with statins reduces stroke risk. A meta-analysis of the statin trials done for CHD risk reduction showed a statistically significant 29-percent risk reduction for stroke, accompanying the 33-percent risk reduction for CHD.[222,226] Transient ischemic episodes are also related to an increased risk of subsequent stroke.[227] Use of HRT has been associated with a lower risk of fatal stroke, but no change in overall incidence of stroke, compared to nonusers. In the Nurses' Health Study, current hormone use was associated with an increased risk of ischemic, but not hemorrhagic, stroke. For all strokes, there was a dose-response effect, with higher doses of estrogen associated with a higher risk.[228]

In terms of active treatment of stroke, there are no clear recommendations. Early administration of aspirin seems to reduce the stroke-related death and recurrence, as shown in the Chinese Acute Stroke Trial (CAST).[229,230] Where transient ischemic episodes and stroke are associated with atrial fibrillation, warfarin may reduce the risk of stroke.[231] Carotid endarterectomy and aspirin therapy may be helpful in symptomatic severe carotid stenoses.[232] The only clinical trial to assess the effect of continuous CEEs combined with MPA is the HERS trial.[233] Over a followup of 4.1 years, 149 women had 1 or more strokes out of a total of 2,763 women. HRT was not significantly associated with risk of nonfatal or fatal stroke or transient ischemic attack. It was therefore concluded that HRT had no significant effect on the risk of stroke in this higher risk group of menopausal women with CVD.

## 10. Peripheral Vascular Disease

Peripheral vascular disease occurs relatively commonly in women, and like all CVD, there is an accelerated incidence with age in women.[234] Smoking is the most prevalent risk factor for peripheral vascular disease in women, as it is in men.[235] Insulin resistance, increased BMI, elevated fibrinogen, and elevated blood pressure are also risk factors.[235–237] Cessation of smoking and treatment of the underlying metabolic problem, if possible, may lead to improvement. Peripheral vascular disease carries an increased risk for CHD, which is nongender-dependent.[237] If surgery is indicated for severe peripheral vascular disease, smoking cessation is essential, and antiplatelet therapy may also be helpful.[238,239] The effect of HRT on peripheral vascular disease is not known.

***There is an increase in risk of venous thromboembolic events in women taking estrogen compared with those that do not.***

## 11. Venous Thromboembolism

Recent epidemiological studies and limited clinical trial data have shown consistently that there is an increase in risk of venous thromboembolic events in women taking estrogen compared with those that do not. The studies to date indicate that there may be a fourfold increase in RR initially, with a persistent twofold increase in risk thereafter.[240–243] The increased risk for venous thromboembolism was similar in women using an estrogen plus a progestin.[240,243] In unselected women, observational studies report an annual incidence of 6–18 events per 10,000 in subjects of all ages; thus a twofold increase in risk due to HRT might result in an

excess risk of 6–18 per 10,000 per year, and a fourfold increase might result in 18–54 excess cases per 10,000 per year. The recent large randomized HERS study reported a statistically significant increase in risk of venous thromboembolic events among women randomized to hormone compared to placebo.[101] In a more detailed evaluation of the HERS population,[244] HRT was associated with a relative hazard of 2.7 and an excess risk of venous thrombosis of 39 events per 10,000 women per year. This higher risk was associated with older age, lower limb fractures, and cancer. An interesting observation was that the relative hazard for pulmonary embolism appeared to decline with time, but the relative hazard for deep venous thrombosis did not. This may have been a chance finding. The relative hazard for venous thrombosis seemed to remain elevated for 30 days after the discontinuation of HRT. The mechanisms for the increase in venous thromboembolism may involve alterations in coagulation factors; to date, no clear mechanism has been identified. Possible interactions with deficiencies of antithrombin-III, protein C and S, the prothrombin 20210G→A mutation, and factor V Leiden may result in the increased risk for venous thromboembolism. The interaction of activated protein C resistance with estrogen or estrogen plus progestin therapy has been confirmed in at least one study.[245] Women with thrombophilia should be counseled about the further increase in risk if they use HRT. It should be recommended that women who take HRT discontinue the therapy perioperatively or following trauma during the period of immobilization and restart HRT when they return to normal activity.[246] Women at very high risk of venous thromboembolism, such as those with cancer, disorders of blood viscosity, or a prior history of venous thromboembolism should avoid menopausal HRT.[244] An association has been shown between the use of HRT and MI in postmenopausal hypertensive women with the prothrombin 20210G→A variant. Confirmation of this finding in other studies may allow better risk assessment associated with HRT in women.[247]

## 12. Pulmonary Disease

At present, we have only little knowledge of the influences of sexual hormones on respiratory function. In fact, ERs (specifically ERβ) have only recently been found in lung, thus providing a rationale to further investigate new mechanisms for otherwise well-known pathologies.

### 12.1 Asthma in Postmenopausal Women

Estrogen may play a role in the pathophysiology of asthma. A prospective review of HRT and asthma incidence in premenopausal and postmenopausal women aged 34–68 years conducted during a 135 person-year followup of 1 year, 726 new cases of asthma were documented. Postmenopausal women with no previous history of hormone use had a significantly lower age-adjusted risk of asthma than premenopausal women (RR = 0.65; 95 percent CI 0.46–0.92.). Users of 10 or more years duration had twice the age-adjusted risk of asthma compared with women who never used HRT (95 percent CI = 1.39–2.87). There appears to be a positive dose response between the daily dose of CEE and asthma risk.[248] In a study in asthmatic women, it was demonstrated that peak expiratory flow was adversely affected by HRT.

In the treatment of asthma, inhaled corticosteroids have been shown to decrease serum osteocalcin levels in postmenopausal asthmatic women.[249] Although it is clear that oral corticosteroids can result in an enhancement of postmenopausal osteoporosis, inhaled corticosteroids (beclomethasone) have also been shown to disturb Type I collagen synthesis when high-dose corticosteroids are used.[250] It is unknown, however, whether inhaled beclomethasone impairs the ability of osteoblasts to form bone. It is also unknown whether there are any detrimental longer term effects on bone with prolonged inhaled corticosteroids.

### 12.2 Miscellaneous Conditions

Pulmonary lymphangioleiomyomatosis is a disease confined to women in their reproductive, years and there are some reports that hormonal factors play a role in the development of the disease before and after the menopause and that hormonal treatment may be beneficial in older women.[251] There is one report which suggests that estrogen medication without progesterone in postmenopausal heterozygous women with cystic fibrosis can cause false-negative tests. This report suggested a balance between progesterone and estrogen for cystic fibrosis lectin activity.[252] Obstructive sleep apnea syndrome has been associated with massive obesity in the appearance of this syndrome in women.[253]

## 13. Conclusions

CVD remains the commonest single cause of female mortality and morbidity in the Western World. Despite the apparent protection offered by endogenous sex hormones in their premenopausal years, the greater longevity of women exposes them to a similar lifetime risk of coronary and other vascular disease compared to men. Women tend to develop disease at a later age than men, and are more likely to have complicating co-morbidities such as hypertension and diabetes mellitus, which contribute to poorer short term outcomes following coronary events or revascularization. The atherogenic risk profile of older women is appreciably more adverse than that of younger women, though it is uncertain whether age or hormones are the primary determinant of the evolution of the adverse risk profile. HRT has been shown to consistently and markedly improve the lipid risk profile, though a benefit on cardiovascular outcomes, such as MI or cardiac mortality, has not yet been demonstrated. A lack of benefit may be due to countervailing adverse changes in coagulation or inflammatory mechanisms. In view of gender differences in atherosclerotic plaque and the vascular remodeling effects of estrogen and progesterone, HRT may still prove to have an important role in the management of CVD in women.

Except for asthma, there appears to be little impact of menopause or HRT on the pulmonary system although further research is warranted.

## 14. Future Needs

- RCTs are urgently required to investigate the potential benefits and risks of different hormone preparations (different estrogens, progestins, combinations, and routes of administration) in women with and without prior CHD. Low-dose oral estrogens, nonoral preparations, SERMs and androgens have to be investigated in trials with clinical outcomes.
- Future clinical trials of prevention treatments and treatments of existing disease should include sufficient women to allow for an adequate assessment of the effects in women and men.
- Except for asthma, very few data exist on the effect of the menopause or HRT on the respiratory system, and investigation of the effects on important disease entities should be considered.

***CVD remains the commonest single cause of female mortality and morbidity in the Western World.***

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# Chapter 9: Osteoporosis and Oral Bone Loss in Aging Women: Risks and Therapy

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***Osteoporosis affects a large proportion of the population of elderly women throughout the world.***

## Key Points[a]

1. Osteoporosis affects a large proportion of the population of elderly women throughout the world.
2. The loss of estrogen at menopause contributes significantly to skeletal bone loss, although the mechanism is not completely understood.
3. Although there has been major progress in methods for assessing risk for osteoporotic fractures, identifying individuals at greatest need of antiosteoporosis treatment remains an unmet need.
4. Low bone mass at menopause can be due to insufficient bone acquisition during growth or bone loss during adulthood. Adequate nutrition—in particular, but not exclusively, from intake of calcium and vitamin D—and adequate physical activity are the first line of prevention against osteoporosis [C].
5. ERT has been a mainstay in the prevention and treatment of osteoporosis for menopausal women in many countries. HRT has been shown to maintain bone density and favorably influence markers of bone resorption [A]; observational data and some, but not all, controlled clinical trials have demonstrated reduced fracture risk with estrogen or hormone treatment [B].
6. SERMs are two recently developed classes of drugs that have been shown to stabilize bone mass and prevent fracture in postmenopausal women [A]. The long-term effects of these agents are not known.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.)

7. A connection between menopausal estrogen deficiency and oral bone loss is biologically plausible, and many research findings to date [C/D] are consistent with that link. Some early findings support the hypothesis that treatments used to maintain or improve skeletal bone density may favorably affect oral bone status and attendant tooth loss.

## 1. Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.[1] It has been widely recognized in recent years by the medical profession and the public as a significant health concern, especially for elderly women, among whom osteoporosis is more prevalent than among men.[2] In most cases, bone loss proceeds for many years without any symptoms, and a fracture is often the first manifestation of the disease. Although rates of osteoporosis and associated bone fractures increase with age, research findings suggest that severe bone loss and fractures are not natural consequences of aging but may be prevented or substantially delayed.

***Measurement of BMD is the most common clinical diagnostic method for assessing skeletal status and fracture risk.***

Measurement of BMD is the most common clinical diagnostic method for assessing skeletal status and fracture risk. Dual energy x-ray absorptiometry (DEXA) of the hip and spine is the preferred measurement. It is validated by many studies, has the best precision, and is correlated with fracture risk. A WHO expert panel defined osteoporosis as a BMD at the hip more than 2.5 standard deviations (approximately 30 percent) below the peak mean BMD achieved by normal young adults.[3] This same panel defined low bone mass (osteopenia) as a BMD between 1 and 2.5 standard deviations below the young adult peak bone density. The intent of these definitions was to enable cross-cultural evaluation of bone mass, using culturally specific normal ranges. The definitions have allowed a more rational estimation of the numbers of people at risk for osteoporosis-related fractures in different countries and with different ethnicities. In some countries (especially the United States) these definitions have become accepted as diagnostic cut points. While this was not the original intent, it has been a useful development in an environment where reimbursement is still aligned to diagnosis.

Using the WHO definitions of osteoporosis and low bone mass, investigators have estimated that osteoporosis poses a threat for 28 million people in the United States, 80 percent of whom are women.[4] Nationally representative BMD measurements would allow estimations of the prevalence of osteoporosis and cost of osteoporotic fractures in any country. It is important to recognize, however, that BMD is only one of a number of factors that contribute to risk for fracture and that fracture risk is the most important information for deciding who needs treatment or intervention. Other factors that contribute to risk for fracture include age, sex, general nutritional status, genetic background, and overall physical condition. The combination of such factors and BMD measurement in risk assessment appear to be of powerful predictive value.[5,6]

## 2. Epidemiology and Economic Costs of Fracture

The clinical consequence of osteoporosis is bone fracture. While most common sites of fracture are the spine, hip, and wrist, most fractures increase in frequency with age, with the exception of skull fractures.[7] In addition to increased mortality, acute and chronic back pain, disability, loss of height, decreased quality of life, and significant financial and psychosocial costs are also associated with the fractures.[8] Estimates are from age 50 years onward there is almost a 40-percent lifetime risk for any

fracture of the spine, hip, or distal forearm for white women and a 13-percent risk for white men in the United States.[9] At least 90-percent of all hip and spine fractures among elderly, white U.S. women can be attributed to osteoporosis as well as a significant proportion of all other fractures.[10] Less is known about fracture risk in minority populations, although African-American women and men have higher average bone mass values[11] and lower rates of fracture compared with white U.S. women and men.[11]

Rates of fracture and even the male:female ratio of fractures observed vary in different parts of the world.[12] In Europe, hip fracture shows an elevenfold range in apparent incidence among women and a sevenfold range among men between the various countries in data from 17 countries.[13] The highest incidence was found in the northern part of Europe, and the lowest was found in the Mediterranean area. The overall lifetime risk for any fracture in women older than 50 years in most European countries is approximately 30–40 percent,[14] similar to that for white women in the United States, despite the clear variability across cultures. In general, in Europe and elsewhere, the fracture rate is greater in urban areas than in rural areas.[15]

Vertebral fractures are notoriously difficult to detect and quantify. Lateral radiography of the spine may be required to determine their presence. Many fractures identified radiologically are asymptomatic or, even if painful, are not brought to medical attention. Only one-third of vertebral fractures present as clinically apparent fracture events.[14] Symptoms and signs (back pain, height loss, and kyphosis) are under recognized, in part because they are nonspecific. Radiological definitions based on changes in the height of vertebrae, used in clinical trials and in observational studies, can yield widely different estimates of prevalence.[16] In the United States, a prevalence of 25 percent in women over 50 years of age has been estimated.[17] The risk of vertebral fracture in U.S.[18] and Australian[19] women increases fifteenfold to thirtyfold between ages 50 and 90 years. (The risk increase for hip fracture across those years in women is fiftyfold.) Spine fractures also predict other fractures,[20] in particular subsequent spine fractures with the absolute risk of a second spine fracture being approximately 20 percent in the first year after the initial event.[21] In addition, spine fractures are associated with an increase in all-cause mortality rate.[22,23]

Medical expenditures for the treatment of osteoporosis-related fractures exceeded $13 billion in 1995, with the treatment of white women accounting for 75 percent of the costs.[24] As populations age and health care costs increase, the costs of osteoporosis-related fractures will only escalate. Projections based on population growth, particularly the marked increase in the elderly populations, suggest that fractures and their associated costs could triple in the United States by 2040,[25] and clearly this is a worldwide problem.[12] In many countries, especially in Scandinavia, there is an upward trend in fracture prevalence.[26] In part, the trend is due to the aging of the populations, with greater numbers of old and very old people in many populations across the world. However, clear age-specific increases, particularly in hip fracture rate, have been noted in the United States, the United Kingdom, and Scandinavian countries. In the United States, the increase appears to have plateaued.[27] Assuming no change in age- and sex-specific incidence, the annual worldwide total of 1.26 million hip fractures in 1990 is expected to double by 2025 as populations continue to grow older.[28] The greatest increases, due to demographic changes, are expected to be in Asia, in particular, in mainland China.[28]

***The annual worldwide total of 1.26 million hip fractures in 1990 is expected to double by 2025. The greatest increases, due to demographic changes, are expected to be in Asia, in particular, in mainland China.***

## 3. Pathogenesis of Fracture

Fracture is related to bone strength and to the force exerted upon that bone. Because bone mass and bone quality decline with age, less force is required to cause a fracture as age increases. Understanding the skeletal component of fractures requires an understanding of the process of bone remodeling. In addition, it is important to realize that a number of factors can contribute to fracture risk by increasing the likelihood of trauma and that they can be independent of bone mass.

### 3.1 Bone Growth and Remodeling

During childhood, bone grows linearly and can be reshaped to fit the stresses placed on it by the process of modeling. At the cessation of growth, modeling virtually ceases, and bone is continually replaced, but not reshaped, by remodeling, although modeling still occurs, for example, after a fracture, when realignment is necessary. Remodeling[29] can be thought of as a preventive maintenance program to ensure a strong, healthy skeleton, by old bone removal—performed by osteoclasts—and new bone deposition—performed by osteoblasts.

***The mechanism by which estrogen deficiency causes bone loss is still not completely understood.***

Osteoclastic activity also fulfills the important role of calcium, mobilization from the skeleton, crucial which is to the maintenance of blood levels of calcium especially when the nutritional supply of calcium is insufficient. In such situations, bone mass will be lost in an attempt to provide adequate calcium in conditions of calcium deficiency.

Remodeling occurs in foci that are discrete in time and place.[29] It is a process initiated on the surface of bone; therefore, any disturbance of remodeling will preferentially affect sites with large surface areas. Consequently, with increased osteoclastic activity, bone is lost initially from the cancellous (spongy bone) component, which forms only 20 percent of the skeletal mass but provides 80 percent of skeletal surface area. Because there is considerable cancellous bone in the spine and in the ends of long bones, bone loss at those sites is greatest. Excessive bone removal at these sites can completely erode trabeculae, disrupting the architecture.[29] Once trabeculae (and their surface area) are lost, bone loss becomes more evident in cortical bone, especially consequently in later life.

During bone growth, bone mass is gradually accrued in a process that is heavily dependent on genetic factors.[30] It is likely that many genes control so-called peak bone mass, that is, bone mass in young adult life, including the genes that control body size. The search for a specific gene that controls peak bone mass, bone loss, or osteoporosis has been disappointing and will probably remain so. Peak bone mass is also powerfully influenced by factors affecting prenatal, and early childhood, and adolescent growth, including diet and lifestyle. Chronic illness, inadequate diet, or physical inactivity during childhood can reduce peak bone mass.

### 3.2 Impact of Menopause on Bone

After attainment of peak bone mass, bone density is fairly stable in most healthy premenopausal women. There may be some slow bone loss, particularly in the hip, but it is the gradual onset of ovarian failure that heralds the most dramatic changes in skeletal homeostasis. Bone loss accelerates markedly for a few years after natural menopause or oophorectomy, and some loss continues for the remainder of life.[31] Women with very low endogenous estrogen concentrations after menopause may be at particularly high risk for hip and spine fractures.[32] It has been proposed that estrogen deficiency is the cause of both the early, accelerated phase and, at least in part, the late, slow phase of menopausal bone loss.[33]

The mechanism by which estrogen deficiency causes bone loss is still not completely understood. After menopause, there is increased bone turnover, which by itself produces a transient, reversible loss of some bone tissue.[34] Irreversible bone loss is

caused by an imbalance between the amount of bone removed by osteoclasts and the amount of new bone produced by osteoblasts within each remodeling cycle. Considerable attention has focused on the ways in which estrogen might modulate both turnover and remodeling imbalance. Several possible potential second messengers for estrogen's effects have been proposed. Osteoblasts or cells of the osteoblast lineage are thought to control the remodeling process. Communication between osteoclasts and osteoblasts may modify the amount of bone removed by the former cells, perhaps by controlling recruitment or the lifespan of the osteoclast population. Candidates as messengers include the interleukins (especially interleukins 1, 6, and 11), prostaglandins, insulin-like growth factors 1 and 2, TGF-β, and the rank/rank-ligand system.[34,35] Rank ligand is secreted by osteoblasts and mediates osteoclast recruitment and activity through rank, its receptor expressed in osteoclasts. Osteoblasts also secrete osteoprotegerin, a decoy receptor which mops up the ligand and has potential as a mechanism to inhibit osteoclast function and thus prevent bone loss.

It is known that bone loss continues into and may even accelerate in old age.[36] There has been much speculation on the role of estrogen deficiency in mediating the process. It seems evident that estrogen deficiency, plays a role but that, increasingly with age, other factors—including weight loss, physical immobility and frailty, calcium and vitamin D deficiency and secondary hyperparathyroidism, and the effects of intercurrent disease—come into play.

### 3.3 Falls and Bone Fragility

Multiple factors have been associated with an increased likelihood of falling and consequent fracture.[37] Age itself is a strong predictor for falls as individuals become increasingly frail. Other factors implicated with risk of hip fractures include cigarette smoking, low body weight (especially weight loss, perhaps a marker of frailty), previous fracture, and family history of hip fracture.[5] Of particular importance is a personal history of fracture as an adult. A history of peripheral fracture is usually easy to elicit, but determination of spine fracture may require lateral radiography of the spine. Spine fracture predicts risk for future hip fracture, independently of bone density.[20] A single spine fracture almost doubles the risk of hip fracture, and multiple spine fractures further increase the risk. Prevalent spine fracture increases risk for further spine fractures by a factor of 4 to 5. An incident spine fracture (i.e., a newly occurring spine fracture) further increases the risk, such that 20 percent of patients who present with a new spine fracture may be expected to have a second spine fracture within a year.[21]

## 4. Clinical Assessment and Diagnosis

***For women after menopause, clinical evidence of osteoporosis should be sought at every clinical evaluation.***

The initial approach to a patient with osteoporosis or one who may be at risk for osteoporosis is a complete history and physical examination. The physician should determine the presence of any underlying cause of osteoporosis, including the use of any medication that might affect the skeleton, such as thyroid hormone supplements or glucocorticoids. For women after menopause, clinical evidence of osteoporosis should be sought at every clinical evaluation. The principal method for making the diagnosis of osteoporosis is evaluation of the skeleton by a noninvasive measurement of bone density. In conjunction with the patient history and findings of the physical examination, bone density evaluation will determine whether the risk of fracture is sufficiently high to warrant pharmacological intervention. Bone density measurement can also serve to monitor bone loss or the effects of therapy, although its limited precision makes it somewhat less useful for individual monitoring than for risk prediction.[38]

Diagnosis of osteoporosis according to BMD criteria is dependent upon the site assessed (hip, spine, forearm, heel) and the methodology used.[39,40] Measurement in the hip by DEXA is preferred because it is less subject to the age-related artifacts that affect the spine and is a better predictor of hip fracture risk.[41] Where that modality is not available, x-ray absorptiometry or computed tomography may be used to assess the spine, forearm, tibia, or calcaneus. If these instruments are not available ultrasound, can also be used to assess fracture risk, but this modality has somewhat poorer precision and validation.[42]

At present, there are no internationally accepted guidelines for the use of bone densitometry to assess risk for osteoporosis. U.S. data, derived in part from cost-effectiveness analysis in white women, suggest that BMD should be measured in the following patient groups:[43]

1. All women 65 years of age or older, regardless of risk factors.
2. All postmenopausal women under 65 years of age who have, in addition to menopausal status, one or more other risk factors (thinness, current smoking, family history of osteoporosis-related fracture or a personal history of a fragility fracture).
3. Postmenopausal women who present with fractures (to confirm the diagnosis or determine the severity of disease).
4. Women who are considering therapy for osteoporosis, if the results of bone density evaluation would facilitate the decision.
5. Women who have received HRT for prolonged periods.

***At present, there are no internationally accepted guidelines for the use of bone densitometry to assess risk for osteoporosis.***

It would be cost-effective to be able to use a set of clinical risk factors to select women for bone densitometry. A Canadian group recently reported an assessment instrument based on only three factors—age, body weight, and current estrogen usage (yes or no). This instrument showed high sensitivity for selecting women with low BMD according to densitometry.[44] The approach of improved targeting may reduce the number of women who need densitometry for the identification of osteoporosis. In general, BMD measurement should not be performed if the findings would not influence a treatment decision. The presence of a disease (hyperthyroidism) or the use of a drug increasing the risk of osteoporosis (glucocorticoids, anticonvulsants) can also trigger referral for BMD measurement. More recently, an assessment tool for the risk of hip fracture was developed using the population from the study of osteoporotic fractures and was validated against a European cohort. This approach showed that clinical (and easily obtained) risk factors could identify individuals at increased risk of hip fracture and that the risk was amplified when BMD testing was added. [6,7]

## 5. Available Therapy

Efforts to reduce risk for osteoporosis should be encouraged among all adults. For those who are considered at high risk of fracture, pharmacological therapy may be required.

### 5.1 Nonpharmacologic Therapy

In general, risk factor reduction through nonpharmacologic means is considered sufficiently cost-effective that it should be instituted wherever possible in the general population.[43]

Avoidance of tobacco use and moderation in alcohol intake are obvious. All patients should also be encouraged to obtain an adequate calcium and vitamin D intake and to undertake a reasonable program of physical activity.

#### *5.1.1 Calcium*

Controlled clinical trials indicate that among the elderly, adequate calcium and vitamin D intake can reduce bone loss and potentially the risk of fractures, especially vertebral fracture.[45–47] In the only large trial with a hip fracture endpoint, dietary supplementation with calcium and vitamin D for 36 months significantly reduced hip fractures in elderly women whose average age was 82.[48] Calcium should be obtained as a nutrient from the diet to get the benefit of other components of food. Although calcium-fortified foods are becoming increasingly available, not all individuals will be able to increase calcium intake in this way. For those who cannot, supplementation should be encouraged. In the United States, the DRI—the recommended daily intake—for calcium is 1,200 mg for both women and men aged 51 years and older.[49] To achieve this goal, most menopausal women would need to add 500–750 mg of calcium to their usual intake. Selecting foods fortified with calcium can easily achieve this.

#### *5.1.2 Vitamin D*

There may be widespread deficiency of vitamin D in many populations, particularly the elderly, housebound, and institutionalized.[50,51] Inadequate exposure to sunlight, poor diet, and a decrease with age in the ability to absorb available vitamin D all contribute.[52] Because it is inexpensive to provide vitamin D and because many of the controlled trials of calcium also used vitamin D supplementation, supplements of vitamin D are recommended for at-risk populations. The recommended intake of vitamin D is 15 µg (600 IU/day) for persons > 70 years in the United States.[49]

On the other hand, there is a potential for vitamin D toxicity, and a dose of 2,000 IU or 50/lg per day should not be exceeded, except under close monitoring. The toxic effects of vitamin D overdose, mediated through hypercalcemia and hypercalciuria, include irreversible renal and cardiovascular damage due to the deposition of calcium in soft tissues.

#### *5.1.3 Physical Activity*

Most clinical trials have shown fairly modest and unsustained BMD responses to exercise in adults. The type of exercise that promotes a bone response may be different from the type recommended for aerobic fitness; it appears that muscle-building, weight-bearing resistance exercise is required to alter bone density.[53] For the frail elderly, exercise to reduce the risk for a fall is an appropriate intervention as muscle weakness is an important cause of falls. Muscle strength and neuromuscular performance can increase dramatically with proper exercise, [54,55] even in the tenth decade of life.[55] Consequently, where not medically contraindicated, increased physical activity should be encouraged. The most important feature of exercise is the requirement that it become a lifelong habit. Thus, it is better to recommend activities that the individual will enjoy than to provide rigid programs designed specifically to affect the skeleton.

***New bone-specific drugs (e.g., bisphosphonates) and broad-spectrum drugs (e.g., SERMs) that combat osteoporosis and may have beneficial effects in other organ systems are available.***

### 5.2 Pharmacologic Therapy

A decade ago, estrogen and injectable calcitonin were the only available pharmacologic therapies for postmenopausal women with osteoporosis. Now, new bone-specific drugs (e.g., bisphosphonates) and broad-spectrum drugs (e.g., SERMs) that combat osteoporosis and may have beneficial effects in other organ systems are available. PTH, the hormone that controls the mobilization of calcium, is emerging as a treatment with potential to add bone to an aging skeleton.

