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Epidemiology of Breast Cancer

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INCIDENCE, MORTALITY, AND SURVIVAL **Impact in the United States and Gender Effect**

Breast cancer is the second most frequent cause of cancer death among American women, accounting for 15% of all cancer deaths among women and trailing only lung cancer.¹⁰³ Based on data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program,¹⁷¹ 30% of all incident cancers among women are breast cancer, the most frequently diagnosed cancer.¹⁰³ The American Cancer Society estimated that 203,500 cases and 39,600 deaths would occur among U.S. women during 2002. Breast cancer is rare among men, with only 1500 cases and 400 deaths estimated for the year 2002 in the United States.¹⁰³ Based on data from 1995 to 1997, the lifetime risk among U.S. women of being diagnosed with breast cancer is 12.8%, or 1 in 8 women, and the lifetime risk of dying from breast cancer is 3.3%, or 1 in 30 women.¹⁷¹

International Geographic Variation

Globally, breast cancer is the leading cause of cancer death among women, accounting for more than 300,000 deaths in 1990, of which 174,100 occurred in developed countries and 139,500 in developing countries.¹⁶⁴ Estimated 1990 mortality rates (per 100,000 woman-years, age-adjusted, world standard) varied more than sixfold internationally, from less than 4.3 in China to 26.7 in northern Europe. Rates were also low (less than 15) in Japan, other parts of Asia, Africa, and Central America, around 20 in South America and Southern Europe, and highest (more than 23) in Western Europe and North America. From the mid-1970s to the mid-1980s, mortality rates did not change greatly in many of the countries with high rates, whereas increases occurred in many of the countries with low rates, resulting in a narrowing of the international differences.⁴ In contrast to mortality data that generally exist at the national level because death certificates are legal documents, incidence

data from population-based cancer registries are not as widely available. Data from several dozen well-run registries around the world for 1988 to 1992 suggest that incidence rates (age-adjusted, world standard) varied more than threefold. Rates were lowest in parts of China, Japan, India, and Costa Rica (less than 32); intermediate in South America, the Caribbean, and Eastern Europe; and highest in Western Europe, Canada, and North America (Fig. 7-1).¹⁵⁹ Geographic variation was apparent within many countries, but within-country differences were considerably smaller than those among countries. Rates in urban areas generally exceeded those in neighboring rural areas.¹⁵⁰

Migrant Studies

Chinese women living in Shanghai had two thirds the risk of breast cancer compared with those in Hong Kong or Singapore, whereas the rates among Chinese women in Hawaii and San Francisco were more than twice as high (Table 7-1).¹⁵⁹ Similarly, Japanese women in Hawaii, San Francisco, and Los Angeles had rates double those in Japan. Within Israel, women born in Africa or Asia were at reduced risk compared with those born in Israel, Europe, or America. The risk of breast cancer among migrants has approached that of the native-born population and is affected by the time interval since migration; risk is further modified among subsequent generations.^{183,241}

Racial and Ethnic Groups Within the United States

Within the United States during 1988 to 1992, breast cancer incidence rates were highest among white women¹⁵⁹ (Table 7-2). Rates among black women were lower. Rates among Asians and Hispanics were half to two thirds those of whites; American Indian women were at notably low risk.

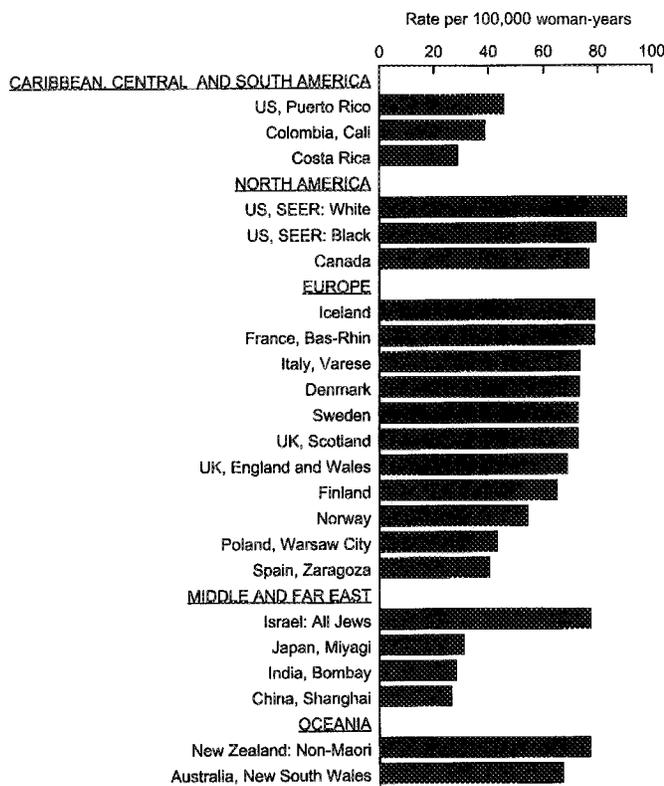


Figure 7-1 International variation in breast cancer incidence rates among women, 1988-1992, per 100,000 woman-years, age-adjusted to the world standard. (From Parkin DM and others: *IARC Sci Publ* 1997; 7:1-1240.)

Geographic Variation Among Whites in the United States

Considerable geographic variation in breast cancer mortality rates has been reported within the United States, with notably high rates in parts of the northeast and low rates across the south.⁴⁸ Figure 7-2 presents the ranked rates by state economic area for white women during 1970 to 1994. The age-adjusted (1970 U.S. standard) rates varied more than twofold, ranging from 16 to 33 per 100,000 woman-years; they were higher than 30 in urban areas of the northeast and mid-west and 20 or lower across the southern and mountain states. The regional excess of breast cancer across the northeast, especially in urban centers, has persisted for over four decades.^{117,140,162} The pattern is most pronounced among postmenopausal women, with little geographic variation among premenopausal women.¹² However, the north-south differences have diminished over time as mortality rates have risen in many areas of the south, including rural areas of Appalachia.¹⁶² National data on survival rates among breast cancer patients are not available, but it is unlikely that geographic variations in survival greatly influence the mortality patterns. Of note are two studies that showed

Table 7-1 Variation in Breast Cancer Incidence Rates among Women, 1988-1992

Group and Place	Cases	Rate*
CHINESE		
China, Shanghai	6084	26.5
Hong Kong	5392	34.0
USA, Los Angeles: Chinese	266	36.8
Singapore: Chinese	2187	39.5
USA, San Francisco: Chinese	459	55.2
USA, Hawaii: Chinese	159	57.6
JAPANESE		
Japan, Osaka	7544	24.3
Japan, Miyagi	2440	31.1
US, Los Angeles: Japanese	319	63.0
US, San Francisco: Japanese	138	68.4
US, Hawaii: Japanese	903	72.9
ISRAELI		
Israel: Jews born in Africa or Asia	1963	56.5
Israel: Jews born in America or Europe	4838	87.9
Israel: Jews born in Israel	1802	90.5

From Parkin DM and others: *IARC Sci Publ* 1997; 7:1-1240.

*Per 100,000 woman-years, age-adjusted using the world standard.

that adjustment for differences in reproductive and socioeconomic variables explained a large part of the observed geographic variation in breast cancer risk.^{119,187} Nonetheless, there continues to be interest in assessing possible effects of dietary and environmental risk factors, as will be discussed later.

Age

The risk of breast cancer increases rapidly with age during childbearing years (Fig. 7-3). After menopause, rates continue to increase, but at a less rapid pace. Incidence rates are higher among blacks than whites during childbearing years, but rates are equal at age 45 years, with substantial excesses among whites of up to 26% apparent thereafter. Mortality rates also show an excess among blacks compared to whites, apparent at all ages. Reasons for the higher rates among blacks are not well understood.

Time Trends

During the four decades from 1950 to 1989, age-adjusted breast cancer mortality rates among white women in the United States changed little, whereas rates increased among nonwhites, approaching and surpassing those among whites around 1990.⁴⁷ Since the early 1980s, breast cancer mortality rates among blacks surpassed those among whites, among whom rates have de-

Table 7-2 Variation by Racial and Ethnic Group Within the United States in Breast Cancer Incidence Rates among Women, 1988-1992

	LOS ANGELES		SAN FRANCISCO		HAWAII		CONNECTICUT		SEATTLE		DETROIT		ATLANTA		NEW MEXICO		IOWA		UTAH			
	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*		
Non-Hispanic																						
White†	15823	103.7	9080	103.3	856	96.5	11135	93.3	10380	92.5	10265	91.9	4253	89.9	2625	86.3	9716	85.3	3394	75.8		
Black	2389	80.9	1056	83.7	—	—	604	84.5	—	—	2328	80.8	1158	72.3	—	—	—	—	—	—	—	—
Filipino	480	69.3	333	65.3	259	57.4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Japanese	319	63.0	138	68.4	903	72.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hispanic																						
White	3186	57.4	815	70.8	—	—	—	—	—	—	—	—	—	—	856	61.3	—	—	—	—	—	—
Chinese	266	36.8	459	55.2	159	57.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Korean	97	21.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hawaiian	—	—	—	—	360	83.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
American	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Indian	—	—	—	—	—	—	—	—	—	—	—	—	—	—	80	28.3	—	—	—	—	—	—

From Parkin DM and others: *IARC Sci Publ* 1997; 7:1-1240.

