Gad Rennert

BACKGROUND

Breast cancer is the most common cancer in women in developed Western countries *[1]* and is becoming ever more significant in many developing countries *[2]*. Although incidence rates are increasing, mortality rates are stable, representing an improved survival rate. This improvement can be attributed to effective means of early detection, mainly mammography, as well as to significant improvement in treatment options.

RISK FACTORS

Breast cancer should be largely viewed as a disease predominantly influenced by risk factors related to lifestyle, as only approximately 15% of all breast cancer cases can be attributed to familial and genetic influences *[3]*. Most known risk factors for breast cancer can be linked to hazardous effects of hormonal exposures *[4]*, although other risk factors such as exposure to ionizing radiation are also relevant in some populations *[5,6]*.

Reproduction-Related Exposures

Early age at menarche, late age at menopause *[4]*, small number of children and nulliparity, late age at first birth *[7]*, and little or no breastfeeding *[8,9]* have all been associated with an increased risk of developing breast cancer. Although several retrospective studies have suggested that induced abortion is related to an increased risk of this disease, this is not seen in prospective studies *[10]*, and its status as a breast cancer risk factor is unclear. The period of exposure to sex hormones before the first full-term pregnancy is a time when the breast tissue is especially susceptible to carcinogenesis. Long-term use of hormone replacement therapy, but apparently not long-term use of oral contraceptives, is also related to increased risk of breast cancer *[11-14]*. Despite the use of mega-doses of hormones in fertility treatments, there is no current evidence that these treatments are hazardous to the breast *[15,16]*. Of major interest are risk factors for which there is a potential to reduce risk at the population level. Use of external hormones and breastfeeding probably are the 2 best candidates. Recent meta-analyses have demonstrated that long-term breastfeeding can be linked with up to a 30% reduction in breast cancer risk.

Benign Breast Disease

History of benign breast disease is also related to increased risk of breast cancer *[17]*. The risk, however, is mostly restricted to women who underwent biopsies, and especially those in whom atypical hyperplasia was found in such biopsies *[18]*.

Nutritional Factors

The role of diet and nutrition in the etiology of breast cancer has been under debate for decades. Dietary fat has been the most investigated food constituent studied in this regard. It is currently believed that a high-fat diet is not directly related to the risk of breast cancer *[19,20]*. Overall caloric intake, and obesity in particular with certain weight-gain patterns, are related to increased breast cancer risk, with different effects between pre- and post-menopausal women *[21,22]*. This is also in line with a proven role of regular physical activity in reducing breast cancer risk *[23]*. High fruit and vegetable consumption is related to decreased breast cancer risk in most, but not all, studies *[24]*. Specifically, the consumption of cruciferous vegetables has been shown in vitro and in vivo to be related to such protection *[25]*. Of all food items studied, regular alcohol consumption, even at moderate levels, has consistently been

found to be related to a mild increase in breast cancer risk in women *[26,27]*.

Other Lifestyle and Environmental Risk Factors

Active and passive smoking have recently been shown to be related to breast cancer risk *[27,28]*. Ionizing radiation has been shown to increase the risk of breast cancer in studies following cohorts exposed to the A-bomb as well as in studies of women exposed to medical radiation *[5,6]*.

Numerous studies have failed to show that environmental hazards, such as exposure to specific pollutants, are substantially related to breast cancer risk. Some have suggested that exposure to polychlorinated biphenyls (known as PCBs) and organochlorines carries increased risk of breast cancer, but these suggestions have not been substantiated in well-designed studies *[29-31]*.

High Breast Density

High breast density, as reflected on mammography films, has been shown to be one of the most significant markers of breast cancer risk *[32]*. Dense breast tissue probably reflects high hormonal exposure and is typical of young women, women using hormone replacement therapy, and those who are *BRCA* gene carriers.

Genetic Factors

An established proportion of all breast cancer cases is caused by mutations in specific genes, mainly the *BRCA* genes. This proportion differs between different ethnic groups, and is especially high among Jewish women of Ashkenazi and Iraqi origin *[33-38]*. In the latter group, up to 10% of all newly diagnosed breast cancers are due to mutations in these genes. In addition to *BRCA* gene mutations, other genes such as *AT* and *p53* are also involved in the development of breast cancer *[3]*. A variety of single nucleotide polymorphisms in genes encoding phase I and phase II enzymes, as well as other enzymes involved in the hormonal metabolism, are thought to interact with hormonal, nutritional, and radiological exposures to increase the risk of breast cancer.