#### *5.2.1 Estrogen Replacement Therapy*

As discussed above (sec. 3.2), strong evidence supports the concept that postmenopausal estrogen deficiency precipitates bone loss. Controlled clinical trials have shown that ERT maintains bone

density and has a favorable effect on markers of bone resorption.[56] Data from observational studies indicate that long-term use of estrogen reduces risk for nonspine fracture[57] and that discontinuation allows bone loss and waning of fracture protection.[57,58] However, there are only a few clinical trials of estrogen's effect on fracture, especially vertebral fracture.[59,60] One randomized, placebo-controlled trial in 464 early postmenopausal women without osteoporosis found a reduction in nonspine fractures over a mean period of 4.3 years in women assigned to estrogen or estrogen plus vitamin D.[61] However, in a trial of 2,763 women selected on the basis of presence of CHD, no difference was found in risks for nonspine fracture in women randomized to receive HRT compared with placebo.[62] A recent meta-analysis of the clinical trial data on the effect of HRT on the prevention of nonspine fractures showed an overall 27-percent decrease in nonspine fractures in women randomized to receive HRT, with the effect attenuated in women over 60 years of age.[63] Since this effect is so much less than expected from observational studies, it is possible that the reduced fracture rates with estrogen use reported in observational studies reflect the selective use of hormones by healthier women—women who, for example, smoke less, exercise more, and have a better diet. (See ch. 4 for bias.) Nevertheless, on the basis of long clinical experience, positive effect on BMD and bone turnover, limited fracture data, putative other benefits, and fairly low cost, estrogen has been considered one of the major medical options for menopausal osteoporosis prevention.

***The first-generation bisphosphonate, etidronate, was shown in a small, placebo-controlled trial to reduce risk for spine but not nonspine fractures.***

#### 5.2.2 Selective Estrogen Receptor Modulator Therapy

SERMs are drugs that behave as estrogen agonists in some tissues, including bone, but behave as estrogen antagonists in other tissues, such as the breast. (See ch. 6.) SERMs include tamoxifen and raloxifene; the latter is the only SERM currently marketed worldwide for osteoporosis. In placebo-controlled trials, raloxifene prevented bone loss in healthy early postmenopausal women[64] and reduced risk for spine fracture in women with osteoporosis (RR reduction about 40 percent) but did not reduce risk for nonspine fractures in older women with osteoporosis.[65]

#### 5.2.3 Bisphosphonates

The bisphosphonates are analogues of pyrophosphate in which the oxygen has been replaced by a carbon atom. They bind avidly to calcium hydroxyapatite in bone, with the potency of different bisphosphonates determined by the side chains on the carbon. The first-generation bisphosphonate, etidronate, was shown in a small, placebo-controlled trial to reduce risk for spine but not nonspine fractures.[66] Recent studies of newer more potent bisphosphonates have shown about a 45–50 percent reduced risk for spine fracture.[67–69] A reduction in the risk of nonspine fractures has also been demonstrated with both alendronate and risedronate.[67–70] Risedronate has been shown to reduce the risk of hip fractures in patients with osteoporosis in the only clinical study conducted thus far in which hip fracture was the primary outcome.[70] Alendronate and risedronate, but not etidronate, are marketed in the United States for the treatment and prevention of osteoporosis; etidronate is available in a number of other countries.

#### 5.2.4 Salmon Calcitonin

The peptide hormone calcitonin is approved in the United States for the treatment of osteoporosis. Some clinical trials have shown a reduction in bone resorption and the preservation of bone mass.[71–74] In the major study completed thus far, calcitonin nasal spray, 200 IU per day, compared with placebo had modest but statistically significant effects on spinal bone mass and bone turnover and reduced, by 33 percent, risk for new spine

fracture in postmenopausal women with osteoporosis.[74] This trial failed to show the effect of calcitonin on peripheral bone density or on the risk of nonspine fracture, furthermore, the 400 IU dose failed to show statistically significant reductions in spine fracture. Although there are no conclusive data on the effect of calcitonin on risk for nonspine fracture, an analysis of pooled results from several studies suggests that salmon calcitonin treatment might provide benefit.[75]

### 5.3 Considerations in Selecting Pharmacologic Therapy

Which pharmacologic agent to select in a given patient is a complex decision that must take into account whether the need is for the prevention or treatment of osteoporosis and for bone-specific or broad-spectrum effects, as well as patient acceptability and tolerability and the cost of the drug being prescribed.

#### *5.3.1 Need for Prevention or Treatment*

Theoretically, for maximum prevention of osteoporosis, drug therapy should probably be initiated at menopause and continued lifelong. However, there are as yet no data on the optimal duration of use for nonestrogen formulations, and long-term prevention is not easily achieved with estrogen therapy, requiring its continuation for 20 to 25 years after menopause.[57,76]

An observational cohort study of 9,704 U.S. women over 65 years of age showed a 71-percent lower RR for hip and wrist fracture and a 50-percent lower RR for all nonspine fractures among those who had started estrogen within 5 years of menopause and who were still taking it.[58] In this same study, the use of estrogen for more than 10 years had little impact on later fracture risk for elderly women who had stopped therapy. A cross-sectional study of 740 white U.S. women aged 60–98 years confirmed that 10 years of estrogen use, begun soon after menopause but stopped, had little effect on bone density many years later.[58] This confirms prospective data, which demonstrate that bone loss begins when estrogen is discontinued.[77,78] In an observational study of 47,050 U.S. women, Barrett-Connor and coworkers were able to separate duration of use from recency of use and found both factors to be important for optimal preservation of bone density.[79]

***The ideal time, from the viewpoint of use of medical resources, for women to begin an osteoporosis drug is at age 60 to 65 years.***

Until recently, it was a popular belief that 6 or more years after menopause was too late to achieve fracture benefit from any treatment. However, data from the late 1980s had shown that preservation of bone mass could be achieved among older women using estrogen.[80] Recent studies have confirmed those data and have shown substantial reductions in risk for fracture when HRT was initiated > 10 years after menopause.[57,58,60] Several large clinical trials have shown that antiresorptive therapy with bisphosphonates[67–70] or raloxifene[65] given to elderly women can rapidly produce substantial reductions in risk for spine fracture (60–68 percent reductions in risk within the first year, and 41–46 percent reductions over 3–4 years). With such excellent responses to treatment when started many years after menopause, it is not surprising, therefore, that the National Osteoporosis Foundation's cost-effectiveness analysis suggests that the ideal time, from the viewpoint of use of medical resources, for women to begin an osteoporosis drug is at age 60 to 65 years.[43] Early postmenopausal prevention using bone-specific drugs is not considered cost-effective because, on average, the incidence of fracture among women remains low until the age of 65 years or more. (See "Cost-Effectiveness" below.) Drug treatment with bone-specific agents may be most effective in those who have osteoporosis, by BMD criteria.[76] Therapy begun after age 80 years in frail individuals may not be effective in reducing hip fracture risk, and in the very elderly, interventions aimed at reducing the impact of trauma, such as hip protectors, would be preferred.[81]

How should this information be incorporated into clinical practice? By targeting for treatment women in whom clinical evidence of osteoporosis has already appeared (height loss, fracture) or who have very low BMD (more than 2.5 standard deviations below the mean value for young adults), treating physicians can make the most efficient use of limited medical resources. Because it appears that bisphosphonates work well to reduce fracture risk in patients with osteoporosis,[68–70] bone density can be used as an indicator for treatment. It may also serve as a patient-motivator; acceptance of HRT was higher in women who had undergone BMD measure, regardless of the result, than in those who had not,[82] and awareness of low bone density has been shown to enhance acceptance of osteoporosis treatments.[83,84]

***The reasons for women wanting or refusing to take estrogen are complex. HRT is usually begun close to menopause for symptom relief, and women will often continue it for these tonic effects.***

#### *5.3.2 Need for Bone-Specific or Broad-Spectrum Effects*

Broad-spectrum therapies, such as estrogen and raloxifene, are thought to act as "health packages" that include improvement of the plasma lipid profile and, possibly, protection against other common diseases of aging. In many instances, however, trial data are not yet available to support the claims for clinical endpoints. Although bone-specific drugs, such as bisphosphonates, appear to provide greater fracture risk reduction than broad-spectrum drugs, especially for nonspine fractures, many postmenopausal women want or need interventions for other health concerns.

### 5.4 Acceptability and Tolerability

The reasons for women wanting or refusing to take estrogen are complex. HRT is usually begun close to menopause for symptom relief, and women will often continue it for these tonic effects.[85] Older women, on the other hand, typically begin hormones and other treatments for health promotion, particularly for prevention of osteoporosis-related fractures.[85]

Long-term drug therapy requires a high degree of patient acceptance—one that is predicated on the patient's perception that treatment benefits outweigh risks and that treatment is convenient, low in cost, and free of side effects. Among U.S. women > 60 years of age, it was found that 68 percent and 48 percent who started estrogen or raloxifene, respectively, had stopped within 24 months.[86] A similarly high discontinuation rate was found in U.S. women who had started alendronate.[87] Side effects are the main reason for stopping antiosteoporosis drugs. Vaginal bleeding and breast tenderness rank high among reasons that older women give for stopping HRT.[85] Gastrointestinal symptoms are the most common reason for stopping alendronate, while vasomotor symptoms are the reason cited by women for discontinuing raloxifene.[65] There are as yet no data on continuation of risedronate. Poor continuation is not fully explained by side effects: nearly one-third of relatively asymptomatic women who complied with a HRT trial regimen for 3 years discontinued the therapy within 2 years after the trial's end.[88] In general, discontinuation rates in clinical settings are several fold greater than those reported from clinical trials; it is likely that patient selection plus the education, motivation, and support provided to participants by clinical trial staff account for some of the differences.

Gastrointestinal side effects with alendronate are more common in women over 70 years of age and in those with active upper gastrointestinal problems, such as gastroesophageal reflux disease or with current nonsteroidal anti-inflammatory drugs (NSAIDs) use.[89] These risks of developing gastrointestinal symptoms may be reduced if patients adhere to dosing guidelines. In other patients who exhibit upper gastrointestinal symptoms while tak-

ing alendronate, administration of the medication weekly may improve tolerability. Once-weekly alendronate 70 mg yielded the same effects on BMD and bone turnover as daily alendronate 10 mg.[90] Risedronate may be less apt to cause gastrointestinal lesions.[91]

### 5.5 Cost Effectiveness

It is clear that greater treatment focus should be on women aged 60 years and older, who are on average 10–15 years postmenopausal. On the basis of age alone, they have a substantially higher risk for fracture than younger women. They also are more likely to have accumulated risk factors, including spine or other osteoporotic fractures. Moreover, older women may be more willing to begin and continue osteoporosis treatment because they correctly perceive that their risk for fracture is more immediate than the risk in younger women. Osteoporosis drugs should be reserved for patients at high proximate risk for fracture. By targeting women over 65 years of age and who have multiple risk factors or all women who have clinical evidence of osteoporosis (height loss, fracture), treating physicians can make more efficient use of limited medical resources and can expose fewer women to drugs whose long-term effects remain uncertain.

### 5.6 Clinical Perspective on Drug Selection Issues

If pharmacologic therapy is indicated for prevention of osteoporosis, estrogen is probably the best choice for early postmenopausal women, because it is low in cost, provides relief of climacteric symptoms, and perhaps lowers risks for certain other diseases of aging. For women at high risk of fracture and in need of treatment—typically those who are elderly with fractures—a bisphosphonate might be considered more appropriate. For many women between these two extremes, who have a moderate risk of fracture (especially vertebral fractures) and who are also seeking other health benefits (reduced risk of breast cancer), raloxifene might be preferred.

Now that a number of effective osteoporosis therapies have become available, two new questions have arisen regarding their use: Should they be combined? How long should they be continued? The therapies in use today are all antiresorptive, and their effects on bone turnover are additive to a degree. For example, estrogen alone or alendronate alone will suppress bone turnover 50–55 percent on average; when added together, bone turnover is suppressed 65–70 percent.[92] The increment in bone density achieved with combination therapy is small, about 1–2 percent over the usual 5-percent increment with either treatment used alone. There are no data to show greater efficacy in fracture reduction, and there is concern that oversuppression of bone turnover could contribute to greater fracture risk by either causing hypermineralized, brittle bone or by impairing bone repair and renewal.[93] The added cost, complexity, and potential side effects also are reasons to exercise caution in the use of combination antiresorptive therapies. However, future study of low dosages of two antiresorptive therapies is warranted; this could produce the desired bone and other effects with lower cost and better tolerability and potentially reduce the adverse effects of these drugs.

In the future, we are likely to see the use of osteoporosis drugs in sequence; for example, a bone anabolic drug (see below) might be used for 1–2 years to stimulate new bone formation, and an antiresorptive drug would be used subsequently to consolidate and maintain the bone gains.

***Osteoporosis drugs should be reserved for patients at high proximate risk for fracture.***

Choosing the right drug regimen for the right woman involves assessment of short-term fracture risk and other nonskeletal health issues. By understanding available regimens and customizing the therapy to the needs of each woman, clinicians are more likely to achieve clinical goals and optimize the chances for long-term continuation. With the

emergence of proved treatment alternatives, it is no longer acceptable to use a "one size fits all" approach to the years after menopause.

## 6. Novel Therapeutic Options

Options in development for the treatment of osteoporosis range from Kyphoplasty™ (a method for filling collapsed spine bodies with a cement) to hip pads designed to reduce the energy transmitted to the hip during a fall. Some potential pharmacologic agents are variants of available agents; others seek to interfere with novel targets in the osteoclast population or to stimulate new bone formation.[94]

***Options in development for the treatment of osteoporosis range from Kyphoplasty™ … to hip pads designed to reduce the energy transmitted to the hip during a fall.***

One very promising approach is the use of PTH. Among menopausal women with osteoporosis who were already receiving HRT, the addition of daily subcutaneous PTH markedly increased spine BMD during years of treatment, compared with no significant change in the group receiving HRT alone.[95] Total-body bone mineral was also increased, with no detrimental effect at any skeletal site, and the increased bone mass was associated with a reduction in rate of spine fracture. The findings were confirmed in a larger study of 1,673 women with osteoporosis and existing spine fractures.[96] Compared to those receiving placebo, those receiving 20 µg recombinant 1—34 PTH subcutaneously and daily, for an average of 18 months, had marked reductions in spine and nonspine fracture risk; a 65-percent reduction was observed for spine fracture, and a 52-percent reduction was observed for nonspine fractures. This very promising therapy, in addition to increasing bone density, increases the area of vertebra and the diameter of peripheral bones. The early and profound fracture reduction may be due, in part, to changes in bone geometry and integrity.

The development of many more therapeutic alternatives can be anticipated as understanding of the genetics and pathophysiology of osteoporosis continues to grow.

## 7. Oral Bone Loss

Oral bone, like the rest of the skeleton, comprises both trabecular and cortical bone and undergoes formation and resorption throughout the lifespan. Unlike the case of the postcranial skeleton, however, fracture rarely results when oral bone loss exceeds gain. Generally, oral bone loss manifests as either loss of tooth-anchoring support or as a diminution of the remaining ridge in areas of partial or complete tooth loss. Residual ridge resorption refers to the loss of oral bone subsequent to the natural loss or removal of teeth. Its rate and extent are highly variable. Progressive residual ridge resorption can interfere with the placement of implants and can result in an inability to stabilize dentures.[97]

Given the chronic and progressive nature of oral bone and attendant tooth loss and the fact that symptoms often do not appear until advanced stages of disease, painful and handicapping outcomes are highest among people in later stages of life. Many older adults report changing the composition of meals, taking a long time to complete a meal, being deterred from eating with others, and feeling social discomfort in smiling, singing, or kissing as a consequence of poor oral health.[98] In fact, the literature is replete with examples of not only the physical but economic, social, and psychological consequences of oral diseases.

### 7.1 Epidemiology

Analyses of U.S. data from the NHANES III indicate that, among women > 18 years of age, 63.8 percent have experienced loss of one or more teeth excluding third molars and 67.1 percent have evidence of moderate periodontal disease, defined as loss of bony tooth support of 2 mm or more.[99] Furthermore, the prevalence of these conditions increases with age in both sexes. Data from the WHO's Global Burden of Disease Study (GBDS) provide a unique opportunity to examine the prevalence of edentulism across eight global regional groupings. Differences in disease definitions and methods prohibit direct comparisons between NHANES and GBDS data, but the global study provides evidence that the condition accounts for significant morbidity worldwide. For example, within the grouping identified as Established Market Economies which includes North America, Western Europe, and Australia, it is estimated that 95 million people were edentulous in 1990.[100] Epidemiologic data for residual ridge resorption are lacking, but clinical impressions suggest that more women than men present with severe residual ridge resorption requiring specialized treatment.

### 7.2 Etiology

The multifactorial nature of oral bone and tooth loss make it difficult to unravel the roles of gender biology, longevity, and health care utilization in their pathogenesis. Women are reported to be more inclined to self-care, more likely to visit a dentist, and more likely to report symptoms such as pain.[101,102] The degree to which such behaviors influence oral disease patterns and health statistics is unknown. For instance, to what extent is tooth loss the result of primary disease experience or dental treatment? And do anecdotal reports of women's greater experiences with severe residual ridge resorption reflect real differences in morbidity or sex differences in longevity and illness behavior?

Despite these voids in understanding, there is a growing body of literature that indicates that oral bone and attending tooth loss are associated with menopausal estrogen deficiency and osteoporosis.[103–123] Not all studies in the topic area have yielded positive results, however.[124–128] Differences in study design—including in population, sample size, approach to skeletal and oral bone assessments, definitions of outcomes, and adjustment for confounding variables—are likely reasons for conflicting findings.

Still, data emerging from controlled clinical studies provide evidence of a significant association between oral bone status and skeletal status.[129–131] These include preliminary findings of a 7-year longitudinal study of osteoporosis and oral bone loss being conducted at the University of Alabama at Birmingham in a subsample of participants (n = 457) enrolled in the observational component of the WHI of the NIH.[129,130] As part of the study protocol, comprehensive medical history and examination data from the core WHI, including hip BMD as determined by DEXA, are linked with oral examination findings and oral bone density measurements by the validated technique of digital subtraction radiography. Analyses of cross-sectional baseline data indicate a strong and significant correlation between hip BMD and lower jaw bone density ($r = 0.78$, $p < 0.001$).[129] Furthermore, preliminary analyses of longitudinal data from the first 85 participants to return for their 3-year followup appointment indicate that the association is clinically important.[124] Among participants with evidence of periodontal bone loss at baseline, those with hip BMD > 1 standard deviation below the reference value for healthy young women had a significantly higher rate of progressive oral bone destruction than participants with hip BMDs within 1 standard deviation of normal ($p < 0.05$).

***It is estimated that 95 million people were edentulous in 1990.***

Data on the relation between skeletal BMD and tooth loss are not yet available from the described WHI cohort, but other studies have examined this issue. The Study for Osteoporotic Fractures Research Group reported an association between tooth loss and the rate of systemic bone loss among 4,524 U.S. women age > 65 who reported being dentate at baseline and who returned approximately 5.7 years later for a followup visit. On adjustment for age, weight, use of estrogen, and smoking status, it was found that women reporting tooth loss had higher annual decreases in hip BMD than women who did not lose teeth (0.68 percent versus 0.54 percent, $p < 0.0029$).[132]

### 7.3 Approaches to Therapy

Bone regenerative procedures, such as guided tissue regeneration and grafting, have already become commonplace for treatment of localized oral bony defects, and their use is likely to expand. State-of-the-art treatment for tooth loss focuses on the placement of single or multiple teeth implants; this approach, too, is gaining wide acceptance. Long-term studies are underway to evaluate the effect of antibiotics on progressive oral bone loss. Another promising area of research is the use of NSAIDs[133] and bisphosphonates[134] to control host inflammatory and/or bone resorptive responses.

***There are several important clinical implications of an association between oral status and skeletal status.***

Given the data relating oral bone loss and osteoporosis, it has been hypothesized that treatments used to maintain or improve skeletal bone density may favorably affect oral bone status and tooth loss. Two large cohort studies have examined the effect of HRT on reported tooth loss.[135,136] Analysis of data on 48,483 participants in the Nurses' Health Study in the United States[136] showed that among women who reported regular dental visits there was an inverse relation between current hormone use and loss of teeth after controlling for age and cigarette smoking. Among the 3,921 women in the Leisure World Cohort Study who provided suitable data with which to assess tooth status, estrogen users had significantly lower age-adjusted tooth loss and edentulism rates compared with nonusers.[111] Studies of the effect of other bone-enhancing agents on tooth loss have been limited, but some trials have demonstrated positive findings. Data obtained from women with normal spine densities enrolled in a randomized nutritional intervention trial indicate that a smaller proportion of women taking calcium supplements reported tooth loss compared with those taking placebo.[137] A pilot trial has provided evidence of a lower RR for progressive oral bone loss among alendronate-treated participants than in placebo controls.[138]

### 7.4 Clinical Perspective on Oral Bone Loss

There are several important clinical implications of an association between oral status and skeletal status. On one side of the issue, it is possible that oral examination and radiographic findings may be useful signs of extra-oral bone diminution. Although preliminary studies along these lines have yielded promising findings, it is too early to know the value of routine dental visit information in signaling the need for skeletal bone evaluations.[139] On the other side, history of skeletal osteopenia may impact the need for, and outcome of, a variety of periodontal and prosthetic procedures including guided tissue regeneration and tooth implantations. If therapy for skeletal bone conditions is undertaken and is successful, the oral cavity may reap benefits as well.

A connection between menopausal estrogen deficiency and oral bone loss is biologically plausible, and many research findings to date are consistent with that link. More research is needed to contextualize the relation fully and to understand the extent to which menopause increases a woman's oral health risks. Even as we await more detailed information, women and their health care providers are advised to incorporate oral health into the menopausal conceptual milieu.

## 8. Future Needs

- We must improve methods for identifying people at risk for fracture; develop inexpensive and accurate machines to measure BMD and bone structural integrity; develop simple clinical means for determining risk of serious falls; and validate algorithms that combine clinical risk factors, bone density, and so forth, to accurately predict an individual's fracture risk in the next 5–10 years.
- Improve interventions; finding ways to enhance long-term compliance with calcium, vitamin D, and exercise; develop drugs that stimulate bone formation, which will restore bone mass and bone structural integrity; learn how to use drugs in combination or in sequence; have a better understanding of the optimal time to start drugs, how long to use them, and effects of their withdrawal; and know more about the long-term safety of drugs, that cumulate in bone, for example, bisphosphonates.
- Understand skeletal factors responsible for maintaining bone mass and bone strength, in particularly bone cytokines and growth factors, the effects of mineralization and hypermineralization on bone strength, and the way that bone anabolic agents signal bone cells.
- Improve tests that monitor bone health, including densitometric, ultrasonographic, and biochemical tests.
- Understand the relationship between oral bone loss and loss in the rest of the skeleton.
- Find therapies that will reduce bone loss that occurs early in life before osteoporosis becomes a clinical problem.

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# Chapter 10: Gynecologic and Urinary Aspects of Menopause

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## Key Points[a]

1. Changes in the menstrual cycle have been described in several clinical studies during the menopausal transition [C].
2. It is important to know how to diagnose endometrial cancer because it is a cause of abnormal uterine bleeding [C,D].
3. Management of uterine bleeding during HRT includes observation, surgery, or specific modifications of the treatment regimen [C,D].
4. Vulvovaginal complaints in menopause are very common, and estrogen is efficacious in their treatment [A,C,D].
5. (UI) is common with aging. The relationship between UI and menopause is not well understood [C,D].
6. Estrogen may benefit urge incontinence; however, it may exacerbate stress UI [A].
7. There are multiple new agents shown to be effective in the treatment of incontinence [A].
8. Some SERMs may increase risk for pelvic organ prolapse [B].

***Changes in the menstrual cycle have been described in several clinical studies during the menopausal transition.***

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = panel expert judgement. (See also table 1–1.)

## 1. Introduction

Perimenopausal women request consultation for gynecologic evaluation when cycle irregularities begin or when hot flushes or other complaints related to hypoestrogenemia occur. In some countries, the gynecologist is the only medical contact for healthy women. Because they routinely perform breast examinations and Papanicolaou tests (Pap smears), gynecologists are often responsible for the management of perimenopausal health issues. Moreover, irregular bleeding and urogenital symptoms are specific gynecologic aspects of menopause. In particular, uterine bleeding is common in menopausal transition women and in women receiving HRT.

***Gynecologists are often responsible for the management of perimenopausal health issues.***

## 2. Perimenopausal Bleeding

Ovarian aging is the cause of menstrual changes occurring before menopause.

### 2.1 Changes in the Menstrual Cycle

The median menstrual cycle is 29 days in the early years after menarche but decreases to 26 days by the age of 40. Studies carried out mostly in industrialized countries show that starting 8–10 years before menopause there is greater variability in the intermenstruum.[1] Intermittent ovulation[2] and long and short cycles intermingled with oligomenorrhea occur in the transition period. Evidence of (irregular) ovarian follicular growth and estradiol production may be detected even after the last menstrual period.[3]

Mean menstrual flow volume is about 35 mL and is usually stable over time. During the menopausal transition, cycles can be abnormal in terms of frequency, duration, and volume according to the following definitions:[4]

- Hypomenorrhea: bleeding occurring at regular intervals but of low volume (< 20 mL).
- Oligomenorrhea: bleeding occurring at intervals > 35 days.
- Spotting: intermenstrual bleeding not necessitating sanitary protection.
- Metrorrhagia: intermenstrual bleeding necessitating sanitary protection.
- Menorrhagia (hypermenorrhea): bleeding occurring at regular intervals but excessive in quantity (> 80 mL).
- Polymenorrhea: bleeding occurring at regular intervals < 21 days.
- Menometrorrhagia: frequent and excessive bleeding without any cyclic pattern.

Dysfunctional uterine bleeding is abnormal uterine bleeding with no demonstrable organic cause. It is a diagnosis of exclusion. Approximately one-half of dysfunctional uterine bleeding occurs between ages 40 and 50,[5] caused by estrogen secretion sufficient to stimulate endometrial growth but insufficient to induce a midcycle surge of LH. In older women, the capacity of follicles to secrete estradiol is diminished; progesterone secretion and the length of the luteal phase subsequently decrease, at which time menstrual irregularities begin. (See also ch. 2, sec. 4.)[6] Decreases in progesterone cause abnormal endometrial structure, which in turn gives rise to uterine bleeding varying from spotting to heavy bleeding.[7]

### 2.2 Endometrial Changes in the Transition Period

Histologic studies of the endometrium in the years before and after menopause show important interindividual and intraindividual variations. Frequently, the endometrium appears out of phase with endocrine events and appears autonomous. In many cases, the endometria are hyperplastic; however, endometrial atrophy is the most common histologic finding after menopause. Trevoux et al. found the greatest degree of variability in endometrial appearance in the year before menopause, when 42 percent of the endometria were atrophic

or hypotrophic, 24 percent were proliferative, 24 percent were secretory (30 percent of those showed luteal delay), and 9 percent showed hyperplasia.[8]

Endometrial hyperplasia, a premalignant lesion, may be simple or complex. Risk for transformation to cancer is much greater when atypia is present (table 10–1).[9,10] Endometrial hyperplasia can revert to normal with administration of a progestin. In a study of 85 patients with endometrial hyperplasia, long-term progestin treatment provided uniform protection against malignant transformation in the 65 without cytological atypia; in the 20 with atypia, however, endometrial cancer developed in 25 percent, even after 2–7 years of progestin treatment.[11]

Whereas hyperplasia is uncommon in young women with normal menstrual cycles (1 percent), it is frequently found in the transition period women (6–13 percent)[12] or in women presenting with abnormal bleeding (4–30 percent).[13]

In patients with abnormal uterine bleeding, cancer of the reproductive tract is found in < 10 percent of those who are in the menopausal transition but in about 25 percent of those who are postmenopausal.[5] Although cancer is not the most common etiology, perimenopausal bleeding should be considered secondary to malignancy until proved otherwise.