—, Data not available.

*Per 100,000 woman-years, age-adjusted using the world standard.

†All whites in Hawaii, Connecticut, Detroit, and Atlanta; all women in Seattle, Iowa, and Utah.

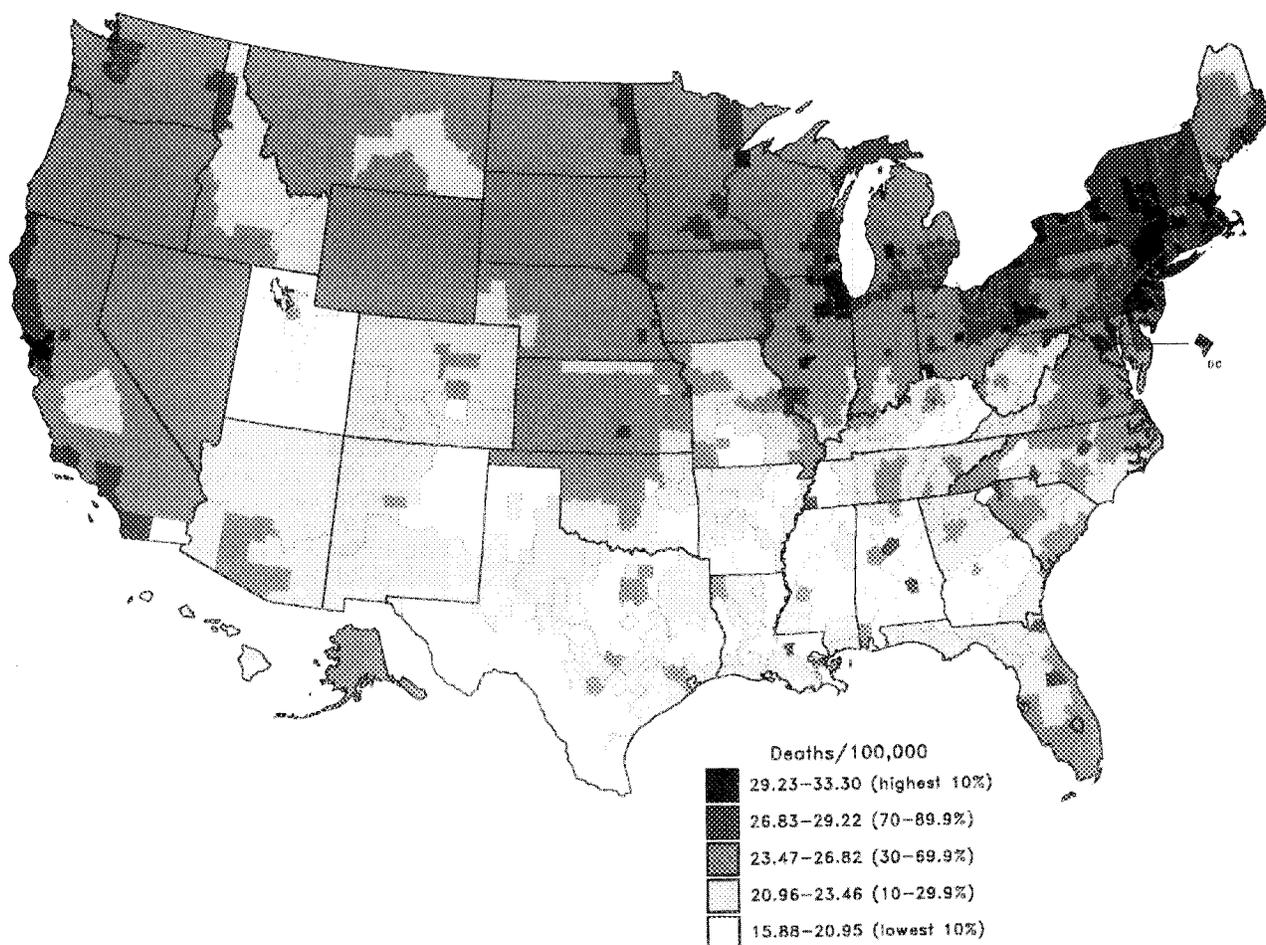


Figure 7-2 Breast cancer mortality rates among white women in the United States by state economic area, 1970–1994, age-adjusted to the 1970 U.S. standard. (From Devesa SS and others: *Atlas of cancer mortality in the United States, 1950–1984*, Washington, DC, 1999, US Government Printing Office.)

clined since the late 1980s¹⁷¹ (Fig. 7-4). In 1997 the rates were 31 and 23 per 100,000 woman-years among blacks and whites, respectively. Incidence rates since the early 1980s generally have shown upward trends among both blacks and whites, with risk consistently 10% to 20% higher among whites. The peaks during the early 1970s most likely were related to increased awareness and detection in response to the Breast Cancer Detection Demonstration Projects and to publicity surrounding the breast cancer diagnosis of several prominent women; the steep increases during the 1980s may have been related to the increasing use of mammography.¹⁴⁵ Increases in mortality will lag behind those in incidence, as the median survival time among women newly diagnosed with breast cancer is now more than 20 years.¹⁷¹ Rising incidence has been more pronounced for estrogen receptor-positive tumors, particularly among older women.⁷² Increases in breast cancer incidence and mortality have been noted internationally in many regions.^{37,203}

The increases in invasive breast cancer incidence were due largely to the diagnosis of localized cases, with rates increasing more than 75% among both white and black women from 1975 to 1977 and 1995 to 1997 (Table 7-3). Rates for regional and distant disease did not change greatly. Although less frequently diagnosed than invasive disease, *in situ* carcinoma rates also rose rapidly. Increases in localized disease occurred among white women of all ages but were most pronounced among those aged 60 to 79 years. When the size of the tumor was considered, the diagnosis of cancers smaller than 2 cm rose much more rapidly than that of larger tumors.¹⁴⁵

Survival

Five-year relative survival rates improved from 75% during the mid-1970s to 86% in the early 1990s among white women and from 63% to 71% among black women, contributing to the observed incidence and

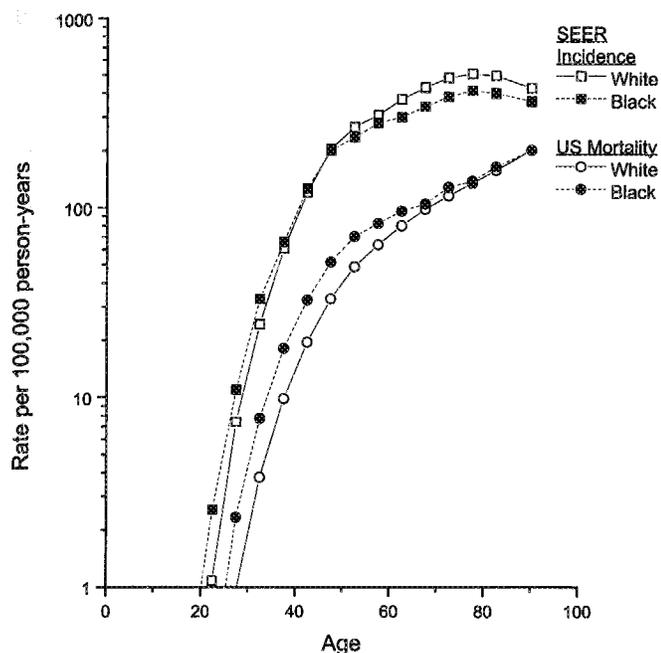


Figure 7-3 Age-specific breast cancer incidence (SEER program) and mortality (United States) curves by race, 1990-1997. (Based on data from Ries LA and others: *SEER Cancer Statistics Review, 1973-1997*, Bethesda, MD, 2000, National Cancer Institute.)