Risk Factor Summary

Differences in prevalence of exposure to these lifestyle and genetic risk factors among women from different countries in the Middle East are probably responsible for the variability in breast cancer incidence seen between countries in this area *[39,40]*. Time trends in the prevalence of the lifestyle risk factors can be directly correlated with time trends in breast cancer incidence. Delay in time of first pregnancy, decrease in number of children and in breastfeeding, increase in use of external hormones, and a move toward high-calorie Western diets are all responsible for the current trends in breast cancer incidence in the developed as well as the developing countries in the Middle East.

RESULTS

Overall Incidence

Breast cancer was the leading tumor in females in all cancer registries involved in this analysis, accounting for as high as 37.6% of all reported tumors in Egyptian females to as low as 27.7% of all reported tumors in Israeli Arab females (Table 8.1). Age-standardized incidence rates (ASRs) per 100,000 females were highest among Israeli Jews (93.1), similar to the rates reported in US SEER females (97.2). These rates were significantly higher than those reported in Cypriot (57.7), Egyptian (49.6), Jordanian (38.0), and Israeli Arab (36.7) females. The high incidence rates described in Israeli Jews were similar to those described in North American and West European countries, while the lower rates in the other

Middle Eastern groups were more similar to rates in Mediterranean Europe, Eastern Europe, and some of Asia and Africa *[41]*.

Male breast cancer was a relatively rare disease, responsible for only 0.2%-0.5% of all malignancies in males in all registries (MECC and US SEER) (see Table 1.6). Nevertheless, the age-standardized rate in Israeli Jewish males (1.1) was almost 40% higher than the rates reported by the US SEER program or the Egyptian registry (0.8) (see Table 1.7).

Age

Marked differences are noted between age-specific breast cancer rates in participating registries. Age-specific rates in almost all age groups were highest in the Israeli Jewish population (Table 8.2). These rates were higher than the US SEER rates in the age groups 35-54 years and were similar to or slightly lower than the US rates for the older age groups. Age-specific rates in females 25-34 years were highest in the Egyptian registry and substantially lower in the Jordanian and Israeli Arab populations. While between 57% and 68% of all breast cancers in the Arab populations of Egypt, Jordan, and Israel were diagnosed before the age of 55 years, only about 44% of the breast cancers among Cypriots and 37% among Israeli Jews were diagnosed in that age group. The Israeli Jewish figure was again much closer to the US SEER figure of 35% (Figure 8.1).

Histology

As shown in Table 8.3, microscopic confirmation was available for the vast majority of the registered malignancies, ranging from 92.0% to 99.4%, with small differences between the participating countries. Classification of tumors into specific histological subgroups was available for 98.6% of the tumors with microscopic diagnosis in Cypriots, 94.2% in Israeli Jews, 91.5% in Israeli Arabs, 91.3% in Egyptians, and 90.7% in Jordanians, as compared with 98.7% of the tumors in the SEER program. Thus, in all of the MECC registries, less than 10% of the microscopically confirmed breast cancers were identified as neoplasm or carcinoma only.

The leading tumor histology in all registries was infiltrating duct carcinoma, followed by lobular carcinoma (Table 8.3). In the SEER program, more infiltrating duct carcinomas were registered with a

Table 8.1. Breast Cancer: Female Breast Cancer Indicators in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001

	Cyprus 1998-2001	Israel (Jews) 1996-2001	Israel (Arabs) 1996-2001	Egypt 1999-2001	Jordan 1996-2001	US SEER* 1999-2001
Number of incident female breast cancer cases	1,066	17,325	762	1,945	2,930	78,802
Breast cancer as proportion of all reported tumors in females	35.4%	31.5%	27.7%	37.6%	32.5%	32.3%
Female breast cancer age-standardized incidence rates†	57.7	93.1	36.7	49.6	38.0	97.2

*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

†Rates are per 100,000 females and are age-standardized to the World Standard Million.

lobular component than in the MECC region registries. Between-country differences were noted mainly in the proportion of lobular carcinomas and adenocarcinomas.