Risk for endometrial cancer increases with age until menopause when it begins to decrease.[14] Other risk factors include diabetes,[15] chronic anovulation, obesity, and estrogen-producing ovarian tumors. There are two types of endometrial cancer. The more prevalent and less aggressive occurs in obese, younger women with high concentrations of circulating estrogen and in postmenopausal women receiving estrogen without progestin. The second, more aggressive type affects older women without signs of hyperestrogenism. Use of unopposed estrogen increases a postmenopausal woman's risk for adenocarcinoma of the endometrium by twofold to ninefold, compared with no estrogen use, and there is a clear association between the duration of replacement therapy and risk.[16–18] Although long-term use of unopposed estrogen, even in very low dosages, in postmenopausal women is the single most important modifiable risk factor for endometrial cancer after obesity, cases of endometrial cancer have been reported during long-term estrogen-progestin replacement therapy,[19] more frequently with cyclic use of progestins[18,19] than with continuous combinations. Menopausal women treated with tamoxifen

***Endometrial hyperplasia can revert to normal with administration of progestin.***

## TABLE 10–1

## Probability That Untreated Endometrial Hyperplasia Will Progress to Carcinoma

| Type of Hyperplasia | Cytologic Atypia | Progression to Carcinoma (percent) |
|---|---|---|
| Simple | Absent | 1 |
| Complex | Absent | 6 |
| Simple | Present | 7 |
| Complex | Present | 33 |

*Sources:* Data are from Kurman et al.[9] and Baak et al.[10]

for breast cancer are at increased risk as well.[20] As noted above, estrogen-induced endometrial carcinoma belongs to the less aggressive type.[21]

### 2.3 Bleeding During Hormone Replacement Therapy

***The use of sex steroid hormones for therapeutic or preventive purposes has introduced a new cause of uterine bleeding, which should be clearly differentiated from organic conditions.***

The use of sex steroid hormones for therapeutic or preventive purposes has introduced a new cause of uterine bleeding, which should be clearly differentiated from organic conditions.

Uterine bleeding due to HRT is a cause of patient concern,[22] inconvenience,[23,24] and discontinuation of use.[25,26] Clinical aspects of the bleeding differ according to the treatment regimen. Nonhysterectomized patients taking unopposed estrogen often have vaginal bleeding;[27] however, the administration of unopposed estrogen should be limited to hysterectomized women. A progestin should be added in all other cases, because sequential addition of a progestin for 10–14 days will in the short-term prevent estrogen-induced hyperplasia.[27] Nevertheless, there is a modest increase in risk for endometrial cancer after 3 years of sequential progestin use.[28,29] Progestin decreases mitotic activity of endometrial cells by secretory conversion of estrogen–primed glandular cells and decidual changes of stromal fibroblasts. In addition, progestin inhibits synthesis of ERs.[30]

Bleeding during HRT may be related to the specific regimen. Other causes of bleeding during hormone replacement are failure of compliance (missed tablets, failure to change patch), absorption problems (intestinal problems, change in diet, use of antibiotics, defective patch compliance, skin problems), endometrial pathology (atrophy, polyps, submucosal leiomyoma, hyperplasia, adenocarcinoma), myometrial pathology, and drug use (anticoagulants, steroids, barbiturates, chemotherapy).

#### *2.3.1 Sequential Estrogen-Progestin Replacement Therapy*

About 95 percent of women receiving sequential combined HRT will experience withdrawal bleeding after the progestin phase. About 6 percent will not bleed at all; the likelihood of no bleeding is higher in older age.[31] The absence of withdrawal bleeding may also be due to pregnancy which should be excluded in perimenopausal women, too little estrogen in the preparation used, or cervical stenosis. The most common forms of irregular bleeding during sequential estrogen-progestin replacement therapy[11] are—

- Bleeding during the estrogen-only phase, which is more likely associated with endometrial pathology than bleeding during the progestin phase.
- Bleeding before day 11 of progestin treatment, a result of incomplete shedding and correctable by a higher progestin dose.
- Prolonged, heavy cyclic bleeding, which may be due to too much estrogen or insufficient progestin in the preparation used, may be due to endometrial pathology, or may represent an abnormal response to replacement therapy.
- Breakthrough bleeding, which is often caused by benign hyperplasia but may be due to an atrophic endometrium associated with an insufficient estrogen dosage.

#### *2.3.2 Continuous Estrogen-Progestin Replacement Therapy*

Continuous administration of a progestin in combination with estrogen has been suggested to prevent the cyclic withdrawal bleeding associated with HRT.[32] Nevertheless, a high incidence of episodes of irregular bleeding (50 percent) has been observed, particularly during the first months.[33,34] Bleeding is usually slight, and the incidence of episodes decreases rapidly with time. Bleeding

usually disappears within 1 year.[34] Because endometrial cancer has been reported during continuous combined regimens, evaluation is needed if bleeding persists.[18]

### 2.4 Diagnosis and Management of Abnormal Uterine Bleeding

Incidence of bleeding episodes without HRT decreases with the time since menopause. In addition to the use of HRT, the differential diagnosis for dysfunctional peri-postmenopausal uterine bleeding includes reproductive tract disorders, systemic disorders, and iatrogenic causes (table 10–2). Complaints of excessive uterine bleeding immediately suggest a genital source; however, bleeding can originate in the urinary or gastrointestinal tract, a confusion more common in elderly patients. It must be reemphasized that perimenopausal uterine bleeding in women not receiving HRT should be considered endometrial cancer until proved otherwise.

Measurement of endometrial thickness is a noninvasive clinical indicator of endometrial normality. Studies comparing ultrasonographic measurement of endometrial thickness with histopathologic

## TABLE 10–2

## Differential Diagnosis of Abnormal Uterine Bleeding at Any Age

| |
|---|
| **Disorders of the Genital Tract** |
| • Complications of early pregnancy |
| • Benign pelvic lesions |
| • Cervicitis |
| Uterine leiomyoma |
| Polyps |
| Adenomyosis |
| Endometritis |
| Traumatic |
| • Malignant pelvic lesions |
| Cervix, endometrium, fallopian tube, ovary, vulva |
| Endometrial hyperplasia |
| **Systemic Disorders** |
| • Coagulation disorders |
| • Liver diseases |
| • Renal failure |
| **Iatrogenic Causes** |
| • Steroids |
| • Anticoagulants |
| • Hemodialysis |
| • Intrauterine contraceptive device (IUD) |

findings on biopsy in women with and without use of HRT showed endometrial thickness < 4 mm to correlate with atrophic endometrium and thickness > 4–7 mm to correlate with increased incidence of endometrial pathology in both groups.[35–39] Endometrial cancer is rarely found when endometrial thickness is < 4 mm (double layer).[40] Ultrasound scanning cannot replace histopathologic assessment in women receiving HRT.[40–43] In women receiving hormones, the endometrium is often thicker than in untreated menopausal women. With sequential estrogen-progestin regimens, endometrial thickness can vary depending on the treatment phase.

Sonography can accurately assess endometrial thickness in the proliferative or postmenopausal phase. Hysteroscopy, however, can easily detect endometrial pathology at any time and allows biopsy under direct vision when a lesion is identified. Thus, several groups consider hysteroscopy to be the gold standard.[5] More recently, sonohysterography, which is less invasive and less expensive than hysteroscopy, has been proposed as a better method for the morphologic evaluation of the endometrium.[44]

***Estrogen is efficacious in treatment, and local estrogens are as effective as systemic in the therapy of genital atrophy.***

Clinical management of abnormal uterine bleeding in perimenopausal patients is addressed according to the diagnosis, observation, surgery, or specific changes in the treatment regimen. For example, in patients with bleeding during the progestin phase of sequential combined HRT, increasing the progestin potency should be beneficial. A drug-free interval of 3 to 7 days can also improve the bleeding pattern. In patients with bleeding during continuous combined HRT, lowering the estrogen and progestin doses can be the answer. In difficult cases, a very weak estrogen (estriol), tibolone, or local therapy for the treatment of vulvovaginal atrophy may be suggested since this therapy is almost always associated with amenorrhea.[45]

## 3. Genital Atrophy and Vulvovaginal Complaints

The inner layer of the vagina is stratified squamous epithelium, the middle layer is muscular, and the outer layer is fibrous.[46] The epithelial cells contain the highest number of nuclear estrogen binding sites of any genital structure. Even higher numbers are noted in the postmenopausal vagina.[47,48] Because estrogen is progressively depleted during postmenopausal years, the percentage of superficial cells decreases. Vaginal secretions, made up mainly of vaginal wall transudate and cervical mucus, also decrease because their production is estrogen-dependent and largely mediated by blood flow.[49,50]

In the atrophic vagina, lubrication with sexual stimulation decreases. The vaginal surface becomes fragile, and petechiae and bleeding often occur after minimal trauma. Because estrogen is also responsible for deposition of glycogen in the vaginal epithelium, the absence of glycogen-containing superficial cells results in decreased production of lactic and acetic acids. This causes abnormally low vaginal pH (3.8 to 4.2) and creates a milieu that favors infection.

Vulvovaginal complaints are very common in postmenopausal women.[51] The most common local complaint is vaginal dryness. The loss of lubrication leads directly to vaginitis, vaginismus, and dyspareunia. Estrogen is efficacious in treatment, and local estrogens are as effective as systemic in the therapy of genital atrophy.[52] Atrophic vaginitis is the most common cause of benign postmenopausal bleeding.

## 4. Pelvic Floor and Urinary Tract

With estrogen loss, relaxation of vaginal tissue and decreased perineal muscle tone occur, a situation associated with decreased sexual response as well as urinary and bowel dysfunction.[53] Kegel (pelvic floor) exercises are often prescribed in the therapy of vaginismus and stress incontinence.

Estrogen deficiency causes atrophic changes of the urethral epithelium and the submucosa. This may lead to incomplete urethral closure and an abnormal urinary flow pattern. In addition, urethral atrophy predisposes to ascending infections and urogenital infections, which constitute a major problem in elderly women.[54,55] It is important to identify patients with recurrent infections because of the significant morbidity, which includes risk for renal impairment. Urinary tract infections are usually secondary to stepwise colonization of the vaginal introitus and urethral mucosa by organisms from the rectal flora. ERT reduces urinary tract infections in postmenopausal years probably by its support of normal vaginal flora.[56]

To ensure continence, urethral pressure must exceed bladder pressure except during micturition. Positive urethral closure pressure is produced by the urethra. All four functional layers of the urethra—epithelium, connective tissue, vascular tissue, and muscle—are affected by estrogen status. In particular, the connective tissue is an important component; collagen is its most abundant structural protein.[57] ERT enhances collagen production by fibroblasts.[58]

## 5. Urinary Incontinence

UI is a common but poorly understood problem. The International Continence Society defines incontinence as involuntary loss of urine that is objectively demonstrable and is a social or hygienic problem.[59] In 1998, a review of published population-based studies of prevalence to determine the estimated prevalence of incontinence stratified by frequency, age, and gender reported rates that varied from 14–35 percent.[60] The Agency for Health Care Policy and Research (AHCPR) estimates that 13 million Americans are incontinent; 11 million are women.[61]

The economic costs can be substantial with direct costs from diagnosis, treatment, and continuing care, including purchase of products for protection, as well as indirect costs from loss of freedom and independent living. A report of incontinence in individuals aged 65 and older in the United States in 1995 revealed a cost of $24.3 billion dollars or $3,565 per individual with incontinence.[62] The Agency for Healthcare Research and Quality (AHRQ) calculates for the United States $16.4 billion is spent every year on incontinence-related care: $11.2 billion for community-based programs and at home, and $5.2 billion in long-term care facilities. Furthermore, $1.1 billion is spent every year on disposable products for adults.

The relationship between menopause and UI is unknown and not well studied. Although many experts quote menopause as a major risk factor for both stress and urge incontinence, there has been limited data to support this. It is theorized the lack of estrogen in menopause can result in thinning of the lining of the urethra, which causes improper closure. Estrogen deficiency also makes the bladder muscles weaken. The combination of a thin, injury-prone urinary tract and weak bladder muscles can cause the urethra to open unexpectedly during physical activity, leading to stress incontinence.

***UI is a common but poorly understood problem.***

### 5.1 Types and Causes of Urinary Incontinence

Established UI can usually be divided into one of four major types: stress incontinence, urge incontinence (detrusor overactivity or instability), mixed incontinence, and overflow incontinence. These disorders often have classic histories or typical physical findings. Neurogenic incontinence may be related to defects in the nervous system, which conducts urination signals between the bladder and the brain. As it is not related to menopause, it will not be discussed.

**Stress Incontinence:** It is diagnosed when, in the absence of a detrusor contraction, the pressure inside the bladder exceeds the pressure in the ure-

thra. Patients typically describe losses of small volumes of urine with activities resulting in transiently increased intra-abdominal pressure (coughing, sneezing, running, laughing). It is thought that these changes become more pronounced following menopause as estrogen deficiency allows atrophy of the genitourinary tissues; however, there is no real evidence that this is the case. Physical examination may reveal evidence of pelvic relaxation, such as cystocele, rectocele, and/or uterine prolapse. Urine loss can usually be demonstrated with coughing while the patient is in the supine position.

**Urge Incontinence:** It is diagnosed when the detrusor muscle contracts, spontaneously or on provocation, during the filling phase of the bladder while the woman is attempting to inhibit micturition.[59] Urge incontinence is more common in older adults. This type of incontinence is also known as detrusor overactivity, detrusor instability, detrusor hyper-reflexia, or uninhibited bladder. Patients with detrusor overactivity have early, forceful detrusor contractions, well before the bladder is full. This creates a sensation of urinary urgency and frequency. Patients with detrusor overactivity tend to lose small to moderate volumes of urine. If the detrusor contraction is strong enough to overcome the urethral resistance, incontinence occurs.

The diagnosis of detrusor overactivity is made primarily by history and confirmed with urodynamic testing. There are no pathognomonic findings on physical examination, although a careful pelvic and rectal examination and neurologic screening can occasionally reveal anatomic abnormalities (e.g., uterine prolapse, fecal impaction) or evidence of neurologic disease.

**Mixed Incontinence:** It is a combination of both stress and urge incontinence and is most common in older women.

**Overflow Incontinence:** In overflow incontinence, the bladder becomes too full because it can't be fully emptied. This condition is rare and is the result of bladder obstruction or injury. Those with overflow incontinence commonly present with symptoms of markedly reduced urinary stream, incomplete or unsuccessful voiding, and frequent or even continuous urinary dribbling. Overflow incontinence is generally due to bladder contractile dysfunction (hypotonic/atonic bladder) or vesicles obstructing urinary outflow. In either case, large bladder volumes result in the intravesicular pressure exceeding intraurethral resistance, and symptoms of urinary dribbling. Physical examination often reveals a distended bladder, and measurement of urine volume after voiding reveals an elevated postvoid residual volume. Patients also demonstrate low urinary flow rates on urodynamic tests.

Other factors can cause incontinence, such as decreased mobility, cognitive impairment, or medications (table 10–3).

### 5.2 Evaluation

Evaluation and treatment for incontinence is dependent on the type of incontinence and the person's age, medical history, and desire for therapy. The assessment for incontinence should include a history; physical examination; and mental, functional, and environmental assessments.

The characteristics of the incontinence are noted, including the onset, frequency, and severity as determined through the person's description of the problem and the pattern of incontinence behavior.

Urinary symptoms provide clues to possible causes of the problem and, when combined with the information obtained from a history and physical examination, a provisional diagnosis can often be made.

The patient should be thoroughly questioned about related urinary symptoms and habits. Symptoms can be classified as obstructive or irritative. Obstructive symptoms include hesitancy, dribbling, intermittency, impaired trajectory, and sensation of incomplete emptying. Irritative symptoms include nocturia, frequency, urgency, and dysuria. Obstructive symptoms often require referral to a specialist, whereas irritative symptoms can often be controlled by behavioral interventions.

## TABLE 10–3

## Other Factors Causing Incontinence

| Drug | Side Effect |
|---|---|
| Antidepressants, antipsychotics, sedatives/hypnotics | Sedation, retention (overflow) |
| Diuretics | Frequency, urgency (OAB) |
| Caffeine | Frequency, urgency (OAB) |
| Anticholinergics | Retention (overflow) |
| Alcohol | Sedation, frequency (OAB) |
| Narcotics | Retention, constipation, sedation (OAB and overflow) |
| Alpha-adrenergic blockers | Decreased urethral tone (stress incontinence) |
| Alpha-adrenergic agonists | Increased urethral tone, retention (overflow) |
| Beta-adrenergic agonists | Inhibited detrusor function, retention (overflow) |
| Calcium channel blockers | Retention (overflow) |
| ACE inhibitors | Cough (stress incontinence) |

OAB = Overactive Bladder

Obtaining a recent medical history can identify acute or reversible causes. Significant past medical history includes the number of births, recurrent urinary tract infections, bladder repair surgeries, and pelvic radiation. The history should include an assessment of memory impairment and environmental barriers. A mental status assessment should be performed if the person has memory loss. Certain environmental barriers, such as the location of the toilet, may be contributing to the incontinence. This is especially true in older persons. In these cases, incontinence may improve with the use of catheters or other urine assistive or collective devices.

### 5.3 Urodynamics

Urodynamic assessment includes a group of tests that measure bladder function. Multichannel urodynamic studies include uroflow, cystometrogram, urethral pressure profiles, and electromyogram. Today, multichannel urodynamic studies to document bladder pressure and capacity, muscle contractibility, urethral length, and sphincter control are performed under the auspice of a gynecologist specializing in disorders of the pelvic floor or an urologist. These studies should be done if surgery on the pelvic floor is being considered for UI.

### 5.4 Treatment

Treatment for incontinence depends on the type of incontinence, its causes, and the capabilities of the patient. The evidence on the effects of clinical interventions will be reviewed below.

#### *5.4.1 Pelvic Muscle Rehabilitation (To Improve Pelvic Muscle Tone and Prevent Leakage)*

*Pelvic Floor Muscle Exercises*

**Kegel Exercises.** Regular, daily exercising of pelvic muscles can improve, and even prevent, urinary incontinence. This is particularly helpful for younger women. Kegel exercises should be performed 30–80 times daily for at least 8 weeks.

**Biofeedback:** Used in conjunction with Kegel exercises, biofeedback helps people gain awareness and control of their pelvic muscles.

***Regular, daily exercising of pelvic muscles can improve, and even prevent, UI.***

One review identified 15 RCTs, 8 of sufficient quality for conclusion in a further analysis.[63] Women performing pelvic floor muscle exercises in comparison with no treatment were more likely to be dry or mildly incontinent than the no treatment group (61 percent versus 3 percent). After 3 months, incontinent episodes were significantly reduced in the treatment group. There was a greater rate of "cure or almost cure" for high intensity home-based pelvic floor muscle exercise versus low intensity (60 percent versus 17 percent). There were five randomized clinical trials comparing biofeedback versus pelvic floor muscle exercise. One trial found biofeedback significantly improved UI, while the other four found no difference.

In a meta-analysis of the five trials identified in the systematic review, the odds ratio (OR) for biofeedback combined with pelvic floor muscle exercises alone, leading to cure was 2.1 (95 percent confidence interval (CI) 0.99–4.4).[64] The authors concluded that biofeedback might be an important adjunct to pelvic floor muscle exercises alone in the treatment of female genuine stress UI. A quantitative statistical analysis of the studies identified leads to different conclusions from those in the systematic review. One randomized clinical trials compared pelvic floor muscle training with bladder training or the two treatments combined.[65] Combination of therapy had the greatest immediate satisfaction in the management of female UI regardless of urodynamic diagnosis. However, each of the three interventions had similar effects 3 months after treatment.

*Vaginal Weight Training*

Small weights are held within the vagina by tightening the vaginal muscles. Vaginal weight training should be performed for 15 minutes, twice daily, for 4 to 6 weeks.

The systematic review described above identified three randomized clinical trials comparing pelvic floor muscle exercise alone or in combination with an intravaginal resistance device (one clinical trial) or biofeedback (two clinical trials).[63] There was no significant difference in the frequency of incontinent episodes per week. One randomized clinical trials compared pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment for genuine stress incontinence. Training of the pelvic floor muscles was superior to electrical stimulation and vaginal cones in the treatment of genuine stress incontinence.[66]

*Pelvic Floor Electrical Stimulation*

Mild electrical pulses stimulate muscle contractions. Pelvic floor electrical stimulation should be performed in conjunction with Kegel exercises.

Two systematic reviews of randomized clinical trials found conflicting evidence on the effects of electrical stimulation of the pelvic floor in women with stress incontinence.[63,65] randomized clinical trials have found it less effective than pelvic floor muscle exercises.

### *5.4.2 Behavioral Therapies (To Assist In Regaining Control of Bladder Function)*

**Bladder Training:** It teaches people to resist the urge to void and to gradually expand the intervals between voiding. Biofeedback and muscle conditioning, known as bladder training, can alter the bladder's schedule for storing and emptying urine. These techniques are effective for urge and overflow incontinence. The evidence on biofeedback is reviewed above.

**Toileting Assistance:** Toileting assistance uses routine or scheduled toileting, habit training schedules, and prompted voiding to empty the bladder

regularly to prevent leaking. Timed voiding (urinating) and bladder training are techniques that use biofeedback. In timed voiding, individuals fill in a chart of voiding and leaking. From the patterns that appear in their chart, they can plan to empty their bladder before they would otherwise leak.

### 5.4.3 Pharmacologic Therapies

*Alpha-Adrenergic Agonists*

Alpha-adrenergic agonist drugs may improve the micturition of patients suffering from forms of incontinence requiring increased muscle tone and urethral resistance. Phenylpropanolamine hydrochloride, the prototype agent in this class, is an independent risk factor for hemorrhagic stroke in women.[67] One systematic review identified one randomized clinical trial on phenylpropanolamine.[63] There was no significant difference between pelvic floor muscle exercise and phenylpropanolamine. New alpha-adrenergic agonists with tissue selectivity are in development—oxymetazoline and methoxamine.

*Muscarinic Receptor Antagonists*

Tolterodine tartrate (Detrol, Pharmacia Corporation, Peapack, NJ) is classified as a muscarinic receptor antagonist: it blocks nerve receptors that respond to the chemical muscarine. Both bladder contraction and salivation (formation of saliva) are controlled by muscarinic receptors. By blocking muscarinic nerve receptors, tolterodine tartrate can reduce symptoms of urinary frequency or urgency and can treat bladder overactivity and urge incontinence.

Two randomized clinical trials showed tolterodine administration resulted in a significant decrease in the frequency of voiding and improved voided volume with few troublesome or severe side effects.[68,69] Two other RCTs compared tolterodine and oxybutinin. One study compared the efficacy and safety of tolterodine given at 1 or 2 mg b.i.d. versus placebo.[70] At week 4, a statistically significant increase in the volume at first contraction ($p = 0.030$) and maximal cystometric capacity ($p = 0.034$) occurred only in the tolterodine 2 mg b.i.d. group. The other studied the clinical efficacy (determined from micturition diaries) and safety of 12 weeks' treatment with either tolterodine 2 mg twice daily, oxybutinin 5 mg three times daily, or placebo in 277 patients with an overactive bladder.[71] Both tolterodine and oxybutinin significantly increased volume voided/micturition compared to placebo. Both treatment groups evoked greater decreases in micturition per 24 hours and incontinence episodes per 24 hours compared to placebo; however, only tolterodine was significantly better than placebo in reducing micturition frequency.

***Tolterodine administration resulted in a significant decrease in the frequency of voiding and improved voided volume.***

*Anticholinergic Medications*

Oxybutynin (brand name Ditropan, Alza Pharmaceuticals, Kalamazoo, MI) prevents urge incontinence by relaxing detrusor muscle. One RCT shows the benefit of oxybutynin in reducing the episodes of incontinence.[72] A once-daily formulation (Ditropan XL) reduced the number of incontinence episodes with less side effects than the short-acting formulation.[73–75] Oxybutinin and tolterodine are equivalent in their effectiveness. A recent RCT of biofeedback, medication, and placebo showed behavioral treatment was significantly more effective than drug treatment and both were more effective than the placebo control condition.[76]

*Estrogen Replacement Therapy*

Estrogen, oral or vaginal, until recently has been thought to improve incontinent episodes, either alone or in conjunction with other treatments, for postmenopausal women with incontinence. Both the urethra and trigone of the bladder are covered by non-keratinized squamous epithelium similar to the vagina.[77] These tissues contain ERs[78,79] and respond to estrogen.[80,81] In the baboon model, ERT increased urethral closure pressures, suggesting that ERT might be effective treatment for incontinence.[82]

There has been one systematic review and 17 uncontrolled trials of estrogen for the treatment of incontinence in women.[83] Although the uncontrolled trials showed subjective improvement of incontinence, three randomized clinical trials found no objective improvement in measures of urine loss. Two subsequent RCTs found no significant difference between treatment and control groups in the number of incontinent episodes at 3 and 6 months of followup.[84,85] Several large observational studies have shown an increased risk of UI in older women on HRT.[86–88] There are no data on the use of vaginal estrogen creams or the estrogen ring for the treatment of incontinence. A randomized clinical trial (HERS) found HRT to be associated with worsening of UI.[89]

*Combined Estrogen/Alpha-Adrenergic Agonist Therapy*

Since ERT appears to heighten the response of nerve receptors in the urethra (the alpha-adrenergic receptors, which increase the tone of striated and smooth muscle), a combination of estrogen and alpha-adrenergic agonists may be beneficial in postmenopausal women who lose bladder control because of insufficiency (malfunction) of the urinary sphincter muscles. Two trials of combination therapy concluded that frequency and nocturia improved more with combined treatment than with estrogen alone.[76] Newer agents in development may offer promise in combination with estrogen. Phenylpropanolamine should no longer be used for the treatment of UI.

***Surgical treatment can be very effective in improving or curing stress incontinence.***

#### *5.4.4 Bulking Injections (Such as Collagen)*

An RCT on periurethral injection of collagen in women with genuine stress incontinence followed for 5 or more years found no evidence to support the use of periurethral collagen injections in women with intrinsic sphincter deficiency.[90] A recent case series of 63 consecutive women who had sphincteric incontinence confirmed by urodynamics and who underwent a total of 131 transurethral collagen injections showed a low short-term cure rate.[91]

#### *5.4.5 Surgical Treatment*

Surgical treatment can be very effective in improving or curing stress incontinence.

### 5.5 Treatment Recommendations for the Chronically Incontinent

Although many people will improve their continence through treatment, some will never become completely dry. They may need to take medications that cause incontinent episodes or have cognitive or physical impairments that keep them from being able to perform pelvic muscle exercises or retrain their bladders. Many will be cared for in long-term care facilities or at home. The AHRQ guideline update makes the following recommendations to help caregivers keep the chronically incontinent drier and reduce their cost of care:

- ***Scheduled toileting.*** Take people to the toilet every 2 to 4 hours or according to their toilet habits.
- ***Prompted voiding.*** Check for dryness, and encourage use of the toilet.
- ***Improved access to toilets.*** Use equipment such as canes, walkers, wheelchairs, and devices that raise the seating level of toilets to make toileting easier.
- ***Managing fluids and diet.*** Eliminate dietary caffeine (for those with urge incontinence), and encourage adequate fiber in the diet.
- ***Disposable absorbent garments.*** Use to keep people dry.
- ***Education***

The AHRQ guideline recommends that patients and professionals learn about the different treatment options for incontinence. Patients and their families should know that incontinence is not

inevitable or shameful but is treatable or at least manageable. All management alternatives should be explained. Professional education about incontinence evaluation and treatment should be included in the basic curricula of undergraduate and graduate training programs of all health care providers, as well as continuing education programs.

## 6. Urinary Tract Infections

Estrogens may increase alpha receptor sensitivity in urethral smooth muscle.[92] In addition, estrogen treatment increases numbers of epithelial cells in the urethra and bladder. Through those mechanisms, estrogen may reduce urinary tract infections.

## 7. Pelvic Organ Prolapse

SERMs may increase risk for pelvic organ prolapse.[93] The possible risk for pelvic organ prolapse with SERMs was first identified in the clinical trials of levormeloxifene. Subsequently, the development of this pharmaceutical was discontinued, primarily for endometrial concerns. However, pelvic organ prolapse was reported to the Food and Drug Administration (FDA) as an adverse event associated with the drug.