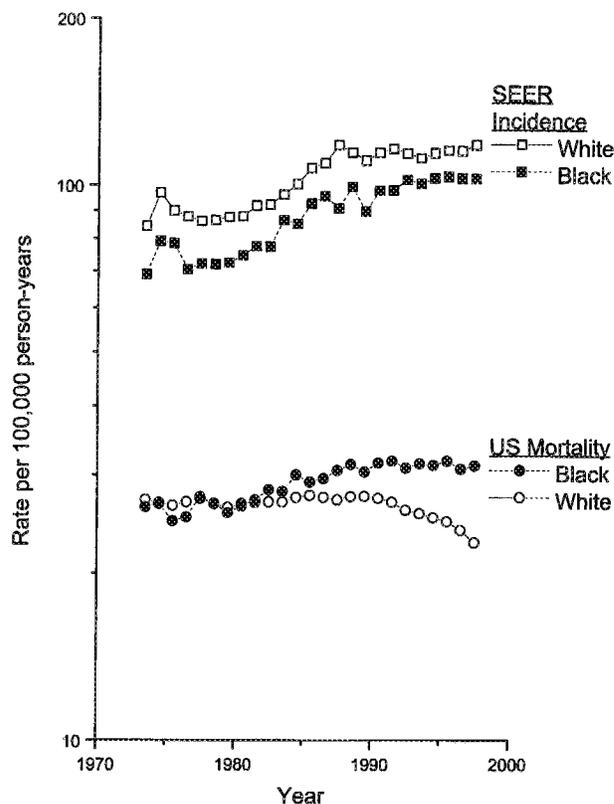


Figure 7-4 Trends in breast cancer incidence (SEER program) and mortality rates (among women in the United States) by race, 1973 to 1997. (Based on data from Ries LA and others: *SEER Cancer Statistics Review, 1973-1997*, Bethesda, MD, 2000, National Cancer Institute.)

mortality patterns.¹⁷¹ Based on more than 120,000 cases diagnosed during 1989 to 1996, more than 60% of breast cancers among white women were diagnosed at a localized stage, and about 30% were diagnosed at a regional stage (Table 7-4). The stage distribution among black women was not as favorable, with localized and regional stages accounting for half and one third of cases, respectively. Survival rates varied markedly by stage at diagnosis, being 89% or more for women with localized disease and 22% or less among those with distant spread. The more favorable prognosis among whites compared to blacks persisted for patients within each stage category, perhaps because of differences in extent of disease within stage category, or effectiveness of treatment.

RISK FACTORS

Demographic Factors

Breast cancer is generally recognized as a disease that occurs more often among women of the upper social classes, as measured by either educational status or family income.¹¹³ Studies seem to indicate that these associ-

ations largely reflect the effect of correlated lifestyle factors, such as later ages at first birth.¹⁰⁰

Never-married women over age 40 have been found to have a higher risk of breast cancer than women who have been married,¹⁰¹ an association attributed to a reduced risk associated with childbearing. Similarly, nuns have been found to have a higher-than-average risk.⁶² There is common reference to the finding that Jewish women have high rates of breast cancer. The extent to which this association is attributable to the effects of correlated variables (e.g., socioeconomic status) has not yet been adequately resolved.

Familial Factors

A family history of breast cancer in a first-degree relative is associated with approximately a doubling of risk.³³ If both mother and a sister have had breast cancer, the risk is even higher. These familial effects are enhanced if the relative had either early-onset cancer or bilateral disease. In addition, familial effects predominate for early-onset cancers. Women with germline mutations in one of two recently identified autosomal dominant breast cancer

Table 7-3 Breast Cancer Incidence Trends by Race, Stage, and Age, SEER, 1975–1977 to 1995–1997

	1975–1977		1995–1997		RATE
	Cases	Rate*	Cases	Rate*	Change (Percent)
WHITES BY STAGE					
In situ	1215	4.4	8123	22.8	18.4 (418.2)
Invasive					
Total	25,854	88.1	43,932	116.6	28.5 (32.3)
Localized	12,617	43.1	28,451	75.6	32.5 (75.4)
Regional	9930	34.1	11,524	31.2	-2.9 (-8.5)
Distant	1932	6.5	2341	6.2	-0.3 (-4.6)
Unstaged	1375	4.4	1616	3.6	-0.8 (-18.2)
BLACKS BY STAGE					
In situ	70	2.8	831	20.8	18.0 (642.9)
Invasive					
Total	1823	73.7	4267	103.3	29.6 (40.1)
Localized	724	29.2	2316	57.0	27.8 (95.2)
Regional	811	32.4	1339	31.8	-0.6 (-1.9)
Distant	204	8.5	356	8.5	-0.0 (-0.5)
Unstaged	84	3.6	256	6.0	2.4 (66.7)
LOCALIZED STAGE AMONG WHITES BY AGE GROUP					
30–39 y	661	20.5	1104	21.6	1.1 (5.4)
40–49 y	2106	73.9	4286	94.0	20.1 (27.2)
50–59 y	3060	104.0	5663	189.8	85.8 (82.5)
60–69 y	2916	131.5	6358	269.5	138.0 (104.9)
70–79 y	2406	165.7	7107	346.3	180.6 (109.0)
≥80y	1356	172.9	3850	296.4	123.5 (71.4)

Based on data from Ries LA and others: *SEER Cancer Statistics Review, 1973–1997*, Bethesda, MD, 2000, National Cancer Institute.

*Per 100,000 woman-years, age-adjusted to the 1970 U.S. standard.

Table 7-4 Distribution of Breast Cancers and 5-year Relative Survival Rates by Stage at Diagnosis among White and Black Women, SEER, 1989–1996

	White	Black
Cases (N)	110,218	10,169
STAGE AT DIAGNOSIS (%)		
Total	100	100
Localized	63	51
Regional	29	34
Distant	6	9
Unstaged	3	5
5-YEAR RELATIVE SURVIVAL RATE (%)		
Total	86.4	71.4
Localized	97.1	89.2
Regional	78.6	63.6
Distant	22.4	14.8
Unstaged	54.7	49.7

From Ries LA and others: *SEER Cancer Statistics Review, 1973–1997*, Bethesda, MD, 2000, National Cancer Institute.

genes—*BRCA1*¹⁴⁴ and *BRCA2*²²⁹—have a lifetime breast cancer risk of 60% to 80%.¹³⁸ However, the normal function of these genes is not fully known, and other candidate genes are emerging.¹⁰⁷ *BRCA1* and *BRCA2* mutations account for less than 10% of all breast cancers,³⁵ but these and other susceptibility genes may pave the way for targeted prevention strategies. A further discussion of the impact of genetic factors on breast cancer occurrence can be found in Chapter 14.

Reproductive Risk Factors

A late age at first birth is an important determinant of breast cancer risk. This was perhaps best demonstrated in MacMahon and colleagues' international study of breast cancer,¹³⁵ in which women with a first birth after age 30 years were shown to have approximately twice the risk of those with a first birth before age 18. Because nulliparous women have a risk similar to that of women with a first birth at around 30 years, it is more hazardous to delay a first birth until after age 30 years than to remain childless. The protective effect of a pregnancy appears only after some delay, with a short-term eleva-

tion in risk following delivery.¹²¹ This transient adverse effect is greatest for women with later ages at first birth. Investigators have speculated that the short-term risk following delivery as well as the more adverse effect of a late pregnancy compared to nulliparity may result from a stimulation of cells that have already become initiated. Although an early age at first birth appears to be the strongest predictor of risk, evidence also exists that delays in the age at subsequent deliveries have an impact on risk.³⁰

Although MacMahon and colleagues' study demonstrates that the relationship with number of births disappears after adjustment for age at first birth, more recent studies suggest that there may indeed be an independent effect of parity for breast cancers detected after about ages 40 to 50 years. Before age 40 years, parity is associated with an increase rather than a decrease in risk,¹⁰¹ presumably reflecting the influence of an adverse effect of a recent delivery.

Several studies suggest that the protective effect of a pregnancy with later-onset breast cancers depends on the pregnancy's being full-term, with no protective effect exerted by shorter-term pregnancies.¹⁵ It has actually been suggested that short-term pregnancies, particularly induced abortions, may exert an adverse effect on breast cancer risk. Study of this issue is complex, given the potential for biased reporting. However, the largest study on the issue of induced abortions, a record linkage effort in Denmark that did not involve recall, suggested no alteration in risk associated with induced abortion.¹⁴¹ Questions remain, however, regarding the effect on breast cancer risk of types of infertility (particularly those associated with hormonal deficiencies) as well as exposure to ovulation-stimulating drugs.²¹⁸ Finally, of interest with respect to reproductive patterns is whether breastfeeding alters the subsequent risk of breast cancer. A number of earlier studies dismissed this as an independent factor, but more recent investigations have shown that longer durations of breastfeeding may exert a protective effect.¹²⁹ Several of these studies suggest that the protective effect may be stronger for early-onset disease.

Menstrual Factors

Numerous studies have shown that women with early onset of menarche are at an increased risk of breast cancer, with those who begin menstruating before 12 years of age having approximately a 50% higher risk than those with menarche at age 15 years or later.¹⁹⁶ Some studies suggest that the effect may be greater for early-onset disease, but the extent to which this reflects better recall by younger women has yet to be resolved. Women who have an early age at menarche have an earlier onset of regular menstrual periods⁵; however, whether menstrual irregularities have an independent influence on breast cancer risk remains unresolved.

Women with late ages at menopause have been shown to be at an increased risk of breast cancer; the relative risk is approximately 2 for a natural menopause after 55 years of age, compared with menopause before 45 years of age.^{16,200} Early menopause resulting from ovarian ablation is similarly associated with a reduction in risk. For instance, oophorectomy before age 40 years is associated with approximately a 50% reduction in risk, compared with natural menopause at 50 years of age, the average age at menopause in the United States.¹⁶ It has been suggested that bilateral oophorectomy at an early age exerts a stronger protective effect than natural menopause at the same age, possibly because of the more precipitous decline in hormones. Hysterectomy at an early age without ovarian ablation is not thought to alter risk further, but additional attention is warranted regarding the reasons for the hysterectomy, which could independently affect risk.