DISCUSSION

The main finding in these data is the high incidence rate of breast cancer in Israeli Jews, compared with a low rate in Arab populations and an intermediate rate in Cypriots. While the proportion of all cases occurring in younger ages was higher among the Arabs, the age-specific rates in practically all age groups were highest in the Israeli Jewish population. A younger age distribution of the cases in Arab populations is a reflection of the younger demographic profile. The use of age-specific rates corrects for this demographic difference. It is of interest, however, that the rates in the very young age groups in Egyptians, but not in Jordanians or Israeli Arabs, were similar to the rates in Israeli Jews, which are among the highest in

Table 8.2. Breast Cancer: Age-Standardized and Age-Specific Incidence Rates among Females in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001*

	Cyprus 1998-2001	Israel (Jews) 1996-2001	Israel (Arabs) 1996-2001	Egypt 1999-2001	Jordan 1996-2001	US SEER† 1999-2001
Total rate‡	57.7	93.1	36.7	49.6	38.0	97.2
Age Groups (Rates)§						
00-04 y	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
05-09 y	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
10-14 y	*0.0*	-	*0.0*	*0.0*	*0.0*	*0.1*
15-19 y	*0.0*	*0.3*	*0.0*	-	-	*0.2*
20-24 y	-	1.7	*0.0*	*1.4*	*0.8*	1.3
25-29 y	*4.9*	9.5	8.7	9.8	5.7	7.1
30-34 y	27.2	27.8	11.8	28.9	20.8	25.2
35-39 y	43.5	69.5	35.2	63.6	47.1	61.7
40-44 y	96.3	124.4	53.4	96.7	73.6	117.5
45-49 y	148.8	205.9	93.5	144.9	82.6	192.1
50-54 y	185.8	275.3	104.2	171.5	129.3	253.1
55-59 y	166.7	310.1	124.0	181.2	114.6	332.4
60-64 y	198.3	346.8	144.0	144.2	134.8	386.8
65-69 y	195.1	359.1	136.8	105.0	131.1	431.1
70-74 y	225.4	405.1	118.7	94.1	103.0	458.7
75+ y	203.7	379.9	96.4	99.6	77.6	458.7

The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

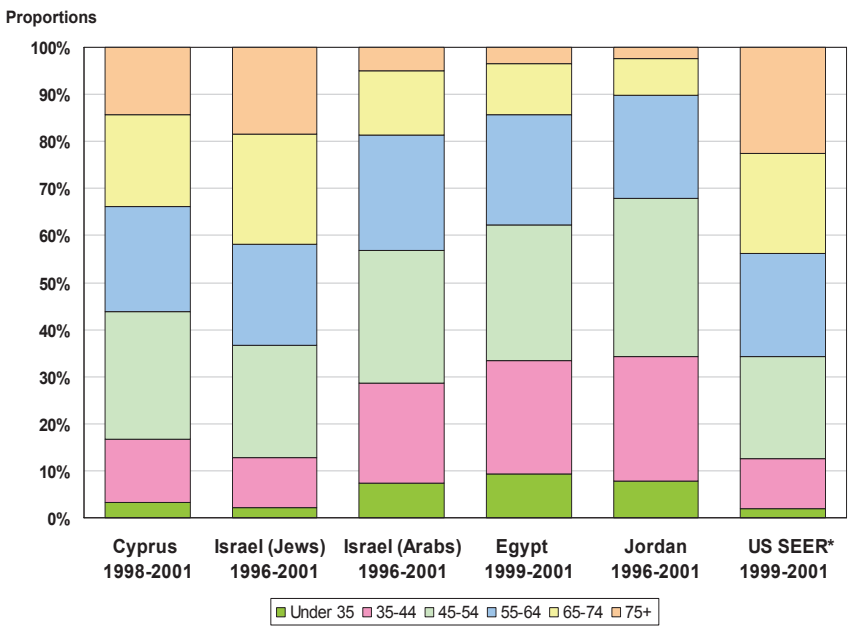
‡Rates are per 100,000 females and are age-standardized to the World Standard Million.

§Rates are per 100,000 females.

the world. Given the fact that the Egyptian registry covers only part of the Egyptian population, a remote possibility that some of these rates reflect a selection into the study cohort of younger women cannot be ignored. Nevertheless, a study of immigrants from the Middle East to Australia did indicate that the Egyptian women had the highest breast cancer rates of all Middle Eastern immigrants *[42]*.