Idoxifene was the second SERM in which a preponderance of prolapse cases was observed in treated versus untreated women. Of the 1,436 nonhysterectomized women enrolled in two clinical trial groups, there were 9 uterine prolapses, 3 cystoceles (bladder prolapse), and 3 cystocele/rectocele (bladder/rectal prolapse) combinations; all were identified in the treated group (there were 14 cases total; 1 subject had uterine prolapse and cystocele/rectocele), and 0 cases were identified in the untreated group (B. MacDonald, personal communication). The cohorts were evenly matched for BMI (a stratification variable) and age. This difference between groups was statistically significant by Fisher's exact test, $p < 0.0001$. Heavy cigarette smoking was an exclusion criterion, and data on parity were not collected. As mentioned earlier, this drug has also been discontinued from development for concerns both with the endometrium and pelvic organ prolapse.

***Estrogen may reduce urinary tract infections.***

In the phase 2 studies of droloxifene, the prevalence of all prolapse disorders at baseline in over 1,000 women was 10 percent, the same in both groups (A. Lee, personal communication). In the phase 3 studies, 300 osteoporotic women on 4 different doses, the incidence of prolapse was the same between groups. Clinical trials with this drug have been closed because of endometrial stimulation. To this author's knowledge, no increase in incidence has been reported with raloxifene[94] or tamoxifen.[95]

While only levormeloxifene and idoxifene showed a problem with prolapse, all SERMs must be evaluated for this adverse effect. Although the predominance of pelvic organ prolapse was higher in the group treated with idoxifene, the overall incidence was lower than that commonly reported in the general population. While confounding factors, such as age, parity, obesity, and cigarette smoking, were not established as equal between groups, the obvious imbalance of prolapse in the treated group should not be ignored.

There are many inconsistencies in the adverse events between groups in the clinical trials on these drugs that cause us to examine the results more carefully. The incidence of prolapse was extraordinarily low in the idoxifene study (0 percent in the untreated group and 1.5 percent in the treated group). Although pelvic organ prolapse is one of the most common indications for gynecologic surgery, there is little epidemiologic information regarding the condition. In one report from Quebec, it accounted for 13 percent of all hysterectomies in all age groups.[96] The idoxifene groups were not necessarily similar for confounding factors, such as age, parity, obesity, cigarette smoking, and other risk factors for pelvic organ prolapse. A difference between groups could explain the differ-

ence in pelvic organ prolapse. The majority of the case reports on idoxifene occurred after rumors surfaced of problems with pelvic organ prolapse in the levormeloxifene phase 3 trial. The investigators may have become sensitized to looking for prolapse after the reports on levormeloxifene.

## 8. Future Needs

- More data are needed on the determinants of endometrial function and on the specific effect of ovarian hormones on skin and different urogenital mucosae.
- New ERβ and ERα agonists and antagonists as well as new progestins are needed.
- There is a need for sensitive methods for early diagnosis at the molecular level of estrogen defects in various tissues, additional noninvasive methods of endometrial testing, and reliable diagnostic indexes for pelvic floor and urogenital syndromes, to improve clinical testing.
- Future clinical trials need to assess the relationship between SERMs and pelvic organ prolapse; future preclinical studies need to investigate whether some SERMs modify or otherwise affect collagen, increasing the elasticity of the pelvic floor tissues and increasing the risk for pelvic organ prolapse.
- Future clinical trial research should include the use of a standardized pelvic exam administered by gynecologists or other clinicians trained in a uniform approach, and consideration should be given to excluding those women with moderate to severe prolapse until the effect of SERMs on the risk of prolapse is better known.

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# Chapter 11: Hormone Replacement Therapy, Related Therapies, and Cancer Epidemiology

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## Key Points[a]

1. There is no appreciable association between short-term (i.e., < 5 years) use of HRT and breast cancer risk. Longer use is associated with a moderate excess breast cancer risk for current users but not former users. Combined HRT may be associated with higher breast cancer risk compared with unopposed estrogen.
2. Combined HRT is not related to a major excess of endometrial cancer, if progestins are given for more than 10–14 days per cycle.
3. The evidence for HRT and ovarian cancer risk is less consistent than that for endometrial and breast cancer, but available data include the possibility that HRT increases ovarian cancer risk.
4. HRT may reduce colorectal cancer risk, but further research is required to confirm and quantify a favorable effect of HRT on colorectal cancer.
5. There is no consistent association between HRT use and liver cancer, other gastrointestinal neoplasms, or melanoma.
6. SERMs may have a favorable effect on breast cancer, CVDs, and bone. Research studies examining these issues with raloxifene therapy are in progress.

***There is no appreciable association between short-term (i.e., < 5 years) use of HRT and breast cancer risk.***

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.) All findings in this chapter belong to evidence category C, as they address side effects rather than interventions. This should not weaken the significance of the results.

## 1. Introduction

Worldwide, breast cancer is by far the most frequent cancer in women and the leading cause of death, accounting for more than 300,000 deaths each years as estimated from 1999 statistics.[1,2] Ovarian cancer adds another 100,000 deaths each year and cancer of the uterus adds 40,000. In the United States, breast cancer (the second leading cause of cancer death in women, after lung or bronchial cancers) and cancers of the ovary and uterus account for 23 percent of cancer deaths in women as estimated for 2000.[3]

***Worldwide, breast cancer is by far the most frequent cancer in women and the leading cause of cancer death in women.***

Menopause and age at menopause have a profound effect on the risk of cancer in women, including breast, endometrium, ovary, and other less common cancers. Although the incidence rises with age, the rate slows around the time of menopause for most cancers, which does not occur with hormone-independent adult cancers, such as lung cancer.[4]

Age at menopause is a recognized risk factor for breast cancer, with risk increasing with later age at menopause.[5–7] It is unclear whether latency effects are involved or whether the association between menopause and breast cancer risk varies by different ages at breast cancer diagnosis.[7–9] The most precise and reliable estimate of the influence of age at menopause on breast cancer risk is given by the collaborative reanalysis of individual data from 51 epidemiologic studies, most conducted in North America or Europe, of 52,705 women with breast cancer.[10] The Collaborative Group believed these studied represented > 90 percent of the observational data available at that time. Thirty-three percent of women had received HRT at some time. Among never users, an increased risk of 2.8 percent per year of delayed menopause was estimated.

Difficulties also exist in understanding and in disentangling the potential effects of type of menopause. Trends similar to those observed for all menopausal types were detected in women experiencing surgical menopause in some studies,[7,11] while they differed in others.[9,12] This is probably attributable to varying definitions of surgical menopause, with some studies including only women with a hysterectomy alone and others also including those with unilateral or bilateral oophorectomy. Inclusion of women with simple hysterectomy leads to an underestimation of the effect of age at menopause, as well as of exogenous hormones, on breast cancer risk.[13]

Pooled data from two case-control studies conducted between 1983 and 1994 in Italy[14] on 3,576 menopausal women with incident, histologically confirmed breast cancer and 3,578 menopausal control subjects admitted to hospital for acute, nonneoplastic, nonhormonal, nongynecological conditions provided information on the role of age and type of menopause. When all types of menopause were considered together, the floating absolute risks (FARs) (which avoid the definition of an arbitrary reference category)[15] were 0.49 for < 35 years, 0.81 for 35–39 years, 0.82 for 40–44 years, 0.88 for 45–47 years, 1.02 for 48–50 years, 1.23 for 51–53 years, and 1.24 for 54–56 years, with a significant linear trend in risk. A stronger association was observed in women reporting natural menopause, with FARs of 0.14 for women with menopause < 35 years versus 1.20 for those with menopause at 54–56 years (ratio between the two extreme FAR estimates = 8.6). No trend with age at menopause was seen among the overall surgical menopause group, or among groups defined by hysterectomy alone, hysterectomy with unilateral oophorectomy, or bilateral oophorectomy. When only women reporting bilateral oophorectomy were considered, a strong linear trend in risk was observed. No heterogeneity emerged when risks were evaluated in separate strata of age at diagnosis/interview.

Later menopause has also been associated with increased risks of ovarian[16] and endometrial can-

cers,[17] and perhaps with a reduced risk of colorectal cancer,[18] although this issue is still open to discussion.

Of major concern is the effect on cancer risk of HRT.[19,20] HRT reduces climacteric symptoms (see ch. 3) and has favorable effects on bone metabolism and osteoporosis (see ch. 9) and possibly on coronary heart disease and other CVDs (see ch. 8).[21–23] It may also reduce the risk of colorectal cancer.[24] Total mortality among women who use HRT is lower than among nonusers, which probably to a large extent reflects favorable health characteristics of women who decide and continue to use HRT.[25]

HRT has also a number of adverse effects, the main ones being a promotional effect on endometrial cancer, and some elevation in the risk of breast and, possibly, ovarian cancers.[20,26,27] These hormonal effects on risk of various neoplasms are considered in the present review.

## 2. Breast Cancer

***Breast cancer incidence varies markedly among countries.***

A summary tabulation of the main risk factors for breast cancer is given in table 11–1.

Breast cancer incidence varies markedly among countries. It is highest in the United States and Northern Europe and lowest in Asia.[28] Numerous observational epidemiologic studies have examined the relationship between HRT and breast cancer, providing answers often

### Table 11–1

### Summary Tabulation of Risk Factors for Breast Cancer

| Factors Influencing Risk | Estimated Relative Risk* |
|---|---|
| Residency in North America or Europe versus Asia | 4–5 |
| Residency in urban areas | 1.5 |
| White race | 2 |
| Higher levels of education or income | 1.5 |
| Mother or sister with breast cancer | 2–3 |
| Nulliparity or late ages at first birth (> 30 versus < 20 yr) | 2–3 |
| Absence of breastfeeding for long durations | 1.5 |
| Early ages at menarche (< 3 versus > 15 yr) | 1.5 |
| Late ages at natural menopause (> 55 versus < 45) | 2 |
| Recent use of estrogens or combined estrogen-progestin replacement therapy | 1.4–1.8 |
| Use of oral contraceptives (premenopausal risk only) | 1.2 |
| High cumulative doses of tamoxifen | 0.5 |
| Biopsy confirmed proliferative breast disease or dense mammographic patterns | 2–5 |
| Overweight (postmenopausal risk only) (BMI > 28 versus < 22) | 2 |
| Radiation to chest in moderate to high doses | 1.5–2 |
| History of breast cancer in one breast | 2–4 |
| History of primary cancer in endometrium, ovary | 1.5–2 |

*Relative risks depend on the population under investigation and reference group employed.

difficult to compare because of complex methodological issues, statistical power. and potential confounding variables.

### 2.1 Hormone Replacement Therapy and Breast Cancer

***There are no available data from clinical trials investigating the relationship between HRT and breast cancer.***

As with age at menopause, most information on HRT and breast cancer derives from a reanalysis of individual data from 51 epidemiologic studies, conducted in 21 countries and including 52,705 women with breast cancer and 108,411 controls.[10] This showed a 2.3 percent (95 percent CI, 1.1 to 3.6 percent) increase in the RR of breast cancer for each year of HRT use among current or recent users (who stopped use 1 to 4 years previously). This corresponds to an RR of 1.35 (95 percent CI 1.20 to 1.49) for those who had used HRT for 5 years or more and to a cumulative excess for women who began use of HRT at age 50 of approximately 2 cases/1,000 women for 5-year users, 6 cases/1,000 women for 10-year users, and 12 cases/1,000 women for 15-year users compared with never users. This increase was comparable with the effect of later menopause on breast cancer. This elevated risk, however, leveled off after stopping HRT use, with no significant excess risk observed at 5 or more years after stopping, as compared to never users.

The use of HRT for a short time (i.e., < 5 years) to control menopausal symptoms is not related to any material increase in the risk of breast cancer, whereas long-term use increases breast cancer risk in current users.[10,21,29] The biologic mechanism underlying this association remains unclear. Changes in the composition of the breast tissue have been documented, with greater mammographic density (an established risk factor for breast cancer) noted following hormone use.[30,31] Also of interest is whether genetic factors, including polymorphisms in hormone-metabolizing genes, might be etiologically involved. Further research in this area is critically needed.

Another open question is the impact on breast cancer risk of the combination of estrogen and progestin, a replacement therapy effective in reducing the excess endometrial cancer risk associated with estrogen use alone.[32] There are biologic reasons to suspect an unfavorable effect of added progestin on breast carcinogenesis, since ovulatory cycles are related to breast cancer risk and breast mitotic activity is higher during the luteal phase of the cycle (when progesterone levels are at their highest).[33,34] An early report of a Swedish cohort study[35] suggested that combined HRT may be more strongly related to breast cancer risk than estrogen alone, with a nonsignificantly elevated RR of 1.2 for ever use and of 4.4 for more than 6 years use of combined HRT (95 percent CI 0.9 to 22.4), based on 10 cases (hence a wide CI); the RR was 1.8 (1.0 to 3.1) for > 9 year use of estrogen alone, on the basis of data on 23 cases). An update of the same study[36] confirmed these findings, showing RRs of 1.4 (95 percent CI 0.9 to 2.3) after 1 to 6 years and 1.7 (95 percent CI 1.1 to 2.6) after more than 6 years of use of combined HRT. The excess risk, however, appeared confined to recent users. No excess risk relative to short-term users was shown for users of estrogen alone. Three other studies from Britain,[37] Denmark,[38] and Sweden [39] showed an association between combined HRT and breast cancer. A report from the American Nurses' Health Study cohort[40] confirmed some excess breast cancer risk among current long-term HRT users versus never users: the RRs were 1.3 (95 percent CI 1.1 to 1.5) for conjugated estrogen users, 1.3 (95 percent CI 1.0 to 1.7) for other estrogen users, and 1.4 (95 percent CI 1.2 to 1.7) for estrogen plus progestin. A large case-control study (N = 3,345 and 3,454) in Sweden risk showed a significant increasing risk with duration of different types of combined estrogen-progestin use (OR of 3.0 for women treated for more than 10 years).[41]

A recent report of 46,355 participants followed for a mean of 10.2 years in the Breast Cancer Detection and Demonstration Project (BCDDP)

showed that women who had used combined estrogen and progesterone had a 40-percent increased incidence rate (RR 1.4, 95 percent CI, 1.1 to 1.8) of developing breast cancer compared with never users.[42] Furthermore, the risk from combined HRT was greater than with unopposed estrogen (RR 1.2, 95 percent CI 1.0 to 1.4), compared to cases in which HRT had never been used. The increased risk was limited to recent use of hormones (current use or use within previous 4 years). The increased risk was also largely confined to women with a BMIs ≤ 24.4 or less, which indicates that there could be a threshold effect of HRT since heavier women are likely to have a higher average level of endogenous estrogen that in itself increases risk. After menopause, adipose tissue is the major source of endogenous estrogen, which may account for the continued slow rise in incidence of hormone-dependent cancers in postmenopausal women in countries with a high prevalence of overweight and obesity.[4,17]

Likewise, a population-based case-control study (N = 1,897 and 1,637) conducted among postmenopausal women from Los Angeles County[43] found an OR of 1.1 (95 percent CI 0.97 to 1.15) for each 5 years of ERT use, but of 1.2 (95 percent CI 1.07 to 1.45) for each 5 years of combined estrogen-progestin treatment, suggesting that the addition of a progestin to HRT enhances the risk of breast cancer relative to estrogen use alone.

The reanalysis of individual data from 51 studies,[10] however, found a similar excess breast cancer risk for women using estrogen alone and combined estrogen-progestin replacement treatment, and no marked differences in relation to hormone types or doses of HRT preparations, although little information was available about long duration of use of any specific preparation. The issue, therefore, remains open to discussion and further quantification.[44]

A case-control study from Washington State[45] suggested that combined HRT increases the risk of lobular but not ductal breast carcinoma, but the findings are inconclusive due to the small number of exposed cases.

There are no available data from clinical trials investigating the relationship between HRT and breast cancer, but the PEPI trial reported that increased mammographic density was observed in 3.5 percent of the estrogen-only group and in 16 to 23 percent of the different estrogen/progestin regimens.[46] Some studies have suggested that mammographic parenchymal density may adversely affect diagnostic accuracy.

Another major issue is the time-risk relationship after stopping HRT. The effect of steroid hormones is thought to be on the later stages of carcinogenesis (i.e., they are promoters);[47] consequently, the increased breast cancer risk associated with HRT should decline within a few years after stopping use.

Although the absence of a long-term cumulative risk is clearly reassuring,[48] a 20- to 30-percent excess risk of breast cancer in women aged 50 to 65 years—when HRT use is most frequent—has to be weighed against the benefits of HRT on the bone and perhaps on the cardiovascular system, since the incidence of breast cancer is high in the sixth decade of life.[49–51]

***In conclusion, evidence from observational epidemiologic studies indicates that the risk of breast cancer is elevated among women using HRT.***

Another open question is whether the relation between HRT and breast cancer risk differs at various ages. Since there are indications that it is influenced by age at diagnosis, with a higher RR in older women,[40,52] any risk-benefit ratio is particularly critical and must be carefully and individually assessed for elderly women using HRT after menopause.[53,50] However, in reanalysis of individual data from the 51 studies, no significant interaction was observed between the RR for HRT use and age,[10] although elderly women were at a greater absolute risk of breast cancer given increasing incidence trends with age.

Although HRT has been related to an increased incidence of breast cancer, use appears to lead to lower mortality from breast cancer or to improved prognosis in some,[53–60] although not all,[25,61] studies. Although some of these effects may be due to increased medical surveillance and detection of early-stage tumors among hormone users,[57] a favorable effect of hormone use on the characteristics of breast tumors cannot be dismissed.[62]

***Epidemiologic evidence now confirms the existence of a relationship between estrogen use and endometrial cancer.***

Although a diagnosis of breast cancer has been conventionally viewed as a contraindication for subsequent HRT use, as breast cancer patients remain at risk for recurrence of their cancers for many years,[63] this notion is being questioned;[4] recent data show favorable effects of HRT on breast cancer prognosis. Although the few studies that have addressed this issue seem to indicate no adverse effects of HRT use among breast cancer survivors, sample sizes have been limited.[65] Additional studies are needed.[66]

In conclusion, evidence from observational epidemiologic studies indicates that the risk of breast cancer is elevated among women using HRT, increases with longer duration of use is reduced after cessation of use and levels off about 5 years after stopping use. Recommendations for prolonged HRT use must be considered on an individual basis, taking into account the presence of other risk factors for breast cancer, such as family history of breast cancer or a personal history of benign breast disease.

## 3. Endometrial Cancer

A summary tabulation of the main risk factors for endometrial cancer is given in table 11–2.

The possibility that HRT could increase endometrial cancer risk was suggested on the basis of a substantial rise in the incidence of endometrial cancer in the United States (particularly in California) in the early 1970s, following widespread unopposed HRT use.[17] Two case-control studies, published in 1975 in the same issue of the *New England Journal of Medicine*, confirmed this observation.[67,68] The possibility that this relationship might merely reflect a detection bias was raised, either through increased medical surveillance of HRT users or because estrogens caused bleeding of existing tumors, prompting the diagnosis of endometrial cancer. The presence of more differentiated neoplasms, and, hence, better survival rates after cancer diagnosis in HRT users, was also reported.[69]

Epidemiologic evidence now confirms the existence of a relationship between estrogen use and endometrial cancer and confirms the persistence of elevated risk several years after cessation of use.[70] The risk is about two to three times greater in ever than in never users of estrogen, with a summary the RR from a meta-analysis of published studies of 2.3 (95 percent CI 2.1 to 2.5);[71] the risk estimates were similar for cohort (RR 1.7) and case-control studies using hospital (OR 2.2) or population (OR 2.4) controls. The summary risk was directly related to duration of use: the RR was 1.4 (95 percent CI 1.0–1.8) for use < 1 year, 2.8 (95 percent CI 2.3–3.5) for 1–5 years, 5.9 (95 percent CI 4.7–7.5) for 5–9 years, and 9.5 (95 percent CI 7.4–12.3) for > 10 years; the RR was inversely related to time elapsed since last use,[71] suggesting that estrogen has a late-stage effect in endometrial[47,72] as well as in breast carcinogenesis.

Similarly to breast cancer, estrogen-associated risks for endometrial cancer tend to be higher in leaner than overweight women, who have higher endogenous estrogen levels and availability. The

## TABLE 11–2

## Summary Tabulation of Risk Factors for Endometrial Cancer

| Factors Influencing Risk | Estimated Relative Risk* |
|---|---|
| Residency in North America or Europe versus Asia | 4–5 |
| White race | 1.5–2 |
| Higher levels of education or income | 1.5–2 |
| Nulliparity | 3 |
| History of infertility | 2–3 |
| Menstrual irregularities | 1.5 |
| Early ages at menarche (< 13 versus > 15 yr) | 1.5–2 |
| Late age at natural menopause (> 55 versus < 45 yr) | 2 |
| Long-term use of ERT | 5–10 |
| Use of oral contraceptives | 0.3–0.5 |
| High cumulative doses of tamoxifen | 3–7 |
| Overweight (BMI > 28 versus < 22) | 2–5 |
| Stein-Leventhal disease or estrogen-producing tumors | > 5 |
| Histories of diabetes, hypertension, gallbladder disease, or thyroid disease | 1.3–3 |
| Cigarette smoking | 0.5 |

*Relative risks depend on the population under investigation and reference group employed.

combined effect of exogenous and endogenous estrogens is additive rather than multiplicative, suggesting that exogenous estrogens and obesity act through similar biologic mechanisms on the risk of the disease.[73] Estrogens and obesity appear, therefore, to have an additive rather than a multiplicative interaction, which suggests either an upper risk threshold and/or some limiting factor (e.g., sex hormone receptors), which stops the estrogen-raising effect of obesity and exogenous estrogen accumulating beyond a certain level.[73]

Some studies suggest a greater excess risk of HRT among smokers,[74] who tend to have lower estrogen availability,[75] and a lower HRT-related risk among women who had a history of use of combined OCs.[74,76] Others[77] failed to delineate a subgroup that is exempt from the increased risk of endometrial cancer associated with use of unopposed estrogen.

Data on the type, dose, or regimen of estrogen use do not provide a clear assessment of risk, and in general, there appears to be no clear relationship with type of preparation, its potency and bioavailability, dose and duration, although users of high-dose preparations tend to have a higher risk.[74,78] In the meta-analysis by Grady et al.,[71] the RR was 3.9 (95 percent CI 1.6 to 9.5) for users of 0.3 mg conjugated estrogens, 3.4 (95 percent CI 2.0 to 5.6) for users of 0.625 mg, and 5.8 (95 percent CI 4.5–7.5) for users of > 1.25 mg; it is not clear whether duration and other time factors could be adequately controlled in these analyses. The RR was 2.5 (95 percent CI 2.1 to 2.9) for users of conjugated estrogens and 1.3 (95 percent CI 1.1 to 1.6) for users of synthetic estrogens. With reference to pattern or regimen of use, the RR was 3.0 (95 percent CI 2.4 to 3.8) for intermittent and

cyclic use and 2.9 (95 percent CI 2.2 to 3.8) for continuous regimens.[71] It is not clear whether differences in the baseline characteristics of women using the various preparations may explain these apparent differences in RR.

In terms of population attributable risks, it has been estimated that unopposed estrogen treatment was related to more than 50 percent of cases of endometrial cancer in North America in the late 1970s[70] and 10–25 percent of cases in selected European countries in the 1980s.[76,79]

The cyclic addition of progestin to estrogen (for at least 7 days in each treatment cycle) protects against endometrial hyperplasia, which is considered an endometrial cancer precursor, as shown by a multicenter randomized clinical trial.[32] However, data on long-term consequences are not completely reassuring, since of 41 patients treated for a mean duration of 8 years, 6 patients experienced breakthrough bleeding and 2 had adenocarcinoma of the endometrium.[80]

***Descriptive studies are consistent with the absence of a major effect of HRT on ovarian carcinogenesis.***

The summary RR from a meta-analysis[71] of endometrial cancer in women using cyclic combined HRT was 0.8 (95 percent CI 0.6 to 2.2). However, the results from cohort and case-control studies were inconsistent, with the pooled RR being 0.4 for the cohort studies and 1.8 for the case-control studies.

The number of days per month of progestin addition is an important determinant of risk. One study[81] suggested that the RR was reduced from 2.4 for women using progestins for less than 10 days per month to 1.1 for women using them for ten days or more per month. In a population-based case-control study (N = 832 cases and 1,114 controls),[82] the RR for ever users was 3.1 (95 percent CI 1.7 to 5.7) for women with fewer than 10 days of added progestin per month and 1.3 (95 percent CI 0.8 to 2.2) for those with 10 to 21 days of added progestin. Another study of 833 cases and 791 population controls from Los Angeles County[83] showed RRs per 5 years of use of 2.2 (95 percent CI 2.0 to 2.5) for unopposed estrogen, 1.9 (95 percent CI 1.3 to 2.6) for estrogen plus progestin for less than 10 days per month, and 1.1 (95 percent CI 0.8 to 1.4) when progestin was given for 10 days or more.

A case-control (N = 709 and 3,368) study conducted in Sweden on endometrial cancer in menopausal women[84] confirmed a strong association with unopposed estrogen (OR = 6.2 for estradiol and 6.6 for conjugated estrogens for 5 or more years of use). The association was considerably less strong for the combination of estrogen and progestin (OR = 1.6, 95 percent CI 1.1 to 2.4), and the excess risk was restricted to cyclic progestin usage. The risk was below unity for continuous use of progestin (OR = 0.2, 95 percent CI 0.1 to 0.8 for use lasting 5 years or longer).

A record linkage study conducted in Sweden on a cohort of 8,438 women at risk of endometrial cancer[36] has shown—on the basis of 66 observed cases versus 34.8 expected—an RR of 4.2 (95 percent CI 2.5–8.4) for 6 years or more of use of unopposed estrogen and of 1.4 (95 percent CI 0.6–3.3) for combined estrogen and progestin replacement therapy.

In a case-control study conducted between 1994 and 1998 in Ontario, Canada (521 cases and 513 controls), the RR was 4.1 (95 percent CI 2.2–7.7) for use of > 5 years unopposed HRT, and around 1.5 (of borderline significance) for various types of combined replacement therapies, although the numbers of subjects were small in most subgroups.[85]

Thus, although the use of estrogen alone may increase endometrial cancer risk, several studies indicate that combined replacement therapy is not related to a major excess of endometrial cancer, if progestin is given for more than 10 or 14 days in each cycle.[86]

## 4. Ovarian Cancer

Descriptive studies are consistent with the absence of a major effect of HRT on ovarian carcinogenesis.[87] Major findings of cohort and case-control studies and reanalyses of individual data on HRT and ovarian cancer risk are shown in table 11–3.[88–106]

Two cohort studies have shown no relationship between use of HRT and ovarian cancer risk. They are the Walnut Creek Study on Contraception,[88] based on 16,638 women followed for 13 years (RR = 1.0), and a Swedish cohort study,[91] based on 23,246 women followed for an average of 8.6 years (RR 0.99, 95 percent CI 0.76–1.27). In contrast, in the American Cancer Society Cancer Prevention Study II (CPS-II),[89] based on mortality data of 240,073 women followed for 7 years, the RR was 1.4 (95 percent CI 0.9–2.1) for 6–10 years of use and 1.7 (95 percent CI 1.1–2.8) for ≥ 11 years of use of HRT; this elevated risk was not explained by other known or likely risk factors for ovarian cancer. The 14-year followup of the same CPS-II study[93] confirmed the relationship between HRT and ovarian cancer. The RR was 1.5 (95 percent CI 1.1–2.0) for ever use and 2.2 (95 percent CI 1.5–3.2) for baseline users (i.e., current users at interview). Among former users, the RR decreased with time since last use.

At least 12 case-control studies (see table 11–3) and a reanalysis of individual data of 12 U.S. case control studies have provided data on HRT and ovarian cancer risk. Of these, seven studies—including two from the United States,[94,98] one population-based case-control investigation from Canada,[103] and four European studies, from the United Kingdom,[99] Greece,[96,100] and Italy[101]—reported an increased RR (i.e., between 1.2 and 1.6) when compared to control subjects. In some, and particularly in the largest European studies,[99,101] the elevated risk estimates were significant. Other case-control studies published since 1980, including three in the United States,[92,97,104] one in Italy,[95] and two in Australia,[102,107] found no clear relationship between ever use of HRT and ovarian cancer risk.