Exogenous Hormones

Given the recognized importance of ovarian hormones in the etiology of breast cancer, much attention has focused on the relationship to risk of exogenous hormone use, including oral contraceptives and menopausal hormones.

Oral Contraceptives

Oral contraceptives have been extensively studied in relation to breast cancer risk, with varying conclusions. Although the majority of studies have not confirmed an overall excess risk associated with oral contraceptive use, a number of studies (including several meta-analyses) have suggested an increased risk associated with long-term use for early-onset cancers, usually defined as cancers occurring prior to 45 years of age.^{17,81,174,219} In the largest analysis, which involved pooling of data from 54 studies on 53,297 women with breast cancer and 100,239 without breast cancer, current and recent users were at increased risk (RR=1.24, 95% confidence interval CI, 1.15–1.33), with no evidence of an effect with duration of use.³⁸ The increased risk associated with recent use subsided within 10 years of cessation of oral contraceptive use. These findings suggest that the increased risk of breast cancer observed among young, long-term users may have been due primarily to recent use, raising the possibility that oral contraceptives might act as late-stage promoters.

Given that an influence of oral contraceptives on the breast has been hypothesized to be greatest before the cellular differentiation that occurs with a first pregnancy, a number of investigations have evaluated effects of use of oral contraceptives prior to a first pregnancy. In the pooled analysis,³⁸ a significant trend of increasing risk with first use before age 20 years was observed. Among women diagnosed at ages 30 to 34 years, the relative risk associated with recent oral contraceptive

use was 1.54 if use began before age 20 years and 1.13 if use began at older ages. However, in several studies not included in the meta-analysis, no such increase in risk was observed.^{219,224}

Studies have also attempted to determine whether the effects of oral contraceptives on breast cancer risk are influenced by the presence of other breast cancer risk factors. Of particular interest has been whether effects are different in subjects with a family history of breast cancer. However, neither this factor, nor various other factors (including weight and alcohol use), appear to modify oral contraceptive relationships. Recent studies indicating that oral contraceptives may increase the risk of breast cancer more in subjects who are *BRCA1* or *BRCA2* mutation carriers²⁰⁵ or who have a family history of breast cancer⁷³ were based on small numbers and require further confirmation.

There has also been interest in whether specific formulations of oral contraceptives have unique influences on breast cancer risk. No consistent relationships have been seen with either dose of the progestin or estrogen considered, although methodologically it has been difficult to define this information and to consider it systematically. Only limited data on the newer formulations of pills are available.³⁸ Also of interest is whether injectable progestogen contraceptives are associated with alterations in breast cancer risk. In a recent study in South Africa no association was found with this exposure, in either older or younger women.¹⁸⁰

Menopausal Hormones

The relationship of hormone replacement therapy (HRT) to breast cancer risk was recently assessed in a reanalysis of data from 51 epidemiologic studies, encompassing 52,705 women with breast cancer and 108,411 controls from 21 countries.³⁹ This showed a 2.3% (95% CI 1.1–3.6) increase in the RR of breast cancer for each year of HRT use. This corresponded to a RR of 1.35 for users of 5 or more years and to a cumulative excess for women who began use of hormones at age 50 of approximately 2 cases/1000 women for 5-year users, 6 cases/1000 for 10-year users, and 12 cases/1000 women for 15-year users. This increase was comparable with the effect on breast cancer risk of later menopause. The increased risk, however, was restricted to recent users, with no material excess observed 5 or more years after discontinuation.

It has become increasingly accepted that longer-term estrogen use among recent users is associated with some elevation in breast cancer risk, but it is less resolved whether the addition of progestins to estrogens affects risk. Although this regimen has become increasingly common given the recognized advantages in reducing endometrial cancer risk,²³⁰ there is evidence that added progestins may adversely affect breast cancer risk. Notably, *in vitro* studies have shown that breast mitotic activity is higher during the luteal phase of the men-

strual cycle, when progesterone levels are at their highest. A number of studies have provided support for the notion of a more deleterious effect of combined therapy. These include results from two large cohort studies, the Nurses' Healthy Study³⁶ and the follow-up study of participants in the Breast Cancer Detection Demonstration Project (BCDDP).¹⁷⁹ Both studies showed a relative risk (RR) of 1.4 for combined therapy as compared respectively in the two studies with RRs of 1.3 and 1.2 for estrogens alone. In the BCDDP study, the increased risk was limited to users within the prior 4 years and was largely confined to thin women, with the latter relationship possibly reflecting that heavier women may be less affected because of higher levels of endogenous hormones. A potentially adverse effect for combined therapy has also been noted in two case control studies, in Sweden¹³⁶ and Los Angeles County.¹⁷⁵ The Los Angeles study found a RR of 1.2 (95% CI 1.1–1.4) for each 5 years of use of combined therapy, as compared with a RR of 1.1 (95% CI 0.9–1.2) for each 5 years of estrogen use. The Swedish study also supported a notion of a duration effect, with the risk rising to 2.4 for users of 10 or more years. Findings also suggest a particular predisposition of combined therapy to the risk of lobular breast cancers,¹²⁷ possibly explaining recent increases in this tumor type.¹²⁶

Selective Estrogen Receptor Modulators

Given the recognized adverse effects of HRT, much recent attention has focused on selective estrogen receptor modulators (SERMs), such as tamoxifen, which function as estrogen agonists in some tissues (e.g., bone and endometrium) and estrogen antagonists in others (e.g., breast). These agents presumably will offer many of the same advantages as HRT, while eliminating some of the disadvantages (no increase in breast cancer risk). Data indicate that these agents offer substantial advantages in terms of reducing breast cancer risk, with the most convincing data deriving from the National Surgical Adjuvant Breast and Bowel Project (NSABP).⁶¹ This trial, focused on women at an increased risk of breast cancer, found after 69 months of follow-up that those who had received tamoxifen had a 49% lower risk of invasive breast cancer than placebo-treated women. The beneficial effect pertained to women of all ages, but was most apparent among women with a history of lobular carcinoma *in situ* or atypical hyperplasia; in addition, the risk reduction was limited to estrogen receptor-positive tumors. Two other trials, one in Britain¹⁶⁹ and the other in Italy,²¹⁰ however, did not find an effect of tamoxifen on breast cancer risk. This may have reflected limited sample sizes, high drop-out rates, or use of other drugs (including HRT) among trial participants.

Studies are also evaluating the relationship of other SERMs to breast cancer risk. In the recently published Multiple Outcomes of Raloxifene Evaluation (MORE)

trial of osteoporotic women, 120 mg of raloxifene daily decreased breast cancer risk by 76%.⁴⁴

Furthermore, a trial is under way to evaluate the relative effectiveness of tamoxifen versus raloxifene in reducing breast cancer risk. Given that tamoxifen has previously been linked with an increased risk of endometrial cancer,⁶¹ while raloxifene was associated with an increased risk of thromboembolic disease,⁴⁴ the Study of Tamoxifen and Raloxifene (STAR) trial will assess the relative adversity of both drugs. In addition, there is growing enthusiasm for the potential preventive effects of phytoestrogens, termed by some as "natural" SERMs.²¹

Diethylstilbestrol

Further support for a role of exogenous hormones in the etiology of breast cancer derives from studies of women exposed to diethylstilbestrol (DES), a drug used between 1938 and 1971 for the prevention of threatened, spontaneous abortions. Follow-up studies of the mothers have nearly all found an increased risk of subsequent breast cancer, on the order of 30% to 40%.^{40,137} Dissimilar to other exogenous hormones, the increased risk is not related to how recent the use was and excesses are usually not observed until 10 or more years after exposure. Although the daughters who were exposed in utero to DES are at increased risk of vaginal adenocarcinomas, so far they do not appear to be at an increased risk of breast cancer.⁸⁶ Further follow-up studies are under way to monitor changes in breast cancer risk as the cohorts age.

Medical History

Although most studies indicate that women with a history of a biopsy-proven benign breast disease are at an increased risk of subsequent breast cancer, the interpretation of the association is complex. The association appears dependent not only on the indications for biopsy, but also on the histologic characteristics of the lesions. One study suggested that only proliferative forms of benign breast disease predisposed to subsequent breast cancer risk,⁵² with atypical hyperplastic lesions being most predictive. The specific types of benign breast disease associated with the highest risk of subsequent breast cancer, however, have varied across studies,¹¹⁴ possibly because of difficulties in standard classification of these lesions. Further examination of effects is needed, as well as evaluation of factors that might promote the progression of benign lesions to subsequent cancer.

