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].

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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.

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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.

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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) ≥ 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: Former users:	1.5 (0.8–2.7) 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 5–14 yr ≥ 15 yr	1.3 (0.9–2.0) 1.1 (0.6–1.8) 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 Opposed HRT Any HRT (recent use)		0.5 (0.3–0.9) 0.5 (0.3–1.1) 0.7 (0.6–0.9)	0.90 (0.46–1.76) 1.1 (0.5–2.5) 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 Past use	0.3 (0.1–1.0) 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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