The combined analysis of individual data from 12 United States case-control studies, based on 2,197 white women with invasive epithelial ovarian cancer and 8,893 white controls,[105] found a pooled multivariate RR of invasive ovarian cancer for ever HRT use of 0.9 (95 percent CI 0.7–1.3) in hospital-based and 1.1 (95 percent CI 0.9–1.4) in population-based studies; the analysis found no consistent duration-risk relation, after allowance for age, study, parity, and OC use. The overall RR per year of use was 0.98 for hospital-based and 1.02 for population-based studies; neither estimate was significant. The RR for ever HRT use was 1.1 (95 percent CI 0.7–1.9) in a reanalysis of original data considering 327 cases of borderline epithelial ovarian cancers.[106]

***Thus, the evidence on HRT and ovarian cancer is less consistent than that for endometrial and breast cancer, but a moderate association remains open to debate.***

A collaborative reanalysis of four European studies from the United Kingdom, Italy, and Greece, based on 1,470 ovarian cancer patients and 3,271 hospital controls found an OR of 1.71 (95 percent CI 1.30–2.25) for ever HRT use, a weak direct positive relationship with duration of use, and some indication that the excess RR for ovarian cancer declined with time since last use.[108] The overall RR estimate from a meta-analysis of all published data was 1.15 (95 percent CI 1.0–1.3) for ever use and 1.27 (95 percent CI 1.0–1.6) for > 10 years of use.[109]

It is not clear whether HRT is related to any specific histologic type of ovarian cancer. A Canadian study[103] found ORs of 1.4 for serous, 1.9 for endometrioid, and 0.7 for mucinous tumors, with significant trends in risk with duration of use for serous and endometrioid tumors. Purdie et al.[107] also found an elevated risk of endometrioid and clear cell ovarian cancers associated with unopposed estrogen use (RR 2.6, 95 percent CI 1.3–4.9).

## TABLE 11–3

## Selected Studies on Hormone Replacement Therapy in Menopause and Ovarian Cancer Risk, 1980–1997

| *Cohort Studies* | | | | |
|---|---|---|---|---|
| **Reference** | **Outcome** | **No. of Cases (Age Group)** | **Relative Risks for Ever HRT Use** | **Observations** |
| Petitti et al.,[88] 1987, U.S.A. | Mortality | 6 | 1.0 | 13-year mortality followup of the Walnut Creek Study on Contraception. |
| Rodriguez et al.,[89] 1995, U.S.A. | Mortality | 436 | 1.2 | Direct relationship with duration. The RR was 1.4 for 6–10 years and 1.7 for ≥ 11 years of use. |
| Adami et al.,[90] 1989, Sweden | Incidence | 64 | 1.0 | Cohort of 23,246 women prescribed HRT, followed for an average of 6.7 years. |
| Schairer et al.,[91] 1997, Sweden | Mortality | 52 | 1.0 | As above, followup for mortality 8.6 years. |
| *Case-Control Studies* | | | | |
| **Reference** | **Study Design** | **No. of Cases (Age Group)** | **Relative Risks for Ever HRT Use** | **Observations** |
| Hildreth et al.,[92] 1981, U.S.A. | Hospital-based | 62 (65–74) | 0.9 | Nonsignificant (95% CI 0.5–1.6). |
| Weiss et al.,[94] 1982, U.S.A. | Population-based | 112 (36–55) | 1.3 | No consistent duration-risk relationship. Stronger association for endometrioid neoplasms. |
| Franceschi et al.,[95] 1982, Italy | Hospital-based | 161 (19–69) | 1.0 | Adjusted for age, area of residence, and hysterectomy. |
| Tzonou et al.,[96] 1984, Greece | Hospital-based | 112 (postmenopause) | 1.6 | Nonsignificant. |

**TABLE 11–3 *(continued)***

| ***Case-Control Studies*** *(continued)* | | | | |
|---|---|---|---|---|
| **Reference** | **Study Design** | **No. of Cases (Age Group)** | **Relative Risks for Ever HRT Use** | **Observations** |
| Harlow et al.,[97] 1988, U.S.A. | Hospital-based | 116 (20–59) | 0.9 | Borderline ovarian neoplasms. No consistent duration-risk relationship. |
| Kaufman et al.,[98] 1989, U.S.A. | Hospital-based | 377 (18–69) | 1.2 | Unopposed estrogen only. No association with combined treatment (OR 0.7) or with specific histotypes. Some duration-risk relationship. |
| Booth et al.,[99] 1989, UK | Hospital-based | 158 (< 65) | 1.5 | Nonsignificant (95% CI 0.9–2.6). No association with specific histotypes. |
| Polychronopoulou et al.,[100] 1993, Greece | Hospital-based | 152 (30–64) | 1.4 | Nonsignificant (95% CI 0.4–4.9). |
| Parazzini et al.,[101] 1994, Italy | Hospital-based | 953 (23–74) | 1.6 | Adjusted for major covariates, including oral contraceptive use. 95% CI 1.2–2.3. Modest duration-risk relationship. |
| Purdie et al.,[102] 1995, Australia | Population-based | 824 (18–79) | 1.0 | Multivariate OR, 95% CI 0.8–1.3. |
| Risch et al.,[103] 1996, Ontario, Canada | Population-based | 367 | 1.3 | Multivariate OR 2.0 for serous and 2.8 for mucinous for ≥ 4 years of use. No association with mucinous tumours. |
| Hempling et al.,[104] 1997, U.S.A. | Hospital-based | 491 | 0.9 | Other cancers as controls. No duration-risk relationship. |

**TABLE 11–3 *(continued)***

| *Overviews* | | | | |
|---|---|---|---|---|
| **Reference** | **Study Design** | **No. of Cases (Age Group)** | **Relative Risks for Ever HRT Use** | **Observations** |
| Whittemore et al.,[105] 1992, U.S.A. | Pooled analysis of 12 U.S. hospital- and population-based case-control studies | 2,197 (all ages) | 0.9/1.1 | Invasive cancers. No duration-risk relationship. |
| Harris et al.,[106] 1992, U.S.A. | As above | 327 (all ages) | 0.9/1.1 | Borderline ovarian neoplasms. Hospital-based/population-based studies. No duration-risk relationship. |

Thus, a strong association between HRT and invasive or borderline malignant epithelial ovarian neoplasms can be excluded, although relationships with histological subtypes may exist. However, it is possible that ovarian cancers in women who had used HRT are more often classified as endometrioid tumors, and there is a lack of clear understanding of the biologic meaning of histologic type.

Very little information is available on the addition of progestin to estrogen preparations. In a cohort of 4,544 women, recruited since 1978 from 21 menopause clinics in Britain and followed to 1988,[55] HRT use could not be related to ovarian cancer risk increase (RR = 0.63); similarly, in a multicenter case-control study (N = 377 cases and 2,030 controls) conducted between 1976 and 1985 in various United States areas (Kaufman et al., 1989),[98] only 2 percent of cases and controls had ever used combination HRT, and the multivariate RR was 0.7 (95 percent CI 0.2–1.8).

Thus, the evidence on HRT and ovarian cancer is less consistent than that for endometrial and breast cancer, but a moderate association remains open to debate.

## 5. COLORECTAL CANCER

Colorectal cancer is the most frequent cancer in nonsmokers of both sexes combined in Western countries.[87,110] Similar incidences between the two sexes are seen for colon cancer, while a male predominance is found for rectal cancer.

During the last two decades, mortality rates from colorectal cancer in many developed countries have declined in women but not in men.[24,87] A role of exogenous female hormones (i.e., OCs, and HRT) on these trends is possible.

Eight cohort studies (see table 11–4) reported information on HRT use and colorectal cancer risk, for a total of over 2,400 cases. Most studies showed RRs around or below unity. A significant inverse relation was found in two cohort investigations, including the largest one focusing on fatal colon cancers (table 11–4).[56,90,111–119] Findings from a recent study also suggested that HRT use may improve short-term survival after a diagnosis of colon cancer.[120]

Of 12 case-control studies (see table 11–5)[18,121–134] for a total of over 5,000 cases, five reported 20–40 percent significant risk reductions among ever users of HRT. Two additional investigations showed moderate, nonsignificant inverse relationships.

Studies showing an inverse relationship between HRT use and colorectal cancer were among the largest and best controlled ones. The apparent protection tended to be stronger among recent users. Differences in RRs by duration of HRT use and anatomic subsite were not consistent, but the protective effect seemed stronger in most recent publications. Available studies support the possibility of an inverse relationship between colorectal cancer and HRT, but prevention and surveillance bias cannot be ruled out.[135]

Very few studies have allowed distinguishing unopposed from opposed estrogen, and all included few subjects exposed to opposed estrogen only. Among these, one cohort study[56] and one case-control investigation[132] suggested an inverse relationship of opposed estrogen with cancer of the colon, as for HRT of any type. Differences in RRs by anatomic subsite were not consistent, but the data for rectal cancer are scantier than for colon cancer. Finally, risk reduction has appeared stronger in more recent publications.

A meta-analysis of 20 studies published up to December 1996[136] found an overall RR for ever HRT use of 0.85 (95 percent CI 0.7–0.9). The protection was greater for current or recent users (RR 0.69, 95 percent CI 0.5–0.9) and users of more than 5 years (RR 0.73, 95 percent CI 0.5–1.0).

Taken together, available data suggest the possibility of a real inverse association between colon cancer and HRT. A causal interpretation of the above findings is, however, hampered by (1) the time-related risk pattern observed; (2) the potential for prevention bias (i.e., a more favourable pattern of risk factor exposure)[137] or surveillance bias in women taking HRT;[8] and (3) lack of clear understanding of the possible mechanisms of action of HRT on colorectal mucosa. Postmenopausal women treated with HRT tend to be of higher social class and more educated.[137,139] This selection may imply a healthier lifestyle (e.g., more frequent consumption of vegetables, higher levels of physical activity, and lower prevalence of being overweight). In addition, long-term HRT users are, by definition, compliant, which is, *per se*, a favorable health indicator.[137] (See also ch. 4.)

The inverse relation between colorectal cancer risk and HRT tends to emerge soon after first exposure [113,127] and seems to level off 5–10 years after cessation. The apparent protection increases with duration in some[116,127] but not all[113,132] studies. Such a pattern of risk seems compatible with the possibility that HRT acts as a promoting agent.[140] Of the few studies on precursors for colorectal cancer, a large prospective investigation[127] found a decreased risk for large colorectal adenomas but no effect on risk for small adenomas. Of concern is the possibility that women may discontinue HRT when symptoms of disease develop,[138] leaving mainly healthy women in the category of current users. However, no difference in risk was found between current users and recent users (i.e., those who had stopped HRT in the past 5 years).[113]

***Colorectal cancer is the most frequent cancer in nonsmokers of both sexes combined in Western countries.***

Sex hormones modify hepatic cholesterol production and alter bile acid concentration.[141] Secondary bile acids are believed to favor malignant changes in the colonic epithelium, and exogenous estrogens, which decrease secondary bile acid production and can alter intestinal microflora, could, therefore, protect against colorectal cancer. Issa et al.[142] suggested that methylation-associated inactivation of the ER gene in ageing colorectal mucosa could predispose to colorectal tumorigenesis. Exogenous estrogen may thus counteract the natural decline of circulating estrogen in postmenopausal women. However, data on reproductive and men-

## TABLE 11–4

## Cohort Studies on Hormone Replacement Therapy and Colorectal Cancer

| Reference | Country | Population (Followup) No Cancer | RR (95% Confidence Interval) (Ever versus Never Users) | | | | Duration of Use | Recency of Use | Adjustment Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Colon-Rectum | Colon | Rectum | | | |
| Wu et al.,[111] 1987 | California, U.S.A. | 7,345 (4 years) 68 | | 1.00 (n. s.) | — | — | No effect (RR = 1.02, 0.6–1.8, for ≥ 8-year use) | Not shown | Age. |
| Adami et al.,[90] 1989 and Persson et al.[56] 1996 | Sweden | 22,597 (13 years) 233 62 deaths | HRT | — | 0.9 (0.7–1.1) | 0.9 (0.7–1.2) | No effect | Not shown | Age. RR for colon mortality = 0.6, 0.4–0.9. |
| | | | Estriol | | 1.0 (0.8–1.3) | 0.8 (0.5–1.2) | | | |
| | | | Opposed HRT | — | 0.6 (0.4–1.0) | 0.8 (0.4–1.3) | | | |
| | | | Any type | | 0.9 (0.7–1.2) | 0.9 (0.7–1.1) | | | |
| Chute et al.,[112] 1991 and Grodstein et al.,[113] 1998 | U.S.A., Nurses' Health Study | 59,002 (14 years) 470 | Current users | 0.7 (0.5–0.8) | 0.6 (0.5–0.9) | 0.7 (0.4–1.1) | No effect (RR = 0.7, 0.5–1.0, for ≥ 5 year use) | No risk reduction after 5 years of discontinuation (RR = 0.9, 0.8–1.2) | Age, BMI, OC use, cancer family history, diet, alcohol, smoking, and age at menopause. |
| | | | Past users | 0.8 (0.7–1.1) | 0.7 (0.7–1.1) | 0.8 (0.5–1.2) | | | |
| Bostick et al.,[114] 1994 and Folsom et al.,[115] 1995 | Iowa, U.S.A. | 41,837 (6 years) 293 | Former users | | 0.8 (0.6–1.1) | — | Inverse trend (RR = 0.31 for ≤ 5 year use) | No effect | Age, BMI, W/H ratio, alcohol, exercise, and medical history. |
| | | | Current users | | 0.7 (0.5–1.1) | | | | |

**TABLE 11–4 *(continued)***

| Reference | Country | Population (Followup) No Cancer | RR (95% Confidence Interval) (Ever versus Never Users) | | | | Duration of Use | Recency of Use | Adjustment Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Colon-Rectum | Colon | Rectum | | | |
| Calle et al.,[116] 1995 | U.S.A., CPS-II | 422,373 (7 years) 897 deaths | — | | 0.7 (0.6–0.8) | — | Significant trend (RR = 0.5, 0.4–0.8, for > 11 year use) | Stronger effect among current users (RR = 0.5, 0.4–0.8) | |
| Risch and Howe,[117] 1995 | Canada | 32,973 (14 years) 230 | | 1.0 (0.7–1.5) | 1.3 (0.9–1.9) | 0.6 (0.3–1.2) | RR = 0.7 (0.2–2.6 for ≥ 5 years) | Not shown | Age. Linkage study. |
| Troisi et al.,[118] 1997 | U.S.A., BCDDP | 33,779 (7.7 years) 313 | Unopposed HRT Opposed HRT | — | 1.1 (0.7–1.5) | 1.2 (0.7–2.3) | No effect | RR for recent use = 0.78 (0.55–1.1) | Age (but unaltered by education, BMI, parity and OC use). |
| | | | Any HRT | | 1.4 (0.7–2.5) | — | | | |
| | | | | 0.99 (0.79–1.2) | 1.1 (0.81–1.6) | 1.1 (0.59–1.9) | | | |
| Paganini-Hill,[119] 1999 | U.S.A., Leisure World Cohort | 7,701 (14.5 years) 249 | | 0.81 (0.63–1.04) | 0.70⁺ (0.45–1.09) | 0.52⁺ (0.21–1.31) | RR = 0.75 For ≥ 15 years | 0.66 (0.44–0.98) | Age. Significant trend with recency of use. |

BCDDP = Breast Cancer Detection Demonstration Project, BMI = Body Mass Index, W/H Ratio = Waist/Hip Ratio, OC = Oral Contraceptives.
⁺ = Recent users (≤ 1 year)

## TABLE 11–5

## Case-Control Studies on Hormone Replacement Therapy and Colorectal Cancer

| Reference | Country | Case: Control (Type of Controls) | RR (95% Confidence Interval) (Ever versus Never Users) | | | | Duration of Use | Recency of Use | Adjustment Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Colon-Rectum | Colon | Rectum | | | |
| Weiss et al.,[121] 1981 | Washington, U.S.A. | 143:707 (population) | | ≤ 5 yr: 1.1 (0.7–1.9)<br>≥ 6 yr: 1.0 (0.6–1.6) | — | — | No trend | Not shown | Age. |
| Potter and McMichael,[122] 1983 | Adelaide, Australia | 155:311 (population) | | — | 0.8 (0.4–1.5) | 1.5 (0.8–3.0) | | | Reproductive variables (diet was uninfluent). |
| Davis et al.,[123] 1989 | Canada | 720:349 (cancer patients) | Current users:<br>Former users: | 1.5 (0.8–2.7)<br>1.1 (0.7–1.9) | — | — | No trend | Not shown | Age and parity. No distinction was possible between HRT and OC use. |
| Furner et al.,[124] 1989 | Chicago, U.S.A. | 90:208 (spouses) | | 0.5 (0.3–0.9) | — | 0.2 (0.0–0.8) | No trend | Not shown | Age, parity, and hysterectomy. |
| Negri et al.,[18] 1989; Fernandez et al.,[125] 1996; Talamini et al.,[126] 1998; Fernandez et al.,[127] 1998 | Italy | 1,536:3,110 (hospital) | | 0.6 (0.4–0.8) | 0.6 (0.5–0.9) | 0.5 (0.3–0.7) | Significant (RR for ≥ 2 yr use = 0.5, 0.3–0.8) | RR ≥ 10 yr since last use: 0.5 (0.3–1.0) | Age, education, cancer family history, BMI, parity, menopause, OC, and energy intake. |

**TABLE 11–5 *(continued)***

| Reference | Country | Population Followup | RR (95% Confidence Interval) (Ever versus Never Users) | | | | Duration of Use | Recency of Use | Adjustment Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Colon-Rectum | Colon | Rectum | | | |
| Peters et al.,[128] 1990 | Los Angeles, U.S.A. | 327:327 (neighbours) | | < 5 yr<br>5–14 yr<br>≥ 15 yr | 1.3 (0.9–2.0)<br>1.1 (0.6–1.8)<br>1.1 (0.6–1.9) | — | No effect | Not shown | Cancer family history, parity, menopause, exercise, fat, alcohol, and calcium intake. |
| Wu-Williams et al.,[129] 1991 | North America and China | 189:494 (neighbours) | North America | | 2.1 p = 0.14 | 0.5 p = 0.23 | Not shown Mostly short duration use | Not shown | Unadjusted (but unaltered by exercise, saturated fat intake, and years in the U.S.A.). Artificial menopause was a risk factor in China. |
| | | 206:618 (neighbours) | China | | — p = 0.01 | p = 0.56 | | | |
| Gerhardsson de Verdier and London,[130] 1992 | Sweden | 299:276 (population) | | — | 0.6 (0.4–1.0) | 0.7 (0.4–1.3) | No trend | Not shown | Age. Hormone use included both HRT and OC, but mostly HRT. |
| Jacobs et al.,[131] 1994 | Seattle, U.S.A. | 148:138 (population) | | — | 0.6 (0.4–1.0) | — | Significant trend (RR ≥ 5 yr use = 0.5, 0.2–0.9) | RR in current users = 0.5, (0.3–1.0) | Age, vitamin intake and hysterectomy. Greater protection in multiparous women. |
| Newcomb and Storer,[132] 1995 | Wisconsin, U.S.A. | 694:1,622 (population) | Unopposed HRT<br>Opposed HRT<br>Any HRT (recent use) | | 0.5 (0.3–0.9)<br>0.5 (0.3–1.1)<br>0.7 (0.6–0.9) | 0.90 (0.46–1.76)<br>1.1 (0.5–2.5)<br>1.2 (0.8–1.6) | Significant trend (p = 0.002) | Lower RR for < 10 yr since last use = 0.5, (0.4–0.8) for colon | Age, alcohol, BMI, cancer family history, and, sigmoidoscopy. |

**TABLE 11–5 *(continued)***

| Reference | Country | Case: Control (Type of Controls - Ever vs. Never Users) | RR (95% Confidence Interval) (Ever versus Never Users) | | | | Duration of Use | Recency of Use | Adjustment Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Colon-Rectum | Colon | Rectum | | | |
| Kampman et al.,[133] 1997 | U.S.A., KPMC | 815:1,019 (KPMC members) | | — | 0.8 (0.7–1.0) | — | No trend | RR for recent use = 0.71 (0.56–0.89) | Age, cancer family history, aspirin and energy intake, OC, and exercise. |
| Yood et al.,[134] 1998 | Detroit, U.S.A. | 60:143 (HMO members) | Current use<br>Past use | 0.3 (0.1–1.0)<br>0.4 (0.1–1.4) | | — | Not shown | Not shown | Age, race, reproductive variables, dietary habits, and colonoscopy. |

BMI = Body Mass Index, HMO = Health Maintenance Organization, KPMC = Kaiser Permanente Medical Care, OC = Oral Contraceptives

strual correlates of colorectal cancer risk are inconclusive. Moderate inverse associations with parity and OC use have been reported, but a favorable role of later age at menopause is still unclear.[131,143,144]

Additional research is needed to confirm a potentially favorable effect of HRT on colorectal cancer. In Western countries, the numbers of deaths from colorectal and breast cancers in women aged 55 or older are similar (27,000 and 34,000, respectively, in 1994 in the United States).[145] Thus, a decrease in incidence or mortality from colorectal cancer could greatly affect the balance of risks and benefits associated with the use of HRT.

## 6. Other Neoplasms

A cohort study in Sweden of 23,244 women followed for 6.7 years suggested a slight excess risk of lung cancer related to the use of estrogen (RR = 1.3, 95 percent CI 0.9–1.7).[90] No information was available on the duration of use or any other risk factors. Two case-control studies in the United States have also examined the relationship between HRT use and risk of adenocarcinoma of the lung. One study of 181 cases found a 70-percent excess risk among HRT users, with the risk increasing to a twofold risk for users who had started treatment 25 or more months previously.[146] In another case-control study (N = 336 and 336), no substantial relationship was found between HRT use and risk.[147]

In the Swedish cohort study mentioned above,[90] a total of 13 cases of biliary tract and liver cancers were observed versus 31.7 expected, corresponding to a RR of 0.4 (95 percent CI 0.2–0.7). In an Italian case-control study, based on 82 histologically confirmed cases of primary liver cancer and 368 control subjects, a decrease in risk related to HRT was also noted (OR = 0.2, 95 percent CI 0.03–1.5).[148] However, no relationship between conjugated estrogen and other estrogen use and hepatocellular carcinoma was observed in another population case-control study involving 74 cases and 162 population controls from Los Angeles County;[149] the RR was 1.1 for ever use, and 1.0 for > 5 years of use. These data are not consistent with an adverse effect of HRT on hepatocellular carcinoma.

Effects of HRT on other cancers, including stomach, pancreas, and skin melanoma, are inconsistent.[20] A suggestion of an inverse relation between HRT use and cervical cancer[150] requires confirmation.

## 7. Other Therapeutic Approaches

Given the recognized adverse effects of HRT, much recent attention has focused on assessing alternative approaches to treating the menopause, including use of tamoxifen and other SERMs. These agents (see also ch.7) are recognized estrogen antagonists at selected target sites, such as breast, while they behave as estrogen agonists in different organ systems (e.g., bone). This may offer many of the same advantages as HRT, while eliminating some of the disadvantages (e.g., increase in the risk of breast cancer), which, in fact, seem to be substantially reduced based on available data.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP), a total of 13,388 U.S. women who were 60 years of age or older or who had a 5-year risk of 1.66 percent or more of developing breast cancer or who had a history of lobular carcinoma in situ were randomly assigned to receive 20 mg daily of tamoxifen or placebo for 5 years.[151] After 69 months of followup, women receiving tamoxifen had a 49 percent lower risk of invasive breast cancer than placebo-treated women. This beneficial effect of tamoxifen applied to women of all ages and was particularly evident in women with a history of lobular carcinoma in situ or atypical hyperplasia. The reduction in risk was limited to ER-positive tumors. Adverse effects of tamoxifen, however, included excess risks of endometrial cancer, stroke, pulmonary embolism, and deep-vein thrombosis, events that occurred more frequently in women aged 50 years or older.

When the same women in NSABP were rerandomized to receive either placebo or more prolonged tamoxifen treatment, no additional advantage was obtained through 7 years of followup after rerandomization from tamoxifen administered beyond 5 years.[152]

Two other clinical trials of tamoxifen in breast cancer prevention have presented interim results. In a British trial, 2,494 women aged 30 to 70 years with a family history of breast cancer were randomly assigned to tamoxifen or placebo and followed for up to 8 years.[153] The risk of invasive or in situ breast cancer was 1.06 in the group given tamoxifen compared to the group given placebo. One difference between this and the U.S. trial study was that the British women were allowed to use HRT during the trial (about one-third of study participants were users). In a trial conducted in Italy, 5,408 women who had a hysterectomy were randomized to 5 years of tamoxifen or placebo.[154] The study was stopped prematurely because of patient drop-out. After a median of 46 months of followup, there was no difference in breast cancer incidence by treatment arm. Despite the inconsistent trial results, the U.S. F.D.A. has approved the use of tamoxifen for breast cancer risk reduction in high-risk women.[155]

***In most studies, HRT has been related to increased ovarian and decreased colorectal cancer risk, but these issues await further investigation.***

Less information is available for other SERMs. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial of 7,705 postmenopausal osteoporotic women under age 81, 60 or 120 mg of raloxifene daily decreased breast cancer risk by 76 percent (RR = 0.24, 95 percent CI, 0.1–0.4) as compared to nonusers.[156] Risk for thromboembolic disease was increased threefold, but there was no increased risk for endometrial cancer in raloxifene-treated compared with placebo-treated women. The U.S. National Cancer Institute and the NSABP are now conducting a large, multicenter study to test tamoxifen versus raloxifene to determine whether raloxifene shows the same risk reduction as tamoxifen and to determine whether the risk for adverse events differs.

In a 5-year osteoporosis prevention trial, mammographic density decreased significantly in women receiving raloxifene and placebo and showed a nonsignificant increase in women receiving ERT.[157] Consequently, raloxifene should not interfere with mammographic detection of breast cancer.

Risk for invasive breast cancer is also being evaluated in 10,101 postmenopausal women with CHD or at high risk for its occurrence randomized to raloxifene or placebo in the RUTH trial.

Research is also beginning to focus on whether more natural approaches to treating the menopause should be recommended. Although there is a growing enthusiasm for use of phytoestrogens, termed by some as natural SERMs,[158] their effects on cancer risk remain unresolved.

## 8. Conclusions

Most potential favorable and adverse effects on cancer risk of HRT are restricted to current users. On the basis of observational epidemiologic data, the RR of breast cancer is moderately elevated in current and recent HRT users, and increases by approximately 2.3 percent per year with longer duration of use, but the effect decreases after cessation and largely, if not totally, disappears after about 5 years.

Unopposed estrogen use is strongly related to endometrial cancer risk, but cyclic combined estrogen-progestin treatment appears to largely or totally reduce this side effect if progestin is used for more than 10 days per cycle. However, combined HRT may be related to higher risk of breast cancer as compared to unopposed estrogen.

In most studies, HRT has been related to increased ovarian and decreased colorectal cancer risk, but these issues await further investigation.

Based on the available evidence, no strong or consistent relationship is present between HRT and liver or other gastrointestinal neoplasms, or melanoma.

## 9. Future Needs

- The breast cancer risk of the combination of estrogen and progestin should be further quantified: there are biological reasons to suspect an unfavorable effect of added progestin on breast carcinogenesis, and some epidemiological studies have suggested an excess risk.
- Research is needed to determine whether the relation between HRT and breast cancer risk differs at various ages. Any risk-benefit ratio is particularly critical and must be carefully and individually assessed for elderly women using HRT after menopause in terms of relative and absolute risk.
- In consideration of the better prognosis of breast cancer in HRT users, future research should further investigate a potentially favorable effect of hormone use on the biologic characteristics of breast tumors.
- Additional studies are needed on HRT use in women with a diagnosis of breast cancer.
- Although use of estrogen alone increases endometrial cancer risk, several studies indicate that combined HRT is not related to a major excess of endometrial cancer if progestin is given more than 10 or 14 days in each cycle. This should be better quantified to provide information for prescription.
- The evidence on HRT and epithelial ovarian cancer risk is less consistent than that for endometrial and breast cancer, though available data suggest a positive relationship.
- Additional research is needed to confirm a potentially favorable effect of HRT on colorectal cancer. In western countries, the number of deaths from colorectal cancers in women aged 55 or older are similar. Thus, a decrease in incidence or mortality from colorectal cancer could greatly affect the balance of risks and benefits associated with the use of HRT.
- Further data on lung and liver cancer would also be useful.
- Research is required on the use of tamoxifen and other SERMs and perhaps more natural approaches to treating the menopause. Although there is growing enthusiasm for use of phytoestrogens, termed by some as “natural” SERMs, their effects on cancer risk, if any, should be better understood.