The appearance of the breast mammographically has also been found to be a predictor of subsequent breast cancer risk. An initially proposed parenchymal pattern classification system took into account the amount of the breast composed of ductal prominence.²²⁶ More recently, direct measurements of dense areas of the breast have been found to be less subjective and stronger indi-

cators of risk. In one study,²³ breasts with areas of density of 75% or more were associated with nearly a five-fold elevation in risk, a magnitude of risk as great if not greater than most other established risk factors.

It is well recognized that women with fractures^{152,153,161} or low bone densities^{26,134,237} are at a decreased risk of breast cancer, with some evidence that this may reflect their low levels of endogenous hormones.²⁶ Although other medical conditions have been suggested to elevate breast cancer risk, inconsistencies prevail. Among those that have received the most attention are thyroid diseases, hypertension, and diabetes. Questions remain as to whether elevations in risk associated with these conditions merely reflect the influence of correlated factors (e.g., weight) or of prescribed medications (e.g., rauwolfia derivatives).

Because silicone breast implants reportedly interfere with the detection of breast lesions, there has been interest in evaluating their relationship to subsequent breast cancer risk. Although several investigations^{8,45} have actually noted a decreased risk of breast cancer associated with breast implants, a subsequent study suggests that this may merely reflect the influence of pre-implantation screening, with there being no long-term alteration in breast cancer risk.¹⁸

Dietary Factors

The relationship of dietary factors to breast cancer risk has been extensively studied, with few consistent results emerging. There has been an extensive focus on effects of consumption of dietary fat, stimulated initially by findings that per capita fat intake correlates internationally with breast cancer mortality rates.⁶ Numerous epidemiologic studies have attempted to confirm this on an individual basis, with most failing to find an association. One meta-analysis of data from case-control studies⁹¹ found that a 100-gram increase in daily total fat intake was associated with a 35% increase in risk. However, results from prospective studies, which are less subject to recall biases, provide no evidence of any such relationship. In a pooled analysis of all cohort studies involving 4980 cases of breast cancer, no reductions in risk were associated with low intakes of total, saturated, monosaturated, or polysaturated fat.⁹⁸ This was true even when fat intakes as low as 15% to 20% of energy were considered.

Nonetheless, debate continues over a potential relationship of breast cancer risk with high-fat diets. There remain questions regarding whether diets high in fat during adolescence might have a potential impact, although several studies that have addressed this have failed to provide confirmatory evidence.^{49,166} Most likely, the debate will continue until results from intervention studies become available, including results from the ongoing Women's Health Initiative.²²⁸

In addition to overall fat intake, research has focused on specific types of fat. Several studies have suggested a possible protective effect for olive oil, a monounsaturated fat,^{139,221} but further studies are needed to confirm the relationship. There has also been interest in a possible protective effect for omega-3 fatty acids (derived from fish), although no definitive results have been obtained.²²¹

A variety of other dietary constituents have been hypothesized to affect breast cancer risk. Diets high in fiber have been suggested as protecting against breast cancer, possibly due to inhibition of the intestinal reabsorption of estrogens excreted via the biliary system. Although there was some evidence in a meta-analysis of 12 case-control studies for a reduced risk associated with high levels of intake of fiber,⁹¹ prospective studies have generally failed to confirm this relationship.^{173,222}

Whether micronutrients could play a role in breast cancer etiology has also been of interest, especially antioxidants that may provide a cellular defense against reactive oxygen species that damage DNA. Vitamin A, which is also a regulator of cellular differentiation, appears from both case-control and cohort studies to be modestly inversely associated with breast cancer risk. In a meta-analysis of case-control studies,⁹¹ a significant protective effect of vitamin A intake was observed, with stronger relationships apparent for carotenoid vitamin A (mainly derived from fruits and vegetables) than preformed vitamin A (retinol, retinyl esters, and related compounds from animal sources). In a large prospective study in Canada, marginally significant reductions in risk were observed with both preformed vitamin A and beta-carotene.¹⁷³ In the Nurses' Health Study, total vitamin A was found to be inversely related to risk, although the effect was restricted to premenopausal women.²³⁸ When specific carotenoids were examined, relationships appeared to be strongest for beta-carotene and lutein-zeaxanthin.

Vitamins C and E have also been examined in relationship to breast cancer risk. Vitamin C has been of interest not only because it is an antioxidant but also because it can block the formation of carcinogenic nitrosamines. Data from case-control studies provide some evidence for a possible protective effect on breast cancer risk^{74,91}; however, cohort studies show no association.^{118,173,208,238} There is little evidence for a relationship of vitamin E to risk,^{64,173,208,238} although dietary consumption of this nutrient is difficult to assess.

Selenium, an important component of the antioxidant enzyme glutathione peroxidase that inhibits cell proliferation, has been shown in animal studies to protect against a variety of cancers, including mammary cancers. Ecologic studies in the United States have shown strong inverse associations between county-specific measures of selenium exposure and breast cancer rates.³¹ Since selenium is not reliably assessed through dietary means, several studies have measured selenium levels in either blood or toenails. The largest U.S. study found no

relationship,⁹⁷ but a study in Finland, where selenium levels are extremely low, showed an increased risk among women in the lowest category of selenium.¹¹¹ However, in a small randomized trial, breast cancer occurred more frequently among those receiving selenium supplements.³² Whether selenium levels with the variations seen in normal U.S. populations have an impact on breast cancer risk remains to be defined.

A potential beneficial impact of consumption of phytoestrogens has been proposed, given that these compounds, which include diidzen and genistein, can increase menstrual cycle length and bind estrogen receptors (ERs). The hypothesis is appealing, given widespread consumption of phytoestrogens in soy products in countries with low rates of breast cancer, such as China and Japan. However, the only epidemiologic data that address the potential impact on breast cancer risk have produced varying results.^{110,124,231,235}

Alcohol Consumption

Although the relationship of breast cancer risk to most dietary factors remains unresolved, fairly consistent data have emerged regarding a potential adverse effect of consumption of alcoholic beverages. Longnecker,¹³¹ in a meta-analysis of 38 case-control and cohort studies, showed a progressive increase in the risk of breast cancer with amount of alcohol consumed, with those consuming three or more drinks per day being at a 40% higher risk than nondrinkers. Results were consistent across case-control and cohort studies. Adjustment for known breast cancer risk factors and dietary variables had little impact on observed relationships.

One report showed that women who drank before age 30 years and later stopped experienced a risk similar to those who continued to drink.⁸⁵ However, in another study, recent adult drinking appeared to be more important than drinking patterns earlier in life.¹³² This would be consistent with the finding that alcohol is most strongly related to late-stage tumors,¹⁸⁸ implying that it acts at a late stage in breast carcinogenesis.

Both intervention and cross-sectional studies have shown alterations in endogenous estrogens associated with alcohol consumption,^{79,170} providing a possible biologic explanation for the relationship of alcohol to breast cancer risk. There is also support for several other possible biologic mechanisms, including alcohol-induced changes in folate levels, increased cell permeability, and direct effects of contaminants in the alcoholic beverages, for example, nitrosamines. Further research is needed to clarify biologic mechanisms underlying the association of alcohol intake and breast cancer risk, particularly as related to levels of consumption and types of alcoholic beverages.

Despite enthusiasm that cessation of alcohol consumption may be a means of reducing breast cancer

risk, it appears that it would have only a minimal impact. Because of the modest association between alcohol and breast cancer and the generally moderate level of alcohol intake among U.S. women, the proportion of breast cancer attributable to alcohol intake appears relatively small, being only 2.1% in one analysis.²⁰¹

Anthropometric Factors

The relationship of body size to breast cancer risk has been extensively investigated, with differing relationships having been observed for premenopausal and postmenopausal diseases. For postmenopausal-onset disease, both weight and body mass index (BMI) (defined as weight in kilograms divided by the square of height in meters) have been fairly consistently related to increases in risk. In a recent large case-control study, subjects in the upper quartile of BMI were at a 40% higher risk than those in the lower quartile.¹⁹⁷ This relationship is believed to be due to the ability of adipose tissue to convert precursor substrates to estrogens.

A number of investigations have attempted to determine how changes in weight over time affect postmenopausal breast cancer risk. Although particular attention has focused on obesity during adolescence, weight gain at older ages has more consistently been shown to be associated with breast cancer risk.¹⁹⁷

In contrast to relationships with postmenopausal breast cancer, body mass appears to be inversely related to premenopausal disease, with thin women being at highest risk. In one meta-analysis, a BMI difference of 8 (i.e., the difference between a thin person and someone morbidly obese) resulted in a relative risk of 0.70 (95% CI 0.5–0.9).²⁰⁴ Although initially the reduced risk was thought to result from difficulties in detecting breast lesions in young, heavy women; however, this does not appear to entirely explain the relationship. Irregular anovulation, and consequently less exposure to endogenous hormones, has been proposed as an additional mechanism underlying the inverse association of body size to premenopausal breast cancer risk.