These differences in incidence rates provide an example of the potential role of lifestyle and genetic factors in breast cancer etiology. As the Arab and Jewish populations differ dramatically with respect to most of the important hormonal risk factors (number of children, total length of breastfeeding, age at first birth, use of external hormones) as well as with respect to diet *[43]*, it is not surprising that such large differences in incidence are evident. Studies comparing the etiology of breast and colon cancers in Jewish and Arab women in Israel have shown major differences in the number of births and prevalence of breastfeeding between the 2 demographic groups and between cases and controls within each of the groups. A major cohort effect has also been observed, with the Israeli Arab population moving toward the behaviors of the Israeli Jewish population (lower number of children and less breastfeeding in the younger cohort). Still, breastfeeding in the Arab populations is highly prevalent and is seen as required by Islam *[44]*. A study in Jordan has indicated that obesity was the only risk factor, of those studied, that was significantly different between women with breast cancer and healthy controls *[45]*. The Mediterranean diet – with high consumption of fruits, vegetables, and olive oil, and low consumption of red meat – is the staple of most Arab populations and is usually correlated with reduced risk of several types of cancer, among them breast cancer *[46-49]*.

Figure 8.1. Breast Cancer: Proportions of New Cases by Age Group in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001



*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

About 10% of all breast cancers in the large Ashkenazi Jewish population carry founder mutations in the *BRCA* genes. The high prevalence of these mutations in the Jewish population is at least partially responsible for the exceptionally high incidence rates in the younger Jewish age groups. It is also potentially responsible for the slightly higher proportion of lobular tumors as well as for the higher breast cancer rate in Jewish males (due to the founder mutation 6174delT in *BRCA2*). Such high-prevalence founder mutations have not been described in the Arab population *[50-52]*. Mutations described in the Cypriot population are rare *[53]*.

Another possible contributing factor to the observed differences in breast cancer rates between Jordan and Egypt and Israel is the difference in screening practices between the countries, although the impact of such a difference is only temporary. Israel has been employing a nationwide, full-coverage mammography screening

program in women over the age of 50 since 1996. Organized screening usually results in a temporary increase in incidence rates. Given the length of time it took to achieve a high screening prevalence, this temporary effect could have an impact for a period of about 10 years.

SUMMARY AND CONCLUSIONS

Breast cancer rates in the Middle East registries included in this analysis express a unique picture of the Israeli Jewish population having one of the highest rates worldwide, and the neighboring Arab populations having some of the lower world rates. Such a major difference between populations living in a relatively small area

Table 8.3. Breast Cancer: Proportions of Microscopic Confirmation and Histologic Type of Female Breast Cancers in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001

	Cyprus 1998-2001	Israel (Jews) 1996-2001	Israel (Arabs) 1996-2001	Egypt 1999-2001	Jordan 1996-2001	US SEER* 1999-2001
Total cases microscopically confirmed	1,062	16,104	718	1,842	2,956	78,489
Microscopically confirmed	98.7%	92.0%	92.9%	99.4%	93.5%	98.9%
Distribution of Microscopically Confirmed Cases						
Histologic distribution†	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Unspecified: Neoplasm, carcinoma[1]	1.4%	5.8%	8.5%	8.7%	9.3%	1.3%
Specified histologic type	98.6%	94.2%	91.5%	91.3%	90.7%	98.7%
Distribution of Microscopically Confirmed and Specified Cases						
Microscopically confirmed and specified	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Infiltrating duct carcinoma[2]	80.7%	77.5%	78.1%	84.7%	81.8%	70.2%
Lobular carcinoma[3]	7.3%	9.7%	8.5%	5.3%	7.4%	8.4%
Infiltrating duct and lobular carcinoma[4]	2.3%	2.7%	3.7%	2.8%	1.8%	8.8%
Adenocarcinoma[5]	7.4%	5.3%	3.5%	1.3%	4.7%	6.9%
Medullary carcinoma[6]	0.3%	1.1%	0.9%	1.0%	1.5%	0.7%
All other	2.0%	3.7%	5.3%	4.9%	2.8%	5.0%

ICD-O-3 codes
[1]8000,8001,8010,8020,8021,8230
[2]8500,8521,8541
[3]8520
[4]8522
[5]8050,8140,8211,8260,8401,8480,8481,8490,8503
[6]8510

*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

†Percentages should sum over a column to 100% (with some rounding). Where a percentage has been suppressed because it is based on only 1 or 2 cases, the remaining percentages will not sum to 100%.

emphasizes the importance of both lifestyle and genetic factors in the causation of breast cancer. It is very important to evaluate the prevalence of risk habits in the area populations and to correlate these exposures with noted differences in incidence. This will allow for a better understanding of the optimal way to combat breast cancer in low- and high-incidence populations.

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