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# Chapter 12: Menopause and Disorders of Neurologic Function, Mental Health, and the Eye

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## Key Points[a]

1. Menopausal ERT appears to help preserve certain cognitive skills immediately after induced menopause [B] and during normal aging [C].
2. Estrogen therapy begun after menopause may reduce risk of Alzheimer's disease [C]. In contrast, limited data from RCTs indicate that estrogen alone begun after the onset of dementia does not seem to improve Alzheimer symptoms [B].
3. In observational studies, ERT does not modify stroke risk in older healthy women [C].
4. For many neurologic disorders (epilepsy, migraine, multiple sclerosis, and Parkinson's disease), observational study findings do not indicate an overall positive or negative impact of menopause or HRT on neurologic symptoms or disability [C]. Some sleep disturbances that occur during the climacteric may benefit from ERT [C].
5. Hormonal changes associated with menopause have shown little direct impact on mood [C]. Although clinical implications are uncertain, limited data suggest a beneficial effect of estrogen on mood [B].
6. There is little evidence that HRT alters risk for age-related maculopathy, cataract, or dry eye [C].
7. Few clinical characteristics or diagnostic procedures identify subgroups of women particularly likely to benefit from HRT for the prevention or treatment of disorders of neurologic function, mental health, or the eye [D]. Despite a strong biologic rationale, clinical data are sparse. Thus, recommendations regarding HRT to prevent or ameliorate those disorders are limited. Well-characterized benefits and risks of HRT for other organ systems override considerations of potential benefit for the brain and eye [D].

***Menopausal ERT appears to help preserve certain cognitive skills immediately after induced menopause and during normal aging.***

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 12–1).

## 1. Introduction

Menopause is associated with sharp declines in concentrations of circulating estrogen and other alterations in the hormonal milieu.[1] The hormonal changes affect a variety of reproductive and nonreproductive tissues, including the CNS eye; HRT with estrogen or other sex steroids may influence brain and eye functions (table 12–1).[2]

***Limited data suggest a beneficial effect of estrogen on mood.***

In the brain and eye,[3,4] as in other target organ systems, estrogen interacts with specific intranuclear receptors to regulate protein synthesis. Within the CNS system, individual neurons can express ERα, the ERβ, neither receptor, or occasionally both receptor types. (See ch. 5.)[3] Androgen and PRs are found in populations of neurons. Within the brain, some estrogen actions occur within a matter of seconds or minutes, too rapidly to involve genomic activation. Those rapid estrogen effects are believed to involve receptors located in the cell membrane.[5] Finally, estrogen can influence brain and eye functions indirectly, through effects on nonneural and nonocular tissues, including the vasculature and the immune system.

Despite a strong biologic rationale, there is no strong evidence based on consistent findings from well-designed RCTs, controlled trials regarding the clinical importance of HRT for the central nervous system and the eye. Relevant preclinical and clinical data are beginning to emerge for several disorders. In some areas, a developing consensus may help guide clinical decisions on prevention and treatment.

Age-associated cognitive decline is considered in this chapter, as are dementia, stroke, epilepsy, migraine, multiple sclerosis, Parkinson's disease, and sleep disorders. With regard to mental health, there are data on mood and schizophrenia. Eye disorders of interest include age-related maculopathy, cataract, and dry eye.

## 2. Age-Associated Cognitive Decline and Neurologic Disorders

Clinical data exist for age-associated cognitive decline in healthy women and for a number of neurologic conditions. Some topics have been reviewed.[6]

### 2.1 Age-Associated Cognitive Decline

Memory and other cognitive abilities change over time during adult life. Changes that represent usual or normal accompaniments of aging are not viewed as pathologic. Modest cognitive decrements initially detectable in middle age are accentuated at elderly age. In general, cognitive tasks that depend on previously learned knowledge are more resistant to decline than tasks involving new information or requiring the manipulation of old information.

#### *2.1.1 Effects of Estrogen*

Considerable data indicate that sex hormones measurably influence brain functioning throughout life. Higher cognitive scores in childhood are associated with a later age at menopause.[7] There is little evidence that menopause per se initiates cognitive deterioration.

As inferred from in vitro and animal studies, estrogen has the potential to modulate cognitive processes.[6] Within the brain, estrogen affects a number of neurotransmitter systems, including cholinergic, noradrenergic, serotoninergic, and dopaminergic pathways,[6] which are involved in aspects of memory and attention. In ovariectomized rodents, estrogen improves memory performance on a variety of behavioral tasks.[8–10] Estrogen interacts with NGF and other neurotrophins,[11] promotes the growth of nerve processes,[12,13] and enhances synaptic plasticity.[14] Estrogen protects neurons from a variety of endogenous and exogenous insults.[15,16] In animal studies, estrogen augments glucose transport into the brain and increases cerebral metabolism.[17,18]

In human studies, estrogen influences the pattern of brain activation during the performance of cog-

## TABLE 12–1

## Estrogen Actions Potentially Germane to Disorders of the Brain and Eye*

| |
|---|
| **Effects on neurotransmitter systems** |
| Acetylcholine<br>Noradrenaline<br>Serotonin<br>Dopamine<br>Others |
| **Neurotrophic actions** |
| Interactions with neurotrophins<br>Neurite extension<br>Synapse formation and synaptic plasticity |
| **Protective actions** |
| Augmentation of blood flow<br>Enhancement of glucose transport into the brain<br>Protection against apoptosis<br>Antioxidant properties<br>Anti-inflammatory properties |
| **Effects on proteins involved in Alzheimer's disease** |
| Apolipoprotein E<br>Amyloid precursor protein |
| **Effects on ocular tissues** |
| **Effects on light transmission through the crystalline lens** |

* Modified from Henderson VW, 1997.[2]

nitive tasks, as inferred from measures of cerebral blood flow.[19–21] Chronic estrogen use is associated with greater increases in relative blood flow in regions of the temporal lobe.[22] As described below, effects of estrogen on cognitive abilities of healthy adult women have been studied in various clinical settings; the findings have been inconsistent but often positive.

**Primary prevention:** The possibility that estrogen might help preserve cognitive function during normal aging has been examined in observational studies.[23] Serum estrogen concentration in postmenopausal women does not appear to be closely related to cognitive skills,[24] although one study reported a positive relationship between levels of bioavailable estradiol and verbal memory but an

inverse relation with nonverbal memory.[25] Healthy, community-dwelling older women who use ERT, with or without a progestin, appear to perform better on cognitive tasks.[26,27] In one well-characterized, longitudinally assessed American cohort, postmenopausal women receiving estrogen performed significantly better on measures of nonverbal and verbal learning and memory than menopausal women who had never used estrogen.[28,29] In other American cohorts estrogen users scored better on specific tests of verbal memory, naming, and abstract reasoning[30] or on cognitive screening tasks.[31,32] In Austria, a population-based study found that postmenopausal women currently using estrogen performed better than nonusers on several psychometric measures; the greatest differences were seen in complex problem-solving tasks and psychomotor speed.[33] In a Dutch patient registry, women receiving HRT performed significantly better on a composite measure of psychomotor speed but did not differ significantly from nonusers on measures of memory or cognitive flexibility.[34] Analyses in two large American cohorts, did not show appreciable differences in a variety of cognitive measures between users and nonusers of postmenopausal estrogen.[35,36] Longitudinal observations imply that estrogen may help preserve cognitive[30] or functional[37] abilities, although current estrogen use failed to protect against cognitive decline on a brief psychometric instrument in another observational study.[31]

***Healthy, community-dwelling older women who use ERT, with or without a progestin, appear to perform better on cognitive tasks.***

**Treatment of symptoms:** Several randomized, controlled clinical trials have examined cognitive effects of estrogen after natural or surgical menopause. Treatment was up to 3 months in duration. Women given estrogen outperformed women given placebo on a variety of psychometric measures.[38,39] On long-term memory tasks, improvement was more apparent when verbal, as opposed to nonverbal, memory was assessed.[38–40] Verbal memory enhancement was also described in a placebo-controlled study of younger women whose ovarian function had been suppressed with a GnRH agonist before "add-back" treatment with estrogen.[41] Positive findings generally occurred in acute studies of relatively younger women after ovarian function was abruptly suppressed;[38,39,41] few clinical trials considered ERT initiated at a later point after natural menopause. In contrast to these generally positive findings, a randomized, placebo-controlled trial of estrogen in 62 women who had previously undergone hysterectomy, conducted by Finnish investigators, detected no benefit of estrogen on measures of psychomotor speed, attention, working memory, or visual memory.[42]

#### *2.1.2 Recommendations for Age-Associated Cognitive Decline*

Recommendations for the primary prevention of age-associated cognitive decline and for the improvement of cognitive skills in otherwise healthy women are derived primarily from inconsistent findings of observational studies and uncontrolled trials and from a limited number of short-term RCTs. In observational studies, women who choose to use estrogen differ in a number of ways from women who do not,[43] and positive findings in such studies may reflect unrecognized bias or confounding.[44] Evidence that estrogen use after menopause is associated with better cognitive skills remains weak. The evidence is somewhat better in short-term studies of younger women with induced menopause. On the basis of available information, the desire to protect against age-associated cognitive decline should not generally affect decisions about whether to use ERT, except possibly in women undergoing surgical menopause.

### 2.2 Dementia

Dementia represents a decline in memory and other cognitive abilities severe enough to have a deleterious effect on daily function. In many regions, Alzheimer's disease is the commonest

cause of dementia;[45] whether its occurrence or progression is affected by estrogen has been of research interest. Very few data directly address whether estrogen might influence dementia due to disorders other than Alzheimer's disease.

#### *2.2.1 Alzheimer's Disease*

As an age-associated disorder, Alzheimer's disease rarely appears before menopause, but its prevalence increases exponentially between the 6th and 10th decades of life.[46] During the first half of the 21st century, it is expected that current trends of an increasing proportion of elderly people in the population will continue for both developed and developing countries, and that the burden of Alzheimer's disease will expand accordingly. Alzheimer's disease is 1.5 to 3 times more common among women than men,[46] in part because of sex differences in longevity.

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the insidious onset of memory loss and other cognitive symptoms that relentlessly worsen over a period of years. Pathologic features include intracellular neurofibrillary tangles and extracellular neuritic plaques. The latter are associated with inflammatory proteins and typically contain a central core composed of β-amyloid. There is evidence that oxidative damage contributes to Alzheimer pathology.

Both genetic and nongenetic factors are implicated in Alzheimer pathogenesis. Autosomal dominant mutations are important causes of early-onset, but not late-onset, illness. For the common, late-onset form of Alzheimer's disease, several genes may modify susceptibility. The best-recognized susceptibility gene encodes the lipid transport protein apolipoprotein E, which is involved in neuronal repair processes. Increased Alzheimer susceptibility is conferred by the apolipoprotein E ε4 allele,[47] which is associated with reduced neuronal sprouting compared with the more common ε3 allele.[48] Sex appears to modify risk: the ε4 allele increases risk more for women than men.[49,50]

Of theoretical benefit in Alzheimer's disease are neurotrophic and neuroprotective effects of estrogen, as well as effects on cholinergic and other neurotransmitter systems. In the laboratory, protective effects against programmed neuronal death (apoptosis),[51] inflammation,[52] and oxidative damage[15,16] appear particularly relevant to Alzheimer pathogenesis. Finally, estrogen increases the expression of apolipoprotein E within select brain regions[53] and inhibits the formation of β-amyloid from its precursor protein.[54] For these reasons, investigators have inquired whether ERT might have roles in preventing or treating Alzheimer's disease.

***Very few data directly address whether estrogen might influence dementia due to disorders other than Alzheimer's disease.***

**Primary Prevention:** In the early 1990s, cross-sectional analyses compared current estrogen use in women with Alzheimer's disease and women in the same age group without dementia.[55–57] Although subject to important bias, results implied that ERT may reduce Alzheimer risk. Several earlier case-control studies had failed to document a link between estrogen use and Alzheimer risk, but since 1994 nine additional studies have assessed the relation between ERT and Alzheimer's disease.[57–66] Most analyses were based on data for estrogen use collected prior to the onset of dementia symptoms,[56–61,63,64] and most, but not all,[59] found an association between the use of estrogen after menopause and protection against Alzheimer's disease. In these case-control and cohort studies, estimates of total reduction in RR are about 50 percent.[60] Estrogen effects were reported for women with and without the ε4 allele of apolipoprotein E.[61]

If ERT reduces Alzheimer risk, it might be expected that greater estrogen exposure would be associated with greater risk reduction. Several studies of estrogen exposure assessed by dosage or duration of use support that contention. In the Leisure World Study, risk estimates for Alzheimer's dis-

ease decreased significantly with increasing dose of the longest used oral estrogen preparation.[60] Significant associations between the duration of estrogen use and the degree of risk reduction were found in analyses from Leisure World,[60] New York City,[61] and Rochester, MN.[66] However, in a longitudinally followed cohort in Baltimore, MD, there was no significant link between duration of use and the magnitude of risk reduction.[63] No data address whether there may be a critical period during which ERT exerts its putative beneficial effects (e.g., the early menopausal period versus the senium). There are no clinical studies on possible beneficial or deleterious effects of dietary estrogens on Alzheimer risk in women, although one study reported a link between higher midlife consumption of tofu, a rich source of isoflavone phytoestrogens, and poor cognitive test performance in men.[67]

**Treatment of Symptoms:** Cholinergic systems of the brain are markedly impaired by pathologic changes of Alzheimer's disease, and medications that increase cholinergic activity by inhibiting the breakdown of acetylcholine are of modest benefit.[68–70] Antioxidants may slow disease progression (e.g., vitamin E)[71] or modestly improve symptoms (e.g., gingko biloba).[72] In observational studies of women with Alzheimer's disease, HRT is associated with milder cognitive deficits,[73,74] although most estrogen use is of long-standing duration. Results from relatively short-term randomized clinical trials of estrogen use are less supportive. Positive results in a 3-week study of conjugated estrogens in 14 women with Alzheimer's disease[75] and suggestive results in an 8-week study of transdermal estradiol in 12 women[76] are offset by decidedly negative findings in two larger trials of conjugated estrogens. One randomized trial in 42 menopausal women with mild to moderate Alzheimer's dementia showed no difference between the estrogen and the placebo group after 16 weeks on the primary cognitive outcome measure or on secondary measures of global change and functional status.[77] Women with mild to moderate Alzheimer symptoms who had undergone hysterectomy were randomized in a second trial to one of two treatment arms using different estrogen dosages (N = 42 and 39) or to placebo (N = 39). At 12 months, there was no benefit of estrogen on measures of global change, cognition, or function.[78] Preliminary observational analysis of concomitant estrogen use in a large, multicenter trial of tacrine raises the possibility that estrogen given in combination with a cholinergic drug may be useful; greatest improvement was observed in the subgroup taking ERT at the time of initial randomization to tacrine.[79]

***Results implied that ERT may reduce Alzheimer risk.***

#### *2.2.2 Vascular Dementia*

Another common cause of dementia is ischemic vascular disease of the brain, particularly multiple strokes, that is, multi-infarct dementia.[45] In some Asian countries, the prevalence of vascular dementia may exceed that of Alzheimer's disease.[80] Symptoms of multi-infarct dementia often begin abruptly, and cognitive decline may occur in a stepwise manner. Neurologic examination typically finds signs of focal brain damage, and radiologic studies, such as MRI usually confirm cerebral infarction. Neuroprotective effects of estrogen could be important. In experimental models of acute cerebral ischemia, estrogen reduces ischemic damage.[81–83] In one observational study, women with vascular dementia were less likely than healthy women to use HRT.[57] Stroke incidence, however, is not closely associated with the use of HRT (see below), and there is no defined role for menopausal estrogen in women with vascular dementia.

#### *2.2.3 Recommendations for Dementia*

Evidence from an increasing number of case-control and cohort studies provides substantial—but not compelling—evidence that use of estrogen after menopause reduces women's risk for Alzheimer's disease. A woman at high risk for

Alzheimer's disease from, for example, genetic predisposition or a strong family history in first-degree relatives, may wish to consider ERT if other potential benefits of treatment are not exceeded by well-recognized potential risks. Decisions concerning estrogen dosage, timing, and treatment duration should be guided by other medical considerations; the literature on Alzheimer's disease allows no consistent guidance. On the basis of data from a small number of RCTs,[77,78] estrogen monotherapy is not useful for the treatment of dementia in women diagnosed with Alzheimer's disease. Short-term side effects, including venous thrombosis,[75] breast tenderness, and withdrawal bleeding, are particularly worrisome in that population. Few data address estrogen effects in forms of dementia other than Alzheimer's disease.

### 2.3 Other Neurologic Disorders

#### *2.3.1 Stroke*

Stroke refers to brain disease caused by ischemic or hemorrhagic abnormalities in the vascular supply to the brain. (See ch. 8, sec. 7.) The incidence of stroke varies widely from country to country.[84] Its incidence rises dramatically with age, and worldwide, stroke is the second leading cause of death.[85] In the Framingham Study in the United States, rates for ischemic stroke are lower in women than men.[84] Atherosclerosis in arteries that supply blood to the brain predisposes to cerebral infarction.[86] Estrogen may reduce these atherosclerotic changes, perhaps due to favorable effects on the serum lipid profile and vascular endothelial function. (See ch. 8, sec. 3.2 and sec. 4.1.1).[87,88] Estrogen increases cerebral blood flow in humans.[89] In rats, estrogen reduces the extent of brain damage caused by acute infarction.[81–83]

In a number of observational studies, HRT is associated with reductions in risk for stroke death of 20–60 percent.[90] However, even in analyses restricted to ischemic stroke, HRT does not appear to reduce stroke incidence.[91,92] This conclusion is supported by secondary analyses in a large clinical trial among postmenopausal women with CHD; after a mean followup of 4 years, HRT had no effect on stroke risk.[93]

Among relatively younger women in the Nurses' Health Study, current hormone use was associated with higher risk of ischemic stroke.[91] There is good evidence that treatment of hypertension, the use of statins after MI, and carotid endarterectomy in patients with severe stenosis can reduce the risk of a first ischemic stroke due to atherothrombotic disease.[94] Because ERT may increase short-term cardiovascular risk,[93] there is a need for caution in beginning estrogen after recent ischemic stroke.

***Stroke incidence, however, is not closely associated with the use of HRT.***

#### *2.3.2 Epilepsy*

Epilepsy is a CNS disorder characterized by recurrent seizures. Epilepsy often begins in early life but can start at any age. Causes are legion. In rats, estrogen increases the excitability of hippocampal neurons[95] and exacerbates epilepsy by lowering the seizure threshold;[96] epileptogenic effects may be opposed by progesterone.[96] In women with so-called catamenial epilepsy, seizures tend to recur immediately preceding or during menstruation and are thought to be triggered by fluctuations in concentrations of ovarian hormones.[97] Catamenial seizures can occur during other phases of the menstrual cycle as well.[98] The use of estrogen-containing OCs does not increase seizure frequency.[99] Effects of menopause on epilepsy have not been well studied. Based on limited questionnaire data, epileptic women probably would not experience a change in seizure frequency or severity with menopause, but HRT may increase seizure frequency.[100,101]

#### *2.3.3 Migraine*

Migraine is a common disorder characterized by recurrent attacks of throbbing headache. Pain is often unilateral and is sometimes preceded by focal neurologic symptoms and accompanied by gastrointestinal symptoms. A questionnaire study

of households selected to be representative of the U.S. population found migraine prevalence to be greatest between ages 35 and 45 years and women to be affected three times as often as men.[102] Headache frequency is influenced by the menstrual cycle and pregnancy. Migraine attacks occur less often during middle age and beyond.[102,103] Menopause per se has been reported to have either little effect[104] or a beneficial effect[105] on migraine frequency. For women undergoing surgical menopause, migraine symptoms may worsen, and occasionally migraine first appears after menopause.[105] Effects of ERT on migraine have not been extensively studied, but estrogen treatment may reduce headache frequency.[106]

***In a number of observational studies, HRT is associated with reductions in risk for stroke death of 20–60 percent.***

#### *2.3.4 Multiple Sclerosis*

Multiple sclerosis, a chronic immunologic disorder of the CNS system, affects women more often than men. Disease incidence is greater among whites and with increasing latitude in temperate regions of the northern and southern hemisphere.[107] Pathologic changes of multiple sclerosis are mediated by T-cell lymphocytes directed against white matter antigens. Neurologic symptoms, which often first appear in early adulthood, depend on the focal distribution of pathologic changes. Exacerbations and remissions are common.

Estrogen influences cell-mediated immunity,[108] but the clinical relevance of estrogen to multiple sclerosis is not well established. Incidence is not increased by the use of OC medications.[109] Among women with multiple sclerosis, pregnancy does not increase long-term disability,[110] even though neurologic relapse often occurs during the postpartum period.[111] Some women experience a worsening of neurologic symptoms immediately prior to or during menstruation.[112,113] Effects of menopause or HRT on the neurologic symptoms or long-term course of multiple sclerosis are unknown.[114]

#### *2.3.5 Parkinson's Disease*

Parkinson's disease is a common, progressive neurodegenerative disorder of the basal ganglia. Symptoms include tremor, rigidity, and reduced movement (bradykinesia). Catecholamine neurotransmitters are characteristically reduced in Parkinson's disease, and most symptoms are attributed to the prominent loss of dopamine-containing neurons in the substantia nigra. Although the substantia nigra does not appear to contain large numbers of ERs in the adult brain,[115] estrogen affects dopamine receptors, the activity of dopaminergic neurons, and motor behaviors mediated by dopamine.[116–118]

There are a few studies of ERT and Parkinson's disease. For postmenopausal women with early Parkinson's disease, a retrospective chart review found estrogen use to be associated with milder Parkinsonian symptoms,[119] and results of a small crossover trial suggested that estrogen may enhance the response to dopaminergic therapy.[120] An American cohort study that compared women with idiopathic Parkinson's disease and women without stroke or dementia found no association between ERT and a Parkinson diagnosis.[121] For women in the cohort who had dementia as well as Parkinson's disease, estrogen use was linked to a significantly reduced likelihood of dual symptoms.

#### *2.3.6 Sleep Disorders*

A common symptom of the climacteric is the hot flush, characterized by an increase in core body temperature followed by cutaneous vasodilation, diaphoresis, tachycardia, and the transient sensation of heat. Troubled sleeping can be caused by hot flushes. Thermoregulatory disturbances in part reflect increased noradrenergic activity,[122] probably at the level of the hypothalamus, which in turn may be modulated by sex steroids. (See ch. 3, sec. 4.) Data from observational studies suggest that menopause is associated with increased sleep disturbances.[123,124] Nocturnal hot flushes are known to disrupt normal sleep patterns;[125,126] sleep disruption

is alleviated by estrogen treatment.[123,127] In a small pilot study, ERT ameliorated sleep apnea syndrome in menopausal women.[128]

#### *2.3.7 Recommendations for Other Neurologic Disorders*

Data from observational studies suggest that ERT does not protect healthy women from the occurrence of stroke. For epilepsy, migraine, multiple sclerosis, and Parkinson's disease, no compelling data indicate that ERT after menopause has substantial effects. Sleep disturbances, particularly during the climacteric and particularly when associated with hot flushes, may improve with ERT, although evidence from RCTs is lacking.

## 3. Disorders of Mental Health

### 3.1 Mood

Women of all ages have higher rates of depression than men.[129,130] Geriatric depression is an important public health concern.[131] Hot flushes and other menopausal symptoms may affect the quality of a woman's life.[132] The menopausal transition does not appear to represent a time of heightened vulnerability to affective disorders.[133]

A number of antidepressant drugs increase CNS levels of noradrenaline and serotonin, suggesting the importance of monoaminergic neurotransmitter systems in regulating mood. Estrogen influences noradrenalin and serotonin. Research findings on women with premenstrual dysphoric disorder or with major depression beginning in the postpartum period point toward the importance of sex hormones. Several short-term studies indicate that ERT given during the perimenopausal or menopausal period can diminish anxiety or enhance mood and subjective sense of well-being.[134–136]

Limited data suggest that severe depression in certain clinical populations is occasionally improved by ERT. Recent clinical experimental studies of postpartum depression indicate that reproductive hormones can be involved in the development of the disorder[137] and that estrogen can be effective in a major depressive episode with postpartum onset.[138] For women with a major depressive disorder, an older randomized, placebo-controlled trial of high-dosage estrogen showed significant amelioration of affective symptoms.[139] Among women with major depression treated with a selective SSRI, retrospective analyses do not strongly suggest important additive effects of concomitant ERT.[140,141]

Older postmenopausal women who use estrogen typically report fewer depressive symptoms than nonusers.[142] In RCTs in postmenopausal women without a diagnosis of depression, ERT has been reported to reduce scores on measures of depressive symptoms[134–136] and to have no effect on mood.[42,43] Apparent beneficial effects of estrogen on mood may be diminished by the concomitant administration of a progestin.[143]

***Data from observational studies suggest that menopause is associated with increased sleep disturbances.***

### 3.2 Schizophrenia

Schizophrenia is a chronic psychotic disorder characterized by delusions, auditory hallucinations, disorganized thought processes, affective blunting, and difficulty in sustaining goal-directed activity. Frequency does not significantly vary according to sex. Symptoms typically appear in the third decade of life, but onset occurs on average 3–5 years later for women than men.[144,145] Late-onset schizophrenia is more common in women,[146] although menopause does not appear to heighten risk.[145] Estrogen effects on dopaminergic or serotonergic systems of the brain could influence schizophrenic symptoms. Among ovulating women, a higher serum estrogen concentration has been associated with milder psychopathology.[147] In a small, open-label trial in women with schizophrenia, estrogen added to

standard antipsychotic drugs increased the speed with which psychotic symptoms improved, although the difference was not sustained.[148]

### 3.3 Recommendations for Mood Disorders and Schizophrenia

***Women of all ages have higher rates of depression than men.***

Possible estrogen effects on schizophrenia are inadequately addressed in the literature, and estrogen should probably not be considered as treatment for a major depressive episode or schizophrenia. There are weak data that estrogen might be considered for mild depressive symptoms attributed to hot flushes, sleep disturbances, or other climacteric symptoms. No data exist whether estrogen could be used as adjunct therapy for other depressive disorders during the menopausal transition or postmenopausal period.

## 4. Disorders of the Eye

Increasing age is often accompanied by visual loss or blindness, and among older people diminished visual acuity affects women more often than men.[149] Two of the most important causes of visual loss in older adults are age-related maculopathy and cataract. Another common problem among older adults is dry eye syndrome; symptoms, while usually not disabling, can be distressing and difficult to eradicate.

Because clinical data on estrogen and eye disorders are limited, visual considerations should not influence practice decisions on the use of HRT.

### 4.1 Age-Related Maculopathy

Maculopathy, which is most severely manifest as macular degeneration, is characterized by atrophy and neovascularization of the central portion of the retina. Age-related maculopathy affects women somewhat more often than men.[150] Although pathophysiologic mechanisms for the condition are unknown, several studies have evaluated possible effects of reproductive events and exogenous hormone use.