Among postmenopausal women, body fat distribution also appears to be a factor influencing risk.⁷⁷⁷ In a number of studies women whose fat was distributed abdominally (i.e., around their waists) were found at higher risk than those with peripheral fat distribution (including fat accumulation on the hips). This effect appeared to be independent of total body size. In the few studies in which body fat distribution has been examined for premenopausal women, inconsistent relationships have been observed.^{77,189}

In addition to body mass, height has begun to emerge as an independent predictor of risk.^{130,189,190,198,206} In a study in the Netherlands, a twofold difference in risk was observed for a 15-cm difference in height. The association with height appears independent of other

breast cancer risk factors, even though many of these are highly correlated with height. A number of possible biologic mechanisms have been proposed for the association with height. Energy restriction during childhood has been suggested as a possible mediating factor, especially given evidence that energy restriction reduces mammary tumors in animals. However, arguing against this hypothesis is that most studies that have shown effects of height have been in well-nourished populations. An additional proposal is that height may be a surrogate for mammary gland mass.¹⁹⁹ An etiologic role for insulin-like growth factors (IGF) has also been proposed, in line with recent studies showing that IGF-1 levels are predictive of premenopausal breast cancer risk.⁸² Growth factors have also been implicated in the reduced risk among women who attain their adult height at older as compared with younger ages (e.g., after age 18 as compared with 13 or younger).¹²⁵

It has long been hypothesized that breast size would be involved with breast cancer risk, although most epidemiologic studies fail to confirm an effect of either chest or bra cup size. These measures, however, are only imprecise correlates of glandular size; thus, results may have been obscured by studies which considered total breast size, which also includes fat tissue.¹⁹⁹ Interestingly enough, in two studies bra size was found to be related to breast cancer risk among thin women,^{53,189} possibly due to bra size being a better predictor of glandular size among thin than heavy women.

Physical Activity

There has been much recent enthusiasm regarding a potential beneficial effect of physical activity on breast cancer risk, especially given its modifiable nature. The relationship appears to be biologically plausible, given that physical activity has been associated with changes in endogenous hormones, menstrual patterns, body fat distribution patterns, and other biologic repercussions which could benefit breast cancer risk (e.g., change in immunologic parameters).⁸⁹ The strongest support for physical activity as a potential preventive mechanism derived from a study of early-onset breast cancers, in which reductions in risk associated with regular physical activity were found to be independent of body size.¹¹ Additional studies, however, have produced conflicting results.* The need for more precision in the approach to measuring physical activity has been stressed, including obtainment of objective measures of physical activity, collection of information on timing and intensity of activity levels, and consideration of all sources of activity (including physical activity resulting from household chores).

*References 65, 149, 172, 181, 209, 232.

Cigarette Smoking

Although cigarette smoking has been found to result in earlier ages at menopause, it has not generally been found to alter breast cancer risk.¹⁵⁶ However, investigators continue to be interested in the effects of smoking at young ages, hypothesized as a possible etiologic factor.¹⁵⁷ It has recently been proposed that effects of cigarette smoking might have been missed because of the inclusion of women exposed to passive smoking in the referent groups of most studies. Of note are several studies that have found higher risks associated with active cigarette smoking when referent groups of truly nonexposed women are used.^{105,123,148} However, several of these studies had methodologic shortcomings, and the relationships of both active and passive cigarette smoking remain open to debate.

Recent interest has focused on whether the effects of cigarette smoking might be modified by genetic factors, including by both single highly penetrant genes as well as by more common polymorphisms involved in the deactivation of constituents of cigarette smoking. In one study, smoking appeared to reduce breast cancer risk among carriers of the *BRCA1* or *BRCA2* gene,¹⁹ a finding that has yet to be replicated or explained on biologic grounds. In another study, smoking appeared to increase risk among individuals who were found to be slow acetylators as defined by N-acetyltransferase genotype.² Subsequent investigations, however, have failed to confirm this subgroup association.^{93,96,147,240}

Hair Dyes

Reports of mutagenic effects of hair dyes have raised concern about their potential effect on breast cancer risk, but most studies that have examined the association have found no link.^{41,75,112,151} Occupational exposures to hair dyes have also been examined in several small studies, with no consistent associations observed.¹¹²

Prenatal Exposures

Recent interest has focused on the role of a variety of prenatal exposures on subsequent breast cancer risk. A number of studies provide support for an increased breast cancer risk among dizygotic twins^{29,54,92,178,217} and a decreased risk for daughters born after a preeclamptic pregnancy.^{54,99,177} These birth characteristics have been hypothesized to reflect effects of prenatal estrogenic exposures. There is some evidence for an increase in breast cancer risk among subjects with high birthweights.^{143,178} A few studies suggest an increased breast cancer risk among daughters born of mothers of advanced ages,^{102,194} although data are not conclusive.¹⁶⁵ Inconsistent findings have been derived regarding the role of birth order, birth length, placental weight, and gestational age. A number of reports show a decrease in

breast cancer risk for daughters who were breast-fed.^{63,195} Whether this association reflects a protective effect of breastfeeding or an adverse effect of supplements has yet to be determined.

Ionizing, Electromagnetic, and Solar Radiation

From studies of women exposed to the atomic bombs in Japan and from observations of women exposed to medical treatments involving repeated exposure to radiation (e.g., fluoroscopic chest radiography for tuberculosis and radiotherapy for acute postpartum mastitis, ankylosing spondylitis, scoliosis, or tinea capitis), it is well established that ionizing radiation to the chest in moderate to high doses (e.g., between 1 and 3 Gy) before the age of 40 years increases breast cancer risk, and the higher the dose the greater the risk.¹⁰⁴ High rates of breast cancer have also been observed following radiotherapy for Hodgkin's disease.⁷⁸ Further, second breast cancers have been linked to radiotherapy for primary breast cancer, but only among women under age 45 years at exposure.¹⁴ Relatively few data are available regarding the effects of low radiation doses from medical or diagnostic exposures. An increase in breast cancer risk has been reported for radium dial painters exposed to a weekly dose of 0.001 to 0.004 Gy¹⁸⁵ and for medical diagnostic radiology workers.²¹³ Common diagnostic procedures, such as chest radiography and mammography, have a mean radiation dose to breast tissue of 0.0002 and 0.00015 Gy, respectively. Less than 1% of breast cancer is estimated to result from general diagnostic radiographic procedures. Because most women receive mammograms after age 40 years, when breast cancer risk associated with radiation appears small, the benefits of mammography are believed to far outweigh any potential risks.

The finding that male electrical line workers have an elevated breast cancer risk⁴⁶ has prompted interest in the etiologic role of electromagnetic fields for female breast cancer. One study of female electrical workers provided some support for the relationship,¹³³ but further confirmatory work is needed. Exposure to electric blankets has also been of interest, but studies in both premenopausal and postmenopausal women have failed to demonstrate a relationship.^{66,207} Because both long-term exposure to 50- to 60-Hz electric fields and uninterrupted light reduce pineal production of melatonin, which can lead to increased production of estrogen and prolactin,¹⁸⁶ there has also been interest in the role of light exposure. One study found that women with profound bilateral blindness had half the risk of breast cancer of sighted women.⁷³

The recognition of a distinct north-south gradient in breast cancer mortality rates and a correlation between these rates and solar radiation has led to the hypothesis that vitamin D or its metabolites might reduce breast cancer risk.⁷¹ Analytic studies have yet to be reported.

Occupational Exposures

The role of occupational exposures in women has only recently become of interest. Several studies have shown high rates of breast cancer in school teachers and nurses, probably owing to their higher socioeconomic status or unique reproductive histories. A conference on occupational risks among women suggested possible breast cancer links with employment in the printing and publishing, telephone, and electrical equipment manufacturing industries.¹⁶⁸ A possible etiologic role for organic solvents, metals/metal oxides, and acid mists has also been raised.²⁴

Environmental Exposures

Recent attention has focused on the potential impact of environmental factors on breast cancer risk, with much of the interest stemming from the recognition that breast cancer mortality rates are high in the industrialized north-eastern United States. Of particular interest had been the relation of risk to organochlorine pesticides, notably DDT (2,2 bis(p-chlorophenyl)-1,1,1-trichloroethane) and polychlorinated biphenyls (PCBs), which have been demonstrated to induce cytochrome P-450 enzymes and to affect steroid metabolism, including the 2/16-hydroxylase pathway. Although one case control study noted significantly higher serum levels of dichlorodiphenyldichloroethylene (DDE) in breast cancer cases than in controls,²²⁷ other studies have failed to confirm this.^{115,142,239} Nonetheless, the relation of organochlorines with breast cancer risk remains of major interest, especially in view of the potential for these substances to interact with environmental phytoestrogens or other xenoestrogens. To understand reasons for the geographic variation in breast cancer rates, studies are also examining the relationship of risk with other environmental agents, including water contaminants, air pollution, toxic waste dumps, and other chemical exposures.