A case-control study from Rotterdam found that women with early surgical menopause were more likely to have macular degeneration than those with late surgical menopause.[151] Early spontaneous menopause was not associated with increased risk. In a cohort from the Blue Mountains region of Australia, increasing years from menarche to menopause, a measure of endogenous estrogen exposure, was associated with reduced odds of early changes of age-related maculopathy.[150]

In a U.S. multicenter case-control study, the use of HRT was associated with decreased risk for neovascular age-related macular degeneration,[152] the form of macular degeneration most commonly associated with severe visual loss. In a population-based cohort in Beaver Dam, WI, there was an inverse relation of borderline significance between the number of years of ERT and maculopathy, although there was no association between ever-use of estrogen and occurrence of maculopathy.[153] Analysis of pooled data from Rotterdam, Blue Mountains, and Beaver Dam failed to confirm an association between the use of menopausal estrogen and age-related maculopathy.[150] Similarly, the U.S. NHANES III found that current, but not past, use of HRT is associated with a lower prevalence of age-related maculopathy.[154] In an analysis of data from the Beaver Dam Eye Study, there was no evidence of a relationship between HRT and 5-year incidence of age-related maculopathy.[155]

***Symptoms of dry eye improved significantly in an RCT of estrogen eye drops in postmenopausal women.***

Maculopathy is among the most serious of the eye disorders, but evidence of estrogen benefit remains tenuous. No data address effects of HRT once maculopathy is evident.

### 4.2 Cataract

Cataract refers to a loss of transparency within the crystalline lens of the eye, which interferes with the transmission of light to the retina. The generic term encompasses different kinds of opacity, including opacities located in the nuclear, cortical, and posterior subcapsular portions of the lens. About 50 percent of the world's blind have cataract. Epidemiologic studies from Australia,[156] Asia,[157] Europe,[158] and North America[159–161] indicate that cataract affects elderly women more often than elderly men. In studies that discriminated among types of cataract, female sex was positively associated with both nuclear[156,161] and cortical[160,161] cataracts.

The relation of cataract formation to menopause or estrogen use has been considered in several observational epidemiologic studies. Early menopause was associated with cataract formation in reports from Beaver Dam and the Nato area of Japan[162,163] but not in a report from Blue Mountains.[164] In Beaver Dam, cortical cataract was more prevalent among older women; premenopausal women in the sixth decade of life had fewer nuclear cataracts than perimenopausal or postmenopausal women of the same age.[162] Transmission of light through the crystalline lens was greater in postmenopausal women receiving ERT than in women not taking estrogen or in men of similar age. The prevalence of cortical cataract was reduced among current estrogen users in the Blue Mountains Eye Study,[164 165] as was the severity of nuclear sclerosis in the Beaver Dam Eye Study.[162] Neither study, however, found an association between cataract and ever-use of menopausal hormones.[162,164] In the Blue Mountains data, but not Beaver Dam, posterior subcapsular opacity was more prevalent among older subjects who were current users of estrogen-progestin replacement therapy.[162,164] In the Beaver Dam Eye Study, there was no evidence of a relationship between HRT and the 5-year incidence of any type of age-related cataract.[155]

Estrogen effect on cataract has not been studied in randomized controlled studies.

### 4.3 Dry Eye

Dry eye, or keratoconjunctivitis sicca, is a common complaint among older adults.[166–168] Symptoms localized to the ocular surface include irritability, burning, itching, and sensations of dryness or the presence of a foreign body. Visual disturbances can occur, and severe manifestations occasionally threaten vision. Dry eye syndrome is pathogenetically heterogeneous and is caused by both decreased tear production and increased evaporative loss of the aqueous component of tears. Dry eye is associated with Sjögren's syndrome and other autoimmune diseases but frequently occurs in the absence of associated systemic illnesses.

***Because clinical data on estrogen and eye disorders are limited, visual considerations should not influence practice decisions on the use of HRT.***

Little evidence links estrogen to dry eye. Women are more likely to report symptoms of dry eye than men;[167–169] not all studies support the finding.[166] In the Beaver Dam Eye Study, the age-adjusted prevalence was 11 percent in men and 17 percent in women.[169] Menstrual status, history of hysterectomy, and use of HRT were not associated with dry eye.[169]

Gonadal steroids are important in the production of different tear components. Androgens may be the most important in the process.[170–172] It is hypothesized that the decline in androgen production after menopause, rather than the menopausal loss of estrogen, contributes to dry eye symptoms in older women.[170] Symptoms of dry eye improved significantly in an RCT of estrogen eye drops in postmenopausal women.[173] Clarification of the roles of hormones and of potential treatment possibilities awaits further investigation.

## 5. Future Needs

- Explore the possibility that SERMs may act as estrogen antagonists in the brain or eye.
- Evaluate in long-term RCTs the potential effects of HRT on age-associated cognitive decline.
- Evaluate in long-term RCTs the potential effects of HRT on primary prevention of Alzheimer's disease and vascular dementia.
- Evaluate the effectiveness of combination therapy with estrogen plus a cholinomimetic drug in RCTs for women with Alzheimer symptoms.
- Evaluate in RCTs the potential effects of HRT on primary prevention of Parkinson's disease and on symptoms of Parkinson's disease.
- Determine in RCTs whether estrogen combined with antidepressants or antipsychotic drugs might enhance the effects of these medications in depressive disorders and schizophrenia, respectively.
- Determine in long-term RCTs whether HRT might reduce incidence of age-associated maculopathy, cataract, or dry eye.
- If estrogen proves beneficial for disorders of neurologic function, mental health, or eye, the timing of therapy and the duration of usage for optimal benefit have to be resolved.
- If estrogen proves beneficial for disorders of neurologic function, mental health, or eye, the possibility that benefit may be altered by a progestin has to be resolved.

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# Chapter 13: Best Clinical Practices: A Comprehensive Approach

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## 1. Introduction

The proportion of women living past the age of menopause has tripled during the past century, and is expected to increase steadily in the foreseeable future. If adulthood is defined as beginning at age 21, the average age at menopause as age 51, and the average life expectancy as age 81, women in the United States, in Europe, and in much of the developed world will live one-half their adult lives in the years after menopause, a time of relative estrogen deficiency compared to their reproductive years.

In recent years, the aging of the female population, together with the availability of "replacement" hormones, led to numerous studies of the menopause. Most of these studies were of middle-class white women living in the United States and Western Europe, with results that may not be relevant to other women. In addition, many studies were clinical or epidemiological observations of associations—less satisfactory for evidence-based medicine than randomized, placebo-controlled, double-blind clinical trials. Results from recent clinical trials studying the benefits of HRT have differed from observational studies. Results from additional large clinical trials, expected in the next 5 years, may further change thinking about the optimal management for the menopausal woman.

The menopause offers the health care provider an opportunity to assess each woman's health, her concerns, and the need for health promotion and disease prevention measures. Today's health care provider has to consider a bewildering array of changing "facts" and sees increasingly informed

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patients with strong personal convictions about the menopause and their need for medication. The provider must be prepared to discuss a variety of menopause or age-related topics, and decide what to recommend for a specific woman—often in less time than ever before.

***The menopause offers the health care provider an opportunity to assess each woman's health, her concerns, and the need for health promotion and disease prevention measures.***

Recommendations should be specific to each woman and her background. There are country-specific and cultural variations in menopause symptoms, the frequency of different postmenopausal diseases, clinical practice, health care resources, and affordable interventions. Country- and culture-specific practice will therefore vary, and appropriately so.

Recent research findings include:

- Increasing recognition of the need to address health promotion beyond the perimenopausal years, and in women with and without menopausal symptoms.
- The risks and benefits of lifestyle, pharmacological, and surgical interventions may change as women age.
- The tailoring of menopausal treatment to the individual woman should be based on her individual clinical profile and concerns.
- For the treatment of the climacteric syndrome, HRT remains the most effective pharmacologic intervention.
- The long-term benefits and risks of HRT continue to be assessed.
- HRT for long-term health promotion, as for osteoporosis, usually requires its continued use.
- New nonhormone therapies offer more options for prevention of common menopausal conditions, to be tested fully in clinical trials.
- Preventive drug therapy can start many years after menopause, particularly with respect to osteoporosis. This, however, may not be optimal.
- The risk for many disease outcomes can be reduced even in old age.

Research results are teaching us to be cautious before assuming that current practice is best. For example, although HRT remains the gold standard for the treatment of vasomotor and urogenital symptoms, as well as for the prevention of bone loss, recent clinical trial results have failed to show benefit for other menopausal conditions, such as incontinence.

***The long-term benefits and risks of HRT continue to be assessed.***

Past perceptions about appropriate indications for the use of HRT were based almost entirely on clinical experience and observational data. These perceptions are being questioned as new knowledge emerges from clinical trials. Some examples follow:

*Perception:* HRT protects against coronary heart disease.

*Evidence:* The prospective randomized clinical trials reported so far have not shown benefit for reducing coronary events in secondary prevention.

***Perception:*** Estrogen prevents memory loss and retards the progression of Alzheimer's disease.

***Evidence:*** Clinical trials have not shown that ERT retards progression of early Alzheimer's disease. Clinical trials of the effects of ERT on memory loss are still ongoing.

***Perception:*** Estrogen improves symptoms of depression.

***Evidence:*** Clinical trial data have shown that ERT improves mood and well-being only in women with vasomotor symptoms and sleep disturbance. No convincing clinical trial data indicate that estrogen therapy in postmenopausal women is an effective treatment for major depression.

***Perception:*** Estrogen improves urinary incontinence.

***Evidence:*** Clinical trials have shown no benefit.

***Perception:*** HRT, unlike oral contraceptives, does not increase the risk of venous thromboembolism.

***Evidence:*** Clinical trials confirm a threefold increased risk of venous thromboembolism with oral ERT.

***Perception:*** HRT during the first 5–10 years after the menopause is sufficient to prevent osteoporosis in later life.

***Evidence:*** Bone loss resumes after stopping HRT, leaving women vulnerable to osteoporosis in later life. Whether estrogen is started early or late, it must be continued into old age to maintain skeletal health.

Although many clinically relevant questions remain unanswered, women seeking advice about the menopause now have more information about and more options for healthy postmenopausal years than ever before. New trial results and new medications may further change recommendations for the assessment and management of the postmenopausal woman.

***New nonhormone therapies offer more options for prevention of common menopausal conditions, to be tested fully in clinical trials.***

We make the following recommendations concerning HRT based on results from clinical trials. Where evidence from clinical trials is not available, we make recommendations based on observational studies. These recommendations are intended as guidelines, not mandates. All interventions should be individualized—tailored to the specific needs and concerns of each woman and designed to provide an optimal quality of life.

## 2. The Menopause Transition

### 2.1 Assessment

Some women sail through the menopause transition with no complaints, others are miserable, and the majority have symptoms that are somewhat bothersome. There is still controversy as to which symptoms are related to menopause and which are associated with or exacerbated by other factors.

Clearly not all symptoms that occur during the menopause transition are due to hormonal changes. Only vasomotor, sleep, and some vulvovaginal symptoms have shown more favorable relief after HRT than placebo, and can therefore be convincingly attributed to changing hormone levels and menopause. At least 25 percent of women in clinical trials report significant improvement in their vasomotor symptoms when taking placebo.

Therefore, convincing evidence of treatment benefit requires a placebo-controlled clinical trial.

Women may visit the physician because they have symptoms they suspect are related to menopause or because they want information about the menopause. In either case, assessment for symptoms provides an opportunity to discuss issues that might otherwise remain unaddressed.

Symptoms directly or indirectly related to the menopause transition include:

- Vasomotor symptoms (hot flushes and night sweats)
- Sleep-related symptoms
- Mood changes
- Sexual dysfunction
- Problems with concentration and memory
- Urogenital symptoms

Symptoms can be queried by using a questionnaire or symptom checklist during the interview. Some find that asking about sexual satisfaction is facilitated by the use of a checklist. When a checklist is used, it is important to go beyond the list to assess the severity and duration of reported symptoms and the degree to which they interfere with the woman's life. For example, hot flushes that are not bothersome do not require treatment.

***It is important to have a dialogue with the patient. Failure to listen and discuss may explain why many women prescribed HRT do not fill the prescription.***

When asking about symptoms, the clinician should be sensitive to each woman's:

- Beliefs and attitudes about menopause, including her medical vs. nonmedical treatment preferences, anxieties, and coping style
- Sociocultural and ethnic background that may affect her concerns and choices
- Work situation, job satisfaction, and stress
- Other life stressors, particularly with personal relationships
- Social supports
- Overall quality of life
- Current use of nonprescription herbal, nutriceutical (a nutritional supplement designed for a specific clinical purpose), or phytoestrogen remedies.

It is important to have a dialogue with the patient. Failure to listen and discuss may explain why many women prescribed HRT do not fill the prescription.

### 2.2 Symptom Prevention and Treatment. Vasomotor Symptoms: Hot Flushes and Night Sweats

#### *2.2.1 Lifestyle*

- Wear layered clothing that can be removed or added as necessary.
- There is conflicting evidence as to whether exercise improves menopause vasomotor symptoms.

#### *2.2.2 Diet*

- Avoid hot spicy foods and beverages, and reduce caffeine.
- Avoid alcohol beverages (excess can cause flushing).

#### *2.2.3 Pharmacotherapy*

- In a systematic review of more than 40 randomized controlled clinical trials, oral and transdermal estrogen each reduced the severity of vasomotor symptoms, and estrogen was effective in doses lower than the usual 0.625 mg of equine estrogens or equivalent.
- Transdermal estradiol and intranasal 17β-estradiol spray are as effective as oral estrogen in reducing hot flushes.

- Oral tibolone is as effective as other forms of HRT such as estradiol valerate or conjugated estrogens in reducing hot flushes.
- Selective ER modulators can increase hot flushes. In clinical trials, approximately 20 percent of women at least 2 years after menopause less than 60 years of age and 10 percent of older women developed hot flushes on raloxifene. Vasomotor symptoms were mild and rarely led to discontinuation of therapy.
- The selective serotonin reuptake inhibitors (SSRIs) venlafaxine and paroxetine have been shown to substantially reduce hot flushes in clinical trials.
- Progestogens in high daily doses (medroxyprogesterone acetate 20 mg per day or megestrol acetate 40 mg per day) also reduced vasomotor symptoms.
- Veralipride (100 mg per day) reduces hot flushes in patients treated with GnRH agonists.
- Propranolol is no more effective than placebo for the reduction of hot flushes, whereas evidence for clonidine's benefit is inconsistent.

#### *2.2.4 Complementary and Alternative Therapies*

- Phytoestrogens have not been shown in most clinical trials to decrease vasomotor symptoms significantly better than placebo. Different results may relate to differences in women (not all of them absorb phytoestrogens equally well) or differences in the products tested. The best single dietary source of phytoestrogens is soy. The U.S. Food and Drug Administration has approved a statement that soy protein at a dose of 25 gm/day may reduce the risk of CVD, based on a modest reduction in total cholesterol level.
- Dong quai has been shown in a clinical trial not to be more effective than placebo for the treatment of hot flushes.
- Evening primrose oil (gamma-linolenic acid) is not more effective than placebo for the reduction of hot flushes.

#### 2.3 Symptom Prevention and Treatment. Urogenital Symptoms

- At least nine RCTs have shown that estrogen improves urogenital symptoms; this is true for oral and transdermal estrogen and for a silicone estradiol-releasing vaginal ring. Vaginal dryness and dyspareunia can be treated with a topical estrogen cream, tablet, or vaginal ring, or with nonhormone moisturizing or lubrication products. In clinical trials, topical estrogen appears to be better than systemic estrogen for relieving these symptoms, and avoids high levels of circulating estrogen.
- In one clinical trial, an estradiol-releasing silicone vaginal ring was also found to reduce the incidence of urinary tract infection.
- Systemic estrogen alone or with a progestin does not reduce incontinence, and in one large clinical trial, HERS, actually increased incontinence.

## 3. Fractures

#### 3.1 Assessment

When discussing osteoporosis, it is important to be sure that the provider and the patient are using the same language. Some patients confuse osteoporosis (fragile bones) with osteoarthritis (painful joints). Other women (and some doctors) mistakenly believe that a diagnosis of osteoporosis means they should not exercise.

***Many factors are associated with an increased fracture risk in women, which may differ by fracture site.***

### *3.1.1 Risk Factors*

Many factors are associated with an increased fracture risk in women, which may differ by fracture site. Most available data are on risk factors for spine or hip fractures in Caucasian women aged 65 and older. Predicting risk in younger women and other ethnic groups is less accurate.

*Nonmodifiable risk factors for fractures:*

- Age—there is an approximate doubling of fracture risk every 7 years
- Family history—history of osteoporotic fracture, especially hip fracture, in either parent or sibling approximately doubles the risk
- Personal history of osteoporotic fracture increases the risk twofold to fivefold
- Early menopause increases risk

*Modifiable risk factors:*

- Weight—there is an increased risk if thin, and a decreased risk if overweight
- Excessive weight loss is a powerful risk factor for bone loss and fracture
- Current smoking—increases the risk of all fractures
- Low calcium intake—increases the risk of hip fracture
- Vitamin D deficiency—can cause secondary hyperparathyroidism and osteoporosis
- Inadequate physical activity
- Factors associated with falls, some of which are modifiable:
    - Limited vision
    - Impaired cognition
    - Balance problems
    - Alcohol excess
    - Poor health, frailty, muscle weakness
    - Medications, particularly sedatives
    - Environmental hazards, such as poor lighting and loose area rugs
- Low bone density is a risk factor for fracture (fracture risk doubles for every 10–12 percent decrease in bone mineral density, a deviation of approximately—1 t-score or—1 z-score (measured by dual energy x ray absorptiometry [DEXA]).

### *3.1.2 Case Finding*

Bone density testing is recommended in the United States for all women aged 65 years or older.

- DEXA of the hip is currently the gold standard for bone density measurements.
- Bone density results should be used in conjunction with information obtained in clinical risk assessment.

## 3.2 Prevention and Treatment

Better bones in old age are a function of peak bone mass (usually achieved around age 25), and subsequent rate of bone loss. Peak bone mass is maximized by an adequate calcium intake, physical activity, and not smoking. Lifestyle changes have been shown to improve bone density in young women and to prevent fractures in older women. They are low-cost, safe, and can be recommended widely.

### *3.2.1 Lifestyle*

- Stop smoking
- Avoid extreme weight loss
- Add weight-bearing, muscle-building, and balance exercises
- Avoid sedatives
- Avoid excess alcohol
- Correct visual impairment
- Fallproof the home

### 3.2.2 Diet

- Correct calcium deficiency. A diet devoid of dairy products rarely provides more than 200 – 250 mg of calcium per day, which does not balance obligatory calcium loss and is associated with increased bone loss. Much of the bone loss can be attenuated by increasing calcium intake. Ideally, the combined diet and supplement intake should be 1,200 mg of calcium each day.
- In correcting dietary calcium deficiency, the first step is to increase calcium-rich foods; each dairy portion contains approximately 300 mg. Calcium-supplemented orange juice or mineral water rich in calcium are useful for women with lactose intolerance.
- If adequate dietary calcium is not likely, calcium supplements should be recommended. Calcium supplementation should be given concomitantly with Vitamin D. Clinical trials have shown that calcium with vitamin D can reduce fracture risk; no clinical trials have shown that vitamin D without calcium significantly reduces fracture risk. Clinical trials consistently show better bone preservation in women who take calcium with estrogen than estrogen alone.
- Supplement vitamin D intake for women 65 and older; 600–800 IU/day together with adequate calcium intake can reduce the risk of fracture in elderly women by about 25 percent.

### 3.2.3 Pharmacotherapy

With growing evidence for efficacy of osteoporosis treatments and with growing concern about drug costs, policymakers have recommended that expensive drugs not be used for osteoporosis prevention. In addition, all medications have risks and side effects. Therefore, aggressive pharmacotherapy should be reserved for women who are at high risk of fracture in the near future.

Practitioners in discussion with their patients must decide between therapy with bone-specific drugs or broad-spectrum drugs (HRT, SERMs).

- Drugs shown in clinical trials to prevent bone loss, that is, to be effective in prevention of osteoporosis, include estrogen, tibolone, raloxifene, alendronate, and risedronate.
- Drugs shown in clinical trials to prevent fractures include raloxifene, alendronate, and risedronate. These clinical trials were conducted in women at increased risk of fracture. Similar large trials have not been conducted using estrogen or tibolone. HERS found no difference in clinical fracture rate or height loss (a marker for vertebral fractures) in women assigned to HRT vs. placebo. Fracture was a preset secondary endpoint in HERS, but women in this trial were not at high risk for fracture.

***Lifestyle changes have been shown to improve bone density in young women and to prevent fractures in older women.***

*Estrogen therapy*

- Bone loss is accelerated during the first 5–10 years following menopause, and postmenopausal estrogen therapy is effective in preserving existing bone, whether begun in old age or at the time of the menopause. Results are similar with estrogen alone or when estrogen is used with a nonandrogenic progestin such as medroxyprogesterone acetate or progesterone. Androgenic progestins such as norethisterone-acetate have a synergistic activity when combined with 17β-estradiol.
- Clinical trials have shown that doses of 0.3 mg per day of conjugated equine estrogen (lower than the previously recommended 0.625 mg per day), 0.5 mg of oral 17β-estradiol, or 25 micrograms of transdermal 17β-estradiol maintain bone in most women when taken with adequate calcium. Smaller doses were better tolerated with regard to fewer episodes of uterine bleeding and less breast tenderness, two major reasons why women discontinue estrogen. Whether

lower dosages of estrogen will be safer (lower rates of venous thomboembolism, breast cancer) remains to be proven.

When medication is indicated, based on a combination of clinical risk factors and low bone mineral density, the choice varies with the age of the patient and the severity of osteoporosis.

- Estrogen must be used continuously to preserve bone. Observational data suggest that bone density in older women who have never received estrogen is similar to bone density in women who used estrogen for 10 years and then discontinued it for another 10 years.
- Hormone treatment of women soon after menopause should be reserved for management of postmenopausal symptoms, but it will preserve bone in most women.

***Aggressive pharmacotherapy should be reserved for women who are at high risk of fracture in the near future.***

*Non-estrogen therapy*

Asymptomatic women 10 or more years postmenopause, without severe osteoporosis, may prefer tibolone or raloxifene. For women aged 60 or older who have osteoporosis but are not at high risk for nonspine fracture, raloxifene can be used to reduce the risk of spine fractures and for its possible other health benefits. Older women, particularly those with severe osteoporosis and prior fracture(s), may prefer alendronate or risedronate for their rapid acting bone-specific effects and reductions in nonspine as well as spine fractures.

Parathyroid hormone treatment by daily injection promises to be particularly effective for women with very severe osteoporosis who need to gain substantial amounts of bone.

The way medications are prescribed influences patient adherence. Beginning with a low dose for women prescribed estrogen helps reduce breast pain and slowly increasing dosage of raloxifene is useful in overcoming the hot flush side effect. Women who cannot tolerate the first medication often tolerate one of the other bone-sparing medications. A few trials have shown improved bone density over single therapy when a bisphosphonate is combined with estrogen or raloxifene, but there are no fracture data in women using these combinations (and the cost of combination therapy precludes routine use).

- Statins have been inconsistently associated with higher bone density. Statins have not been consistent in reducing bone loss or fracture risk, and these skeletal benefits have not been assessed in clinical trials.
- Clinical trial data show that a thiazide diuretic reduces but does not prevent bone loss.
- Observational studies suggest that people using thiazides are less likely to have fractures.

#### *3.2.4 Complementary and Alternative Therapies*

- Soy food (soy protein isolate) has been shown in clinical trials to have little or no benefit for the skeleton when ingested in the usually recommended amounts (20–25 grams of soy protein per day).
- Ipriflavone, a synthetic isoflavone, has been shown in preliminary studies to reduce bone loss but failed to improve bone density or reduce fracture risk in a large clinical study of women with osteoporosis.

## 4. Cardiovascular Disease

### 4.1 Assessment

When assessing a woman's knowledge about heart disease and stroke prevention, it is important to note that cardiovascular disease is a more common cause of morbidity and mortality for women in most of the world than osteoporosis and cancer combined.

### *4.1.1 Risk Factors*

The main risk factors for coronary heart disease are: high blood cholesterol, high blood pressure, diabetes, and cigarette smoking. These same factors also apply to stroke and peripheral arterial disease, but the order of importance differs. High blood pressure is the most important risk factor for stroke, while smoking has been consistently associated with peripheral arterial disease, and high blood cholesterol with CHD.

*Nonmodifiable risk factors*

- Age. For every 10-year increase in age, the risk for heart disease increases about threefold.
- The presence of CHD or other evidence of atherosclerotic arterial disease including stroke or lower extremity arterial disease increases the risk for myocardial infarction (MI) about fivefold. Atrial fibrillation, aortic stenosis, and narrowing of the coronary arteries are also risk factors for stroke.
- Family history of premature CHD (MI before age 55 in men, 65 in women) increases the risk for MI about twofold.
- The importance of a positive family history is amplified in women who smoke cigarettes.

*Modifiable risk factors*

- Cigarette smoking: Compared to smokers, nonsmokers or women who stop smoking have one-third the risk for MI.
- Physical activity: Women who walk briskly for 3 hours per week have a one-third lower risk for MI compared to women who do little exercise.
- Nutrition: Women whose usual diet is low in saturated and trans fats, and relatively high in unsaturated fats (including monounsaturated fats and fish oils), and high in cereal fiber, fruits, and vegetables, have half the risk for MI compared to women who do not have this healthy eating pattern.
- Weight: Lean women (body mass index below 25) have one-quarter less risk than overweight women, and less than one-half the risk of obese women (body mass index above 30).
- Fat distribution: Women with a waist circumference of less than 28 inches (71 cm) have one-third the risk for MI compared to women with a waist circumference of more than 38 inches (96.5 cm). Weight and weight distribution associated risks are not the same in all populations. For example, overweight and central obesity seem to be less important risk factors in African American women than in women of northern European ancestry and Asian American women who seem to be at increased risk at lower weights.

***CVD is a more common cause of morbidity and mortality for women in most of the world than osteoporosis and cancer combined.***

- Psychosocial factors: Life stress situations, depression, and social isolation have been linked to increased risk for MI in women.
- Blood pressure: Women with a systolic blood pressure below 140 mmHg have a risk for MI one-half that of women with a level above 180 mmHg.
- Blood cholesterol: Women with a LDL cholesterol below 130 mg/dL (3.4 mmol/L) have a risk for MI one-half that of women with levels above 190 mg/dL (4.9 mmol/L).
- HDL cholesterol: Women with a HDL cholesterol level above 60 mg/dL (1.6 mmol/L) have a risk for MI which is one-third that of women with a level of less than 40 mg/dL (1.0 mmol/L). Contrary to popular opinion, women with high HDL cholesterol levels are not immune to MI.
- Triglycerides: Women with triglyceride levels below 150 mg/dL (1.7 mmol/L) have a risk of MI one-third lower than women with levels above 240 mg/dL (2.7 mmol/L).

- Diabetes: Women with diabetes by history or glycemia (fasting plasma glucose > 126 mg/dL (7.0 mmol/L) and/or 2 hour postchallenge glucose above 199 mg/dL (11.1 mmol/L) have a two- to fourfold increased risk of MI compared to women without diabetes. About half of women with Type 2 diabetes do not know they have it. Diabetes is often first diagnosed when the patient has a MI.

#### *4.1.2 Other Assessments*

*History*

- Presence of any of the risk factors above.
- Symptoms compatible with transient ischemic attack, CHD, or lower extremity atherosclerosis.
- Use of HRT, antihypertensive drugs, lipid-lowering therapy, aspirin, and medication for diabetes.

*Physical examination*

- Pulses, auscultation for cardiac murmurs, and arterial bruits.
- Blood pressure at first visit. Women who have optimal blood pressure levels (< 130/85 mmHg) are rechecked every 2 years (Europe: women > 40 years: every year), those with normal levels (< 140/90 mmHg) are rechecked every year. Women with levels > 140/90 mmHg need confirmation.
- Height, weight, waist circumference, calculate body mass index.