Psychologic Factors

Although a number of studies have attempted to study the relationship of psychologic factors to breast cancer risk, most have had methodologic shortcomings. Many of these studies have been retrospective, raising the possibility of recall bias. In addition, inherent complexities of measuring psychologic factors present major challenges. Nonetheless, there have been a number of reports of a link between perceived stress and breast cancer.^{42,88} The latest study, based on data from the Nurses' Health study, however, found no relationship between job stress and breast cancer risk.¹

Multiple Primary Cancers

Cancer in one breast is associated with a relative risk of 2 to 4 for developing a second cancer in the contralat-

eral breast, particularly in women with a family history of breast cancer.⁹ Women with breast cancer also experience some increase in the risk of second cancers of the endometrium and ovary, and also possibly of melanoma and of colon, salivary gland, and thyroid cancers.

BIOLOGIC APPROACHES TOWARD UNDERSTANDING ETIOLOGIC FACTORS

Epidemiologic studies have increasingly incorporated biologic probes to clarify etiologic patterns and shed light on biologic mechanisms underlying identified risk factors. These include endogenous hormones as well as a variety of genetic markers. In addition, clinical, pathologic, and other laboratory approaches to define etiologically distinct subsets of disease hold promise for clarifying our understanding of the disease process.

Endogenous Hormones

Factors that increase a woman's lifetime exposure to estrogen (e.g., earlier age at menarche, later age at menopause, and postmenopausal obesity) appear to increase her risk of developing breast cancer.¹⁰⁸ Higher circulating estrogen levels are hypothesized to reflect these exposures, and therefore epidemiologic studies have specifically evaluated breast cancer risk associated with circulating estrogen levels. A recent review of prospective epidemiologic studies concluded that postmenopausal women who develop breast cancer have 15% higher concentrations of serum estradiol and 50% higher urinary estrogen excretion rates than women who remain cancer-free.¹⁹¹ Two subsequent studies^{83,106} confirmed this association but two others^{22,27} did not. Retrospective studies of endogenous sex steroids are extremely problematic and unreliable because hormone levels in cases may be modified by the presence of breast cancer; these studies have been reviewed elsewhere¹⁹¹ and will not be discussed further.

Laboratory data demonstrate that endogenous estrogens have both proliferative²³⁴ and carcinogenic²⁸ effects, but how those actions increase breast cancer risk is poorly understood.¹⁰ In postmenopausal women Hankinson and others⁸³ found positive associations with elevated circulating levels of estradiol, which is the most biologically active estrogen in breast tissue.¹⁰ However, they noted similar increased risks for estrone and estrone sulfate, which are abundant in postmenopausal women, leading to questions as to which endogenous estrogens are most crucial in breast carcinogenesis.⁹⁵ Historically poor⁵⁷ but improving^{58,80} assay reproducibility likely contributes to some of the confusion. Studies must also carefully control for the effects of time since menopause on hormone levels.¹⁹¹ Other measurements, such as sex-hormone binding globulin (which binds estradiol) or percent bioavailable estradiol are also inconsistently associated with risk.^{83,95,106}

A log-log plot of age-specific breast cancer incidence rates shows a decline in the rate of increase after menopause, which suggests that key carcinogenic events occur before rather than after menopause.¹⁶³ Premenopausal serum estrogens might therefore best predict breast cancer risk, but available data are limited.²²³ Premenopausal hormone levels vary substantially throughout the menstrual cycle and are difficult to measure. Valid prospective studies that account for intracycle variation are needed.

The role of other steroid hormones is also unclear. Pike and others¹⁶³ proposed that progesterone augments the carcinogenic effects of estrogens, but the few reported studies to date have not observed such an association.^{87,192} Prolactin, which stimulates breast cell proliferation (e.g., during pregnancy), may indirectly affect breast carcinogenesis²²³ and has been positively associated with postmenopausal breast cancer in a few studies.^{84,212} As the major endogenous estrogen precursor in postmenopausal women,⁹⁵ androgens could indirectly increase risk by raising estrogen levels or directly increase risk by stimulating breast cell proliferation. Prospective studies^{50,83,236} have reported positive associations for testosterone (the most biologically active androgen), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS), but adjustment for estradiol dramatically reduced the strength of these associations. Progesterone, prolactin, androgens, and other steroid hormones have, to date, been insufficiently studied in premenopausal women.

Other Biomarkers

High-penetrance genes, such as *BRCA1* and *BRCA2*, are investigated through linkage studies in families, are rare at the population level, generate high relative risks, and cause cancer with seemingly minimal influence from en-

vironmental factors. In contrast, "susceptibility" or low-penetrance genes are investigated in large epidemiologic studies, are common (i.e., >1%) in populations, generate low relative risks, and are thought to be carcinogenic only in the presence of crucial environmental factors.²⁵ These susceptibility genes are considered "polymorphic" because particular DNA sequences vary between individuals, and each variant has a frequency of at least 1% in the population. Because the environmental exposures that cause most cancers¹²⁸ must be metabolized and because this metabolism is under genetic control, polymorphisms in critical metabolic genes may explain why some women develop breast cancer when exposed to particular environmental agents, such as HRT or oral contraceptives.⁴³ Although the list of candidate polymorphic genes for breast cancer continues to grow, studies to date have generally evaluated polymorphisms in one of two classes: steroid hormone-metabolizing genes or carcinogen-metabolizing genes (Table 7-5).

Polymorphisms in the *ER* gene or steroid hormone-metabolizing genes could affect the relative tissue availability of estrogens and other steroids that affect cell proliferation or DNA damage in breast tissue. Recent reviews^{43,51,193} summarize the genes investigated to date. Multiple isoforms of the cytochrome P450 enzyme "superfamily," such as *CYP17*, *CYP19*, *CYP1A1*, and *CYP1B1*, participate in the biosynthesis and metabolism of estrogens.¹⁹³ A few studies^{60,116,215} reported positive associations for specific alleles, but these associations have generally not been replicated in subsequent studies. Other polymorphisms in catechol-O-methyltransferase (*COMT*), which inactivates catechol estrogens, have been inconsistently associated with breast cancer.¹⁹³

Carcinogen-metabolizing genes control the bioavailability of carcinogens such as heterocyclic amines or metabolites of tobacco smoke. Allelic variations in the *N*-acetyltransferase 1 and 2 (*NAT1* and *NAT2*, respec-

Table 7-5 Examples of Candidate Polymorphic Genes in Breast Cancer

Class	Genes*	Biologic Role	Hypothesized Effect on Breast Cancer
Steroid synthesis and metabolism	<i>CYP17</i>	Control conversion of cholesterol to estradiol, estrone, progesterone, testosterone, androstenedione, and other steroid hormones	Increased tissue exposure to steroids may increase cell proliferation or cause increased DNA damage in breast tissue
	<i>CYP19</i>		
	<i>CYP1A1</i>		
	<i>CYP1B1</i>		
	<i>COMT</i>		
Hormone receptors	<i>ER</i>	Bind estrogen and progesterone to regulate expression of estrogen-responsive genes	Increased ER or PR activity may increase breast tissue proliferation
	<i>PR</i>		
Carcinogen metabolism	<i>NAT1</i>	Control reactivity of and clearance of polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HCAs), nitrosamines, and other carcinogens	Increased reactivity or slower clearance may increase exposure of breast tissue to carcinogens
	<i>NAT2</i>		
	<i>GSTM1</i>		
	<i>GSTT1</i>		
	<i>CYP1A1</i>		

**CYP*, Cytochrome P-450 enzymes; *COMT*, catechol-O-methyl transferase; *DNA*, deoxyribonucleic acid; *ER*, estrogen receptor; *PR*, progesterone receptor; *NAT*, *N*-acetyl transferase; *GSTM1*, glutathione *S*-transferase Mu-1; *GSTT1*, glutathione *S*-transferase Theta-1.

tively) genes distinguish "rapid" acetylators from "slow" acetylators, whose slower detoxification of carcinogens may put them at increased risk. The decreased ability of Mu (*GSTM1*) and Theta (*GSTT1*) variants of the glutathione-S-transferase family to detoxify and excrete numerous carcinogens may increase risk. However, results from investigations of these main effects or gene-environment interactions have been inconsistent.^{43,51}

These polymorphism studies are strongly grounded in biologic plausibility but face substantial methodologic and scientific challenges. The functional significance for most polymorphisms has not yet been determined. In addition, these studies require very large sample sizes and must be designed to avoid bias from ethnic variations in polymorphism frequencies, which could produce confounding by ethnicity (i.e., "population stratification").²¹¹

Gene-Environment Interactions

Despite the lack of valid associations between these polymorphisms and breast cancer risk, studies have rightfully begun to investigate gene-gene and gene-environment interactions: a polymorphism's action may depend upon other events in the complex estrogen metabolism pathway, or certain polymorphisms may exert their effect only at particular substrate concentrations or in the presence of certain exogenous exposures. None of the studies included in the recent reviews^{43,193} or published subsequently¹⁵⁸ appear to have had sufficient sample sizes⁶⁹ to conclusively identify such interactions. Gene-environment studies are also especially prone to bias from even slight misclassification of genetic or environmental factors.⁷⁰ Nonetheless, current and future attempts to understand the combined effects of susceptibility genes and environmental factors should eventually elucidate the crucial—and therefore, preventable—steps in breast carcinogenesis.

Candidate polymorphisms might also mediate the relationship between environmental risk factors and DNA adducts, that is, measurable DNA damage from exposure to particular carcinogens.²²⁰ Exposure to estrogens²⁸ and tobacco smoke¹⁶⁰ can form DNA adducts, but the relevance of these adducts to breast cancer has not been conclusively demonstrated.¹⁷⁶

Epidemiologic studies have also attempted the integration of a number of other biomarkers, including several tumor suppressor genes (e.g., p53) and proto-oncogenes (e.g., *HER-2*). A recent study suggested an important etiologic role for *HER-2*,²³³ although further confirmatory results are needed.

Precursor Conditions

A thorough understanding of the transition from normal breast epithelium to benign hyperplasia to carci-

noma *in situ* to invasive carcinoma remains largely unknown. Some uncertainty arises, no doubt, from historically inconsistent (and continually evolving) nomenclature and classification criteria for precursor lesions.¹³ Collection of etiologically relevant breast tissue samples (both from individuals and from representative populations) has also proved challenging. Nonetheless, atypical ductal hyperplasia (ADH), lobular carcinoma *in situ* (LCIS), and ductal carcinoma *in situ* (DCIS) merit specific attention. DCIS, which encompasses a group of conditions with subtle differences in histologic grade, pathologic type, and extent in the breast, is considered the precursor to invasive carcinoma.¹⁵⁵ LCIS and ADH are thought to be risk predictors.¹²⁰

Relatively more is known about DCIS, which is detected via mammography, than about LCIS or ADH, which are clinically silent and detected incidentally during other procedures. Along with the widespread use of mammography, DCIS incidence increased over 550% from the mid-1970s (annual incidence rate = 2.4 per 100,000) to the mid-1990s (15.8 per 100,000).⁵⁶ Consistent with a role as precursor, the anatomic distribution of DCIS mirrors that of invasive carcinomas.⁵⁶ Available data indicate that not all DCIS or other carcinomas *in situ* progress to invasive carcinoma and not all invasive carcinomas are detected with adjacent or concomitant evidence of carcinoma *in situ*. Traditional treatment for *in situ* disease included total mastectomy, which negated the opportunity to investigate subsequent risk of breast cancer, but in one study approximately one half of untreated DCIS cases evolved into invasive carcinoma within 5 to 8 years.¹⁵⁵ Wårnberg and others²¹⁴ followed 3455 Swedish women diagnosed with CIS for an average of 4.3 years and noted fourfold increased risks of subsequent invasive carcinoma.

DCIS and invasive carcinoma share a similar risk factor profile: age, nulliparity, and family history increase risk, while higher BMI decreases risk, but only in premenopausal or younger women (in whom most DCIS is diagnosed). Other associations slightly differ. In a case-control study of both carcinoma *in situ* and invasive carcinoma among women under age 45, an association between average consumption of at least two alcoholic drinks per day was observed for invasive carcinoma but not for DCIS.²¹⁶ In a prospective cohort study of 39,844 women receiving mammograms,¹⁰⁹ early menarche increased the risk for invasive carcinoma only; however, as in other studies, the magnitude and direction of risk factor associations were nearly identical for the 102 DCIS cases and the 263 cases of invasive carcinoma.

Studies of DCIS or other potential precursors can evaluate natural history and potential treatments, and they offer a number of advantages over studies that use invasive cancer as an outcome.¹⁴⁶ These and other novel approaches should help to identify molecular markers and other factors that can be used to distinguish breast

lesions that will remain benign—and therefore warrant only observation—from breast lesions that will progress to invasive carcinoma and require intervention.

Disease Heterogeneity

The ER, a nuclear receptor protein, binds estrogens; stimulates DNA synthesis, cell division, and cell proliferation in the breast epithelium; and induces the progesterone receptor (PR). A small proportion of normal, nonmalignant breast epithelial cells but a majority of breast tumors express measurable ER and PR.³ Patients diagnosed with tumors that express both ER and PR (i.e., ER+/PR+; approximately 70% of all breast cancers) survive longer, respond better to endocrine (e.g., tamoxifen) therapy, and experience fewer relapses than patients with tumors that express neither (i.e., ER-/PR-; approximately 10% of all breast cancers), even after adjustment for age and stage at diagnosis.¹²² Behavior of discordant tumors—ER+/PR- (15%) or ER-/PR+ (5%)—appears to fall between the two concordant types, but these groups have not been adequately investigated.

ER/PR status strongly predicts clinical prognosis.⁹⁰ Epidemiologic studies have begun to evaluate whether tumors with different ER/PR status reflect different stages in breast carcinogenesis or different subtypes of breast carcinoma. Both case-control and cohort studies reveal distinct profiles for tumors with different receptor status: estrogen-associated risk factors are most strongly associated with ER+/PR+ tumors but only weakly or inversely associated with ER-/PR- tumors. A case-control study of 862 cases and 790 matched controls observed increased risks with earlier age at menarche, nulliparity, or later age at first full-term pregnancy, and higher BMI restricted to ER+/PR+ tumors; a first-degree family history of breast cancer was associated only with ER-/PR- tumors.⁹⁴ The case-control study of Enger and others⁵⁵ investigated the same issues in both premenopausal (424 cases and 714 controls) and postmenopausal (760 cases and 1091 controls) women. Among postmenopausal women, increasing BMI and adult weight gain—which both provide additional exposure to endogenous estrogens through the conversion of androstenedione to estrone in adipose tissue—were positively associated with ER+/PR+ tumors but not associated with ER-/PR- tumors. However, physical activity, which is hypothesized to decrease risk by decreasing the number of lifetime ovulatory cycles, was inversely associated with all tumor types in both premenopausal and postmenopausal women. In the prospective Iowa Women's Health Study, increasing body size increased risk of ER+/PR+ tumors¹⁶⁷ and alcohol intake increased risk of ER-/PR- tumors.⁶⁸ A positive family history of breast cancer increased risk²⁰² and high parity decreased risk¹⁶⁷ of all tumor subtypes.

The data to date generally support the concept that joint ER/PR status defines different subsets of breast cancer with distinct etiologies.¹⁸⁴ However, additional studies with larger numbers of discordant and ER-/PR- tumors are necessary to evaluate these associations and potential interactions. Further investigation of ER variants,⁹⁰ the alpha- and beta-isoforms of ER,¹⁵⁴ and a reported interaction between *BRCA1* and ER⁵⁹ should help to elucidate the function of ER and PR. In addition, continued research into the mechanisms that control ER and PR expression in normal breast tissue, premalignant breast lesions, and invasive breast carcinoma¹²² could potentially transform ER and PR from useful predictors of clinical prognosis to targets for breast cancer prevention.

Similar to ER status, the histopathologic subtypes of breast tumors may reflect different etiologies of heterogeneous breast cancer. Numerous studies have evaluated risk of particular tumor types relative to other tumor types or to women without breast cancer, but results vary widely. Earlier studies suggested that hormonal and socioeconomic factors increased risk of lobular carcinomas in particular.¹⁸² Some³⁴ but not all¹⁸² studies report elevated incidence of lobular carcinomas in women with a family history of breast cancer. A recent prospective cohort study in Denmark, which included 10,790 incident breast cancers, observed similar positive associations between most subtypes and nulliparity and age at first birth, although lobular carcinomas were not associated with number of live births as expected.²²⁵ Recent data indicate that the complex increased risk associated with HRT may be restricted to the rare breast cancers with "favorable histology" (i.e., nonlobular and nonductal carcinomas),⁶⁷ but a subsequent study found increased risks for almost all invasive carcinomas with ductal or lobular histologies.¹⁷⁹ Challenges facing this line of inquiry include the predominance of ductal and lobular carcinomas, which represent approximately 80% to 90% of all breast cancers, a strong correlation between ER status and tumor histology, and the difficult task of uniform histopathologic classification of tumor samples. Nonetheless, identifying the factors that influence tumor histopathology and hormone receptor status in the natural history of breast carcinoma will remain an important task.

CONCLUSION

Although breast cancer is one of the most intensively studied cancers epidemiologically, much remains to be known about the disease. Despite the large number of identified risk factors, only about 55% of the cases of disease are explained by these factors.²⁰ This undoubtedly relates to our poor understanding of the biologic mechanisms underlying most of these factors. For instance, we have known since the 1970s that a late age at first birth increases the risk of breast cancer, but

whether this increase is caused by changes in endogenous hormones, tissue changes, or some other factor has yet to be determined. Fortunately, more epidemiologic studies are integrating the evaluation of risk factors with biochemical markers, which should enhance our understanding of biologic mechanisms. It is hoped that this knowledge will eventually lead to a greater understanding of reasons for the occurrence of the disease of recent major epidemic proportions, and to more effective preventive interventions.

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