***The main risk factors for CHD are: high blood cholesterol, high blood pressure, diabetes, and cigarette smoking.***

*Laboratory tests*

- Fasting glucose, total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol at first visit. For women without known CHD, the desirable lipid levels are LDL cholesterol < 130 mg/dL (3.4 mmol/L), triglycerides < 150 mg/dL (1.7 mmol/L), and HDL cholesterol levels > 45 mg/dL (1.3 mmol/L).
- Repeat measurements that are normal every 5 years.
- Evidence does not support further screening for diabetes. Case finding may be appropriate in persons who have central obesity, high triglycerides, or a positive family history. Repeat glucose tests for women whose fasting blood glucose is elevated because the diagnosis of diabetes needs a confirmatory test. Women whose fasting plasma glucose is between 110 (6.1 mmol/L) and 126 mg/dL (7.0 mmol/L) or whose 2 hour glucose is between 140 (7.8 mmol/L) and 200 mg/dL (11.1 mmol/L) are at high risk of future diabetes.
- In some countries, homocysteine measurement is recommended.

Other tests for CHD, cerebral arterial disease, and peripheral vascular disease as indicated by symptoms. The combined effect of two or more risk factors is more powerful than any single risk factor, and some risk factors commonly occur together. (For example, screening for diabetes may be most appropriate in persons with high blood pressure or high triglyceride levels.) When one risk factor is found, the presence of other factors should be sought and an assessment of overall risk should be made by counting the number of risk factors plus a 10-year risk assessment as in the National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP ATP III) or as an assessment of the 10-year risk as recommended in European guidelines. Risk assessment can be used to motivate the patient to make lifestyle changes and comply with medication.

### 4.2 Prevention and Treatment

Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women, not just those with heart disease risk factors or disease, because the diet, physical activity, and not smoking recommendations represent a return toward the evolutionary norm.

#### 4.2.1 Lifestyle

- At each visit, reinforce nonsmoking status, or strongly encourage patient (and family) to stop smoking and avoid secondhand smoke. Prescribe counseling, nicotine replacement, or other pharmacotherapy as indicated in conjunction with behavioral therapy or a formal smoking cessation program.
- Encourage a minimum of 30 minutes of moderate-intensity dynamic exercise, e.g., brisk walking, at least 3 days a week, supplemented by an increase in daily lifestyle activities. Women who want to do more than the minimum should be encouraged to do so. Recommend medically supervised programs for women who have had a recent MI or revascularization procedure.

***Women with diabetes … have a two- to fourfold increased risk of MI …***

- Encourage gradual weight loss for overweight women through a combination of physical activity and portion control, healthy food choices, and recognition of triggers to overeating. Refer to weight loss support group or formal nutritional counseling when appropriate.
- Encourage positive coping mechanisms for stress (e.g., substitute physical activity for overeating or smoking in response to stressful life situations).

#### 4.2.2 Diet

- Encourage a well-balanced and diversified eating pattern that is low in saturated fat and high in fresh fruits and vegetables and fiber. Prefer fats with higher monounsaturated content (e.g., olive oil, canola oil). Prefer seafood and skinless chicken to red meat. Prefer soft unsaturated margarine to hard margarine or butter. Use skim milk and skim milk products or at most 1 percent milk instead of products with a higher fat content. Limit the intake of high-cholesterol foods, avoid fast-food meals. Consume more than five servings of fruits and vegetables daily. Total dietary fiber intake from food should be 25–30 g per day.
- A clinical trial showed that eating fish two to three times per week reduced the risk of CVD.
- Encourage increased dietary consumption of omega-3 fatty acids.
- A clinical trial showed that a "Mediterranean diet," supplemented with alpha-linoleic acid, significantly reduced the risk of recurrent coronary events in patients with heart disease.
- Diets rich in antioxidant vitamins (i.e., nuts, fruits, and vegetables) are preferred over vitamin supplements.
- Limit salt intake to 6 g per day. A reduced salt/reduced saturated fat diet has been shown to reduce blood pressure in clinical trials.
- Prefer spices to salt in food preparation. Reduce intake of canned and commercial bakery goods, which are usually high in salt.
- Limit alcohol to less than one to two glasses per day: one glass equals 4 ounces of wine (approx. 120 mL), 12 ounces of beer (approx. 360 mL), or 1½ ounces of 80-proof spirits (approx. 45 mL).

#### 4.2.3 Pharmacotherapy

*Blood pressure*

- Achieve and maintain blood pressure < 140/90 mmHg or lower if tolerated. If blood pressure remains above 140/90 mmHg after 3 months of reduced dietary salt, saturated fats and attempted weight loss, or if initial level is above 160/100 mmHg, initiate individualized pharmacotherapy. Goal blood pressure < 130/80 mmHg if diabetic.

  Beta-blockers, low-dose diuretics, and angiotensin converting enzyme inhibitors have been shown in clinical trials to reduce the risk of MI in patients with high blood pressure.

*Lipids and lipoproteins*

- **LDL cholesterol**

  a) In women without CHD or CHD risk equivalents (other forms of atherosclerotic disease, diabetes, or 10-year risk more than 20 percent), the desirable LDL cholesterol level is < 130 mg/dL (3.4 mmol/L).

     ◦ If the LDL cholesterol level is > 130 mg/dL (3.4 mmol/L) and two or more other risk factors are present, or the 10-year risk of MI is more than 10 percent, implement intensive lifestyle intervention and consider pharmacotherapy. If the 10-year risk is less than 10 percent, consider pharmacotherapy if the LDL cholesterol is > 160 mg/dL (4.1 mmol/L).

     ◦ If the LDL cholesterol level is > 190 mg/dL (4.9 mmol/L), pharmacotherapy is usually required.

  b) In women with CHD or CHD equivalents, the desirable LDL cholesterol level is 100 mg/dL (2.6 mmol/L) or lower, and pharmacotherapy is generally required.

- **Triglycerides and HDL cholesterol**

  ◦ If the triglycerides are >150 mg/dL (1.7 mmol/L) and the HDL cholesterol is below 40 mg/dL (1.0 mmol/L), treatment should still be aimed primarily at the LDL level. Lowering triglycerides and raising HDL levels become secondary targets of therapy and may influence the choice of drugs. Women with elevated triglycerides as their only lipid abnormality usually respond to intensive lifestyle measures. Some patients with very high triglyceride levels respond best to fibrates or niacin.

***Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women …***

- **Choice of drugs**

  ◦ Statins are the drugs of choice for high LDL cholesterol levels, irrespective of the levels of triglycerides or HDL cholesterol. Statins have been shown in clinical trials to reduce the risk of MI and stroke.

  For women with moderate elevations of LDL cholesterol, raised triglycerides, and low HDL cholesterol levels, statins are the first choice. Fibrates and niacin have not been shown in randomized clinical trials to reduce CHD risk in women, although recommended in AHA/ACC (American Heart Association/ American College of Cardiology) guidelines for low HDL or high triglycerides. Start statin therapy promptly in patients with acute coronary syndrome.

  HRT given orally reduces LDL cholesterol by 10 percent, raises HDL cholesterol by 10 percent, and raises triglycerides by 20 percent. HRT is not recommended for management of lipid disorders because of the lack of clinical trial evidence showing cardiovascular benefit.

*Diabetes*

- Target preprandial blood glucose in the range of 80–120 mg/dL (4.4–6.7 mmol/L), bedtime 100–140 mg/dL (5.5–7.8 mmol/L), Hgb A1c < 7 percent
- Maintain LDL cholesterol < 100 mg/dL (2.6 mmol/L) and triglycerides < 150 mg/dL (1.7 mmol/L)
- Maintain blood pressure < 130/80 mmHg (optimal < 120/75 mmHg)
- In clinical trials, the initiation of oral HRT is accompanied by a two- to fourfold increased risk of venous thromboembolism and a small early increased risk of CHD and stroke. Based on observational studies, a reduction in risk for CHD after 2 or more years is possible, but the clinical trial evidence is lacking. Some experts

see no reason to discontinue HRT in women who have been treated for many years, in view of the expected benefit for osteoporosis. Based on clinical trial data, an increased risk of venous thromboembolic disease persists for at least 4 years. The absolute increase in risk for venous thromboembolism is small—approximately two excess events in 8,000 treated women. This risk may be reduced in women taking aspirin or statins.

- A history of venous thromboembolic disease is a contraindication to HRT.
- Low-dose aspirin can be recommended for women with established CVD (based on clinical trial data and probably for high-risk women [by inference only]). There is some concern that the risk benefit ratio may be different in women, who seem to have a higher risk of stroke than men. Consider clopidogrel or warfarin if aspirin is contraindicated.
- Beta-blockers: If there are no contraindications (e.g., severe bradycardia, high degree heart block, acute heart failure, asthma, active peripheral vascular disease) start beta-blockers within hours of hospitalization for MI and acute coronary syndromes, or as soon as possible thereafter to lower the risk of reinfarction and of cardiac failure.
- ACE inhibitors. If there are no contraindications (e.g., renal artery stenosis, aortic stenosis, or severe hypotension), start ACE inhibitors within hours of hospitalization for MI, or as soon as possible thereafter, to lower the risk of reinfarction and of cardiac failure. Use ACE inhibitors to lower the risk of MI and death in patients with cardiac failure, left ventricular dysfunction, or high risk for CHD.

#### *4.2.4 Complementary and Alternative Therapies*

- Trials of vitamin E and beta-carotene supplements have failed to show benefit for CVD prevention.

## 5. Cancers (breast, cervix, colorectal, endometrial, ovary, and lung)

The major cancers that occur in postmenopausal women are breast, cervix, colorectal, endometrial, ovary, and lung.

In observational studies, the increased risk of breast cancer after 5 or more years of estrogen replacement therapy is similar to the risk associated with a delayed menopause or with obesity. In some of these studies, breast cancer risk was higher in women who used estrogen plus a progestin and higher in women who used estrogen plus progestin cyclically.

Endometrial cancer is associated with endogenous or unopposed exogenous estrogen levels. An increased risk of endometrial cancer occurs in menopausal women who have low levels of progestin to counterbalance the stimulating effect of estrogen on the endometrium. A 3-year clinical trial has shown that endometrial hyperplasia, a uterine cancer precursor, occurs in 10 percent of women for each year of unopposed estrogen use.

A number of observational epidemiological studies (including both prospective and case-control studies) have consistently shown that women on HRT have reduced risks of developing colorectal cancer or adenoma and of dying from colorectal cancer. There is weak evidence from observational studies that HRT increases the risk of ovarian and lung cancer.

Much of the increased risk for cancers in postmenopausal women can be linked to the effects of age and accumulated lifetime exposure to carcinogens.

### 5.1 Assessment

#### *5.1.1 Risk Factors*

*Nonmodifiable risk factors*

- Family history of breast, ovarian, or colorectal cancer, especially in a first-degree relative.
- Age. Most cancer rates increase with age. The year-by-year increase in breast cancer rates

persists but is less steep in women who do not take estrogen after the menopause.

- Previous history of cancer (invasive and in situ).
- Precursor lesions (benign proliferative breast disease, colorectal polyps, endometrial hyperplasia, and high grade squamous intra-epithelial lesions of the cervix infected with selected variants of human papillomavirus [HPV]).
- Reproductive and menstrual factors: Early menarche and late menopause increase risk for breast cancer, and possibly also endometrial and ovarian cancer. Early first pregnancy and multiparity decrease the risk for breast and ovarian cancers. Multiparity also reduces the risk of endometrial cancer.

***In observational studies, the increased risk of breast cancer after 5 or more years of estrogen replacement therapy is similar to the risk associated with a delayed menopause or with obesity.***

*Modifiable risk factors*

- Estrogen treatment: Excess exogenous estrogen in the postmenopausal years increases risk for breast and endometrial cancers. It is unknown whether lower doses of estrogen will have different risks and benefits. Use of a progestin with the estrogen may increase breast cancer risk, but it decreases endometrial cancer risk if taken in an adequate regimen, either 10–14 days per month or daily. Past oral contraceptive use greater than 1 year decreases endometrial and ovarian cancer risk.
- Overweight: Heavier postmenopausal women are at increased risk for cancer of the breast, endometrium, and colon. The risk for breast cancer in obese women is comparable to that for long-term HRT.
- Nutrition: Women whose usual diet is low in fat and high in vegetables, fruits, and fiber have a reduced risk for colorectal and breast cancer. Recent clinical trials found no reduced risk of colon polyps, a cancer precursor, after either a high-fiber diet or a diet enriched with fruits and vegetables.
- Physical activity: Physically active women may have a reduced risk for colon cancer and possibly also breast and endometrial cancer.
- Cigarette smoking: Women smokers are at increased risk for lung, cervix, colorectal, oral, esophageal, and pancreatic cancers, as well as other less common epithelial cell cancers.
- Alcohol: Alcohol use increases the risk for breast (probably by increasing endogenous estrogen levels) and colon cancer, as well as more rare head and neck cancers.
- Radiation: High doses of radiation, used in the past for certain medical treatments, have been associated with increased risk for several cancers.
- Other exposures: Women infected with specific strains of HPV are at increased risk for cervical cancer.
- High radiographic density on mammogram carries about a twofold increased risk for breast cancer and may delay diagnosis by making mammograms harder to read. A clinical trial showed that this reversible condition occurs within 1 year in about 15 percent of most postmenopausal women treated with estrogen alone and in more than one-third of those treated with estrogen plus a progestin.

### *5.1.2 Case Finding*

*History*

- Presence of any of the risk factors above

*Physical examination*

- Height, weight
- Clinical breast exam

- Pelvic exam
- Colorectal screening (can include fecal occult blood assay, flexible sigmoidoscopy, and colonoscopy).

*Specific tests*

The selection of screening modality and frequency will depend on individual and population prevalence of disease and available resources.[a]

- Mammograms: There is disagreement about the benefit of mammograms before age 50, but women taking HRT and those with other risk factors may want to be tested. Mammograms are usually performed annually or biannually. Because women's risk of breast cancer continues to increase with age, regular mammography screening remains appropriate even in old age although the benefit in women over age 75 has not been tested.
- Cervical smears: In countries where cervical cancer rates increase with age, cervical smears should be continued into old age.
- Pap smears have poor positive predictive value for postmenopausal women and do not have to be performed more often than every 2–3 years after a normal cytological result. The main advantage of an annual Pap smear is that it increases overall adherence to regular examination. Clinical observation shows no effect of HRT on cytologic abnormalities.
- Special methods that include testing for carcinogenic HPV strains reduce the number of false-positive results and the attendant anxiety and cost. In the future, these tests may replace the Pap smear as the gold standard for early detection of cervical cancer.

### 5.2 Prevention and Treatment

Despite a great deal of information on factors that increase cancer risk, there are limited data on what can be done to reduce risk. There have been few clinical trials of prevention modalities. It is not clear that reversing a risk factor will reduce cancer risk. Nevertheless, some practical recommendations can be made.

***Much of the increased risk for cancers in postmenopausal women can be linked to the effects of age and accumulated lifetime exposure to carcinogens.***

#### *5.2.1 Lifestyle*

- Stop smoking.
- Limit alcohol use to less than one to two glasses per day: 1 glass equals 4 ounces of wine (approx. 120 mL), 12 ounces of beer (approx. 360 mL), or 1½ ounces of 80-proof spirits (approx. 45 mL).
- Avoid unnecessary radiation.
- Avoid unopposed ERT if uterus is present.
- Avoid HRT for more than 5 years except in presence of specific indications.
- Avoid postmenopausal weight gain.
- If overweight or obese, lose weight.
- Increase physical activity.

#### *5.2.2 Diet*

- Increase intake of vegetables, fruits, and fiber.
- Decrease fat and red meat intake.

[a] Horton R. Screening mammography—an overview revisited. Lancet 2001;358:1284–1285. Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001;358:1340–1342.

#### 5.2.3 Pharmacotherapy

*Breast Cancer*

- Consider tamoxifen use if high risk for breast cancer; a North American clinical trial found a reduced risk for breast cancer with 5-year use. Tamoxifen increases the risk of endometrial cancer, venous thromboembolism, and vasomotor symptoms.

***Despite much interest in complementary and alternative therapies, there are no trial data on their efficacy in reducing cancer risk.***

- Although raloxifene is not approved for prevention or treatment of breast cancer, a 4-year trial of raloxifene in women with osteoporosis (not at high risk for breast cancer) showed a 90-percent risk reduction for estrogen-receptor positive breast cancer, and no increased risk of uterine cancer. Breast density is not increased with raloxifene use. A trial comparing raloxifene with tamoxifen is underway.
- When prescribing estrogen to women with an intact uterus, prescribe at least 10–14 days per month of progestin, to reduce endometrial cancer risk.
- Do not give progestin to women without a uterus; it is not necessary, and some observational studies suggest that estrogen plus progestin increases the risk of breast cancer more than estrogen alone.

#### 5.2.4 Complementary and Alternative Therapies

- Despite much interest in complementary and alternative therapies, there are no trial data on their efficacy in reducing cancer risk. The most attractive candidate is soy protein, based on observational studies of low breast cancer risk in countries with high soy intake.
- A trial of the effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas, a cancer precursor, failed to show the benefit of such a diet in reducing risk.

*Other: very-high-risk patients*

- Consider removal of at-risk organs.
- Very high risk for breast cancer: additional screening by sonography.
- There is no trial evidence that additional screening such as pelvic ultrasound or Ca125 for women at high risk for ovarian cancer or beginning mammography before age 40 for women at high risk for breast cancer will improve the prognosis.
- Colonoscopy for women at high risk for colorectal cancer can be recommended based on clinical trial data.

## 6. Dementia and Mental Health

For most disorders affecting the central nervous system, there are inadequate data upon which to base practice decisions. Alzheimer's disease merits particular mention, because it is common and a major concern of older women.

### 6.1 Assessment

#### 6.1.1 Risk Factors for Alzheimer's Disease

- The only consistently identified risk factors are age, family history, and apolipoprotein E ε4 allele.
- The risk of developing Alzheimer's disease doubles approximately every 5 years through the ninth decade of life.
- Uncommon forms of the illness that appear before the seventh decade of life are often transmitted as autosomal dominant disorders.
- Dominant inheritance is not characteristic of later-onset dementia, although family history remains a risk factor in this age group.
- Some observational studies suggest other risk factors for Alzheimer's disease, including prior history of head trauma, low educational achievement, presence of CHD, hypertension or hyperlipidemia, prior history of depression, and the

absence of HRT. The evidence for these associations is inconsistent.

- Polypharmacy and thyroid disease are two examples of reversible causes of memory loss in older adults.
- Depressed mood is fairly common in persons with dementia; it may impair cognitive function or be a consequence of it.

#### *6.1.2 Case Finding for Suspected Dementia*

- The medical, neurological, and psychiatric history should focus on potential causes of cognitive and behavioral change, including stroke, endocrine disease (e.g., thyroid disorders), toxic exposures (particularly the excessive use of psychotropic medications or medications with psychotropic side-effects), and depression.

***For most disorders affecting the central nervous system, there are inadequate data upon which to base practice decisions.***

- Family history should be assessed.
- Functional decline should be documented.
- The mental status examination should evaluate both cognition and mood. Commonly used tests for cognitive function are the Mini-Mental State Examination (MMSE) and the short Blessed Test for Orientation-Memory-Concentration. Standard validated questionnaires are available for testing for depressed mood in the elderly (e.g., the Beck Depression Inventory and the Geriatric Depression Scale).
- Laboratory assessment in the patient with dementia usually includes complete blood count; serum electrolytes and glucose; tests of renal, liver, and thyroid function; and B-12 level. Screening for syphilis and HIV should be considered in at-risk populations.
- Brain imaging study (CT scan or MRI scan) is often used to exclude space-occupying lesions, evaluate suspected cerebrovascular disease, or evaluate suspected hydrocephalus. The diagnostic yield for this procedure is low if the neurological examination is normal and the history and examination are otherwise typical for Alzheimer's disease.
- A common cause of cognitive impairment in the elderly is overmedication. A careful review of all medications taken by the patient may lead to the identification of a reversible cause of confusion or memory loss.

### 6.2 Prevention and Treatment

- There are no proven preventive measures for Alzheimer's disease. For prevention of vascular dementia, it is reasonable to follow preventive recommendations listed for CVD.

#### *6.2.1 Lifestyle*

- Ensure a safe, stable, and structured environment.
- Encourage social interventions such as power of attorney and caregiver respite as appropriate.

#### *6.2.2 Diet*

- Diet should be well-balanced.
- Discourage excess alcohol use.
- Discourage smoking, which can pose a fire hazard.

#### *6.2.3 Pharmacotherapy*

- Reduce unnecessary or optional medications.
- Identify and treat depression and other behavioral disturbances when they are distressing to patients or hinder their care.
- There is clinical trial evidence that drugs that inhibit the breakdown of acetylcholine in the brain are often of mild symptomatic benefit.

- There is no clinical trial evidence that estrogen improves symptoms or delays symptomatic progression in women with Alzheimer's disease.
- There are no published long-term clinical trial data on potential effects of HRT on age-associated cognitive decline.
- One clinical trial found that vitamin E slows progression without improving cognition in patients with moderate dementia due to Alzheimer's Disease.
- One clinical trial of antihypertensive medication in cognitively intact older adults with hypertension showed a small but significant difference in the rate of memory loss and the incidence of dementia in those on active treatment.
- One clinical trial found raloxifene was associated with less cognitive decline in two cognitive function tests in older women.

#### *6.2.4 Complementary and Alternative Therapies*

- There is limited trial evidence that gingko biloba may offer mild cognitive benefit when given to patients with dementia.

## 7. Conclusions

In the last 20 years, menopause has become a household word, with much better understanding of its consequences. The growing numbers of postmenopausal women and clinical trials have coincided to draw increasing attention to the perimenopausal and postmenopausal years. Better studies of older therapies and the expanded number of new choices today, with more in development and evaluation, have complicated provider and patient choices, but greatly improved the potential for effective intervention.

# Suggested Reading (Systematic Reviews and Recent Clinical Trials Only)

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# 14. List of Abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| ACE | angiotensin-converting enzyme |
| ACS | acute coronary syndromes |
| ACTH | adrenocorticotropic hormone |
| AF–1 | activation function 1 |
| AF–2 | activation function 2 |
| AHA | American Heart Association |
| AHCPR | Agency for Health Care Policy and Research |
| AHRQ | Agency for Healthcare Research and Quality |
| AIRE | Acute Infarction Ramipril Efficacy |
| AP1 | Activated Protein 1 |
| AR | androgen receptor |
| ArKO | aromatase knockout |
| ATP | Adult Treatment Panel |
| AVP | anteroventral periventricular nucleus |
| BARI | Bypass Angioplasty Revascularization Investigation |
| BCDDP | Breast Cancer Detection and Demonstration Project |
| BERKO | ERβ knockout |
| BMC | bone mineral content |
| BMD | bone mineral density |
| BMI | body mass index |
| CABG | coronary artery bypass graph |
| CAD | coronary artery disease |
| CAMS | Council of Affiliated Menopause Societies |
| CAST | Chinese Acute Stroke Trial |
| CBP | CREB binding protein |
| CEE | conjugated equine estrogen |
| ChAT | choline acetyl transferase |
| CHD | coronary heart disease |
| CI | confidence interval |
| CNS | central nervous system |
| CONSENSUS-I | Cooperative North Scandinavian Enalapril Survival Study |
| CPS-II | Cancer Prevention Study II |

| | |
|---|---|
| CRP | C-reactive protein |
| CT | computed tomography |
| CVD | cardiovascular disease |
| D&C | dilatation and curettage |
| DDT | dichlorodiphenyltrichloroethane |
| DERKO | double ER knockout |
| DES | diethylstilbestrol |
| DEXA | dual energy x-ray absorptiometry |
| DRI | dietary reference intake |
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders, 4th edition |
| ECG | electrocardiogram |
| EGF | epidermal growth factor |
| eNOS | endothelial nitric oxide synthase |
| EPISTENT | Evaluation of IIb/IIIa Platelet Inhibitor for Stenting |
| EpRE/ARE | electrophilic/antioxidant response element |
| ER | estrogen receptor |
| ERA | Estrogen Replacement and Atherosclerosis |
| ERE | estrogen-responsive element |
| ERKO | ERα knockout |
| ERT | estrogen replacement therapy |
| FARs | floating absolute risks |
| FDA | Food and Drug Administration |
| FMP | final menstrual period |
| FSH | follicle-stimulating hormone |
| GABA | gamma-aminobutyric acid |
| GBDS | Global Burden of Disease Study |
| GH | growth hormone |
| GnRH | gonadotropin-releasing hormone |
| GUSTO IIb | Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes |
| HATs | histone acetyl transferases |
| HDL | high density lipoprotein |
| HERS | Heart and Estrogen/Progestin Replacement Study |
| hGH | human growth hormone |
| HMG-CoA | 3-hydroxy-3-methylglutaryl-coenzyme A |
| HOPE | Heart Outcomes Prevention Evaluation |
| HPA | hypothalamo-pituitary axis |
| HPV | human papillomavirus |
| HRT | hormone replacement therapy |
| HSDD | hypoactive sexual desire disorder |
| 5-HT | 5-hydroxytryptamine |
| ICAM-1 | intracellular adhesion unit |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems |

| | |
|---|---|
| ICI | Imperial Chemical Industries PLC |
| IGF-I | insulin-like growth factor |
| IL-1b | interleukin-1b |
| IMS | International Menopause Society |
| ISIS | International Studies of Infarct Survival |
| IU | international unit |
| IUD | intrauterine contraceptive device |
| LBD | ligand-binding domain |
| LDL | low density lipoprotein |
| LH | luteinizing hormone |
| Lp(a) | lipoprotein(a) |
| LV | left ventricular |
| MAPK | mitogen-activated protein kinase |
| MEK | mitogen-activated protein kinase kinase |
| MI | myocardial infarction |
| MMP | matrix metalloproteinases |
| MMSE | Mini-Mental State Examination |
| MORE | Multiple Outcomes of Raloxifene Evaluation |
| MPA | medroxyprogesterone acetate |
| MRI | magnetic resonance imaging |
| NCEP | National Cholesterol Education Program |
| NGF | nerve growth factor |
| NHANES III | Third National Health and Nutrition Examination Survey |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIH | National Institutes of Health |
| NO | nitric oxide |
| NRMI | National Registry of Myocardial Infarction |
| NSABP | National Surgical Adjuvant Breast and Bowel Project |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| OAB | overactive bladder |
| OC | oral contraceptive |
| OR | odds ratio |
| ORWH | Office of Research on Women’s Health |
| PAI | plasminogen activator inhibitor |
| PAMI | Primary Angioplasty in Myocardial Infarction |
| PEPI | Postmenopause Estrogen/Progestin Intervention |
| PIN | prostatic intraepithelial neoplasia |
| PKA | protein kinase A |
| PKC | protein kinase C |
| PPARs | peroxisome proliferator-activated receptors |
| PR | progesterone receptor |
| PRL | prolactin |

| | |
|---|---|
| PTCA | percutaneous transluminal coronary angioplasty |
| PTH | parathyroid hormone |
| RCT | randomized controlled trial |
| RR | relative risk |
| RU486 | mifepristone |
| RUTH | Raloxifene Use for The Heart |
| SAD | sexual aversion disorder |
| SERM | selective estrogen receptor modulator |
| SERT | serotonin reuptake transporter |
| SHBG | sex hormone binding globulin |
| SHEP | Systolic Hypertension in the Elderly Program |
| SSRI | selective serotonin reuptake inhibitors |
| STAR | Study of Tamoxifen and Raloxifene |
| STOP | Swedish Trial in Old Patients |
| STS | Society of Thoracic Surgeons |
| SWAN | Study of Women's Health Across the Nation |
| TGF | transforming growth factor |
| THC | tetrahydrochrysene |
| TNFa | tumor necrosis factor a |
| TPH | tryptophan hydroxylase |
| TTS | transdermal therapeutic systems |
| UI | urinary incontinence |
| VCAM-1 | vascular cell adhesion molecule-1 |
| W/H | waist/hip ratio |
| WHI | Women's Health Initiative |
| WHO | World Health Organization |
| WISDOM | Women's International Study of Long Duration Oestrogen After Menopause |

## For More Information

The NHLBI Health Information Center is a service of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. The NHLBI Health Information Center provides information to health professionals, patients, and the public about the treatment, diagnosis, and prevention of heart, lung, and blood diseases. For more information contact:

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