The Epidemiology of Breast Cancer

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Magnitude of the Problem and Trends With Time in the United States

Breast cancer continues to be a major public health problem in the United States and other Western countries. Among women in the US, more new cases of breast cancer are diagnosed than any other cancer (Fig. 1), and breast cancer is second to lung cancer as a cause of cancer death.[1] The American Cancer Society estimates that, in 1991, 175,000 new cases of breast cancer will be diagnosed among women in this country and that 44,500 deaths from breast cancer will occur.[1] On the basis of current incidence rates, the American Cancer Society has estimated that the chance that a woman will develop breast cancer at some time during her lifetime is now one in nine.[2]

Age-adjusted mortality rates have been relatively constant since 1930. Age-adjusted incidence rates have been slowly rising over the past several decades, but between 1980 and 1987 the incidence rate rose by 32 percent. Until around 1980, most of the increase in incidence rates occurred in postmenopausal women, but now increases are also seen in premenopausal women.[3] Incidence rates have been increasing particularly fast in young black women. The extent to which the apparent increases in incidence rates, especially in white women, are attributable to early case-finding through screening programs and to the detection and removal of lesions that were not previously called cancer is uncertain.

Demographic Characteristics

In Western countries, breast cancer incidence rates increase with age throughout life, but the rate of increase is faster before age 50 than after. At present, incidence rates are higher in white women than in black women over age 45; incidence rates are similar in blacks and whites in the 40-to-44-year age group and are higher in blacks younger than age 40.[3] Breast cancer is more common among women in upper socioeconomic classes than among those in lower socioeconomic classes, among women who have never been married than among those who have been married, among women living in urban areas than among those in rural areas, and among women living in the northern US than among those living in the southern US. Lower than average rates of breast cancer have been recorded for Mexican-Americans, Japanese and Filipino women in Hawaii, American Indians, Seventh-Day Adventists, and Mormons, while Jewish women have a higher-than-average risk.

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Some of the material for this paper has been taken from Berkowitz and Kelsey,[4] Kelsey and Gammon,[206] Kelsey and Berkowitz,[207] and Gammon.[208]

Nuns have a higher risk for breast cancer, presumably because of their usual nulliparous status.[4]

International Trends

For many years, breast cancer incidence and mortality rates have been highest in North America and northern Europe, intermediate in southern Europe and Latin America, and lowest in Asia and Africa. These different geographic areas have also exhibited different shapes in the age-specific incidence curves. Figure 2 shows that in areas of high incidence, illustrated by Connecticut, USA, a slight leveling off in the increase in incidence with age occurs during the menopausal years, followed by a continued rise at a slower rate than during the premenopausal years. In localities with intermediate incidence rates, such as Slovenia, Yugoslavia, the rates tend to level off and stay relatively constant among women over 50 to 55 years of age. In areas with low incidence rates, represented by Miyagi Prefecture, Japan, the rates decline postmenopausally.[5] Studies in migrant populations suggest that environmental rather than genetic factors are largely responsible for the international variation. For example, first-generation Japanese migrants to the US have breast cancer incidence rates similar to women in Japan, whereas incidence rates in second- and third-generation migrants approach those of American-born white women.[6]

In recent years, steep increases in breast cancer incidence and mortality rates have been reported in many Asian, central European, and some South American countries. To date, these increases have been noted in women under age 50; as these younger cohorts age, it is expected that increases in incidence and mortality rates will be seen in the postmenopausal years as well. If so, it has been estimated that the annual incidence of breast cancer worldwide will be more than one million cases by the year 2000.[7]

Reproductive Factors

On average, the older the age at which a woman gives birth to her first child, the greater her risk of breast cancer. Compared with that of nulliparous women, the relative risk—that is, the risk of disease in one group divided by the risk of disease in another—ranges from about 0.5 in women age 20 or younger at the birth of their first child to about 1.4 in women over age 35 at the birth of their first child.[8] The reasons for the association between age at first full-term pregnancy and risk for breast cancer are uncertain, but probably result either from changes in breast tissue, such that the tissue is rendered less susceptible to carcinogenic agents, or from changes in the hormonal milieu.

Recent investigations have reported that the number of pregnancies a woman has affects her breast cancer risk independently of age at first birth; for example, the relative risk associated with five or more pregnancies has been estimated to be

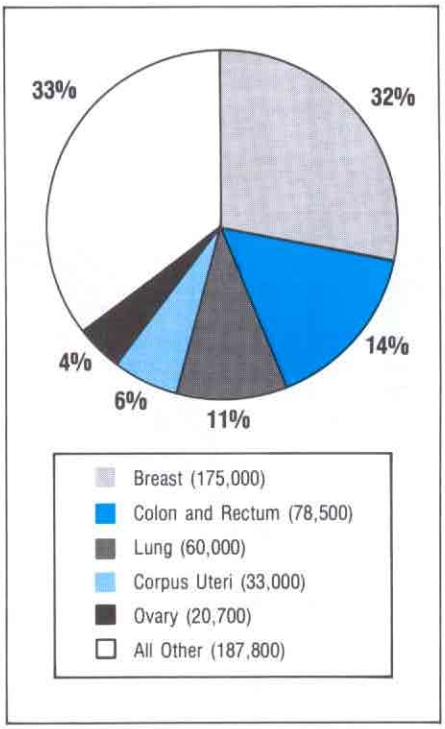

Fig. 1. Estimated number of cancers and percentage of all cancers in females in 1991, by site. Data from Boring et al.[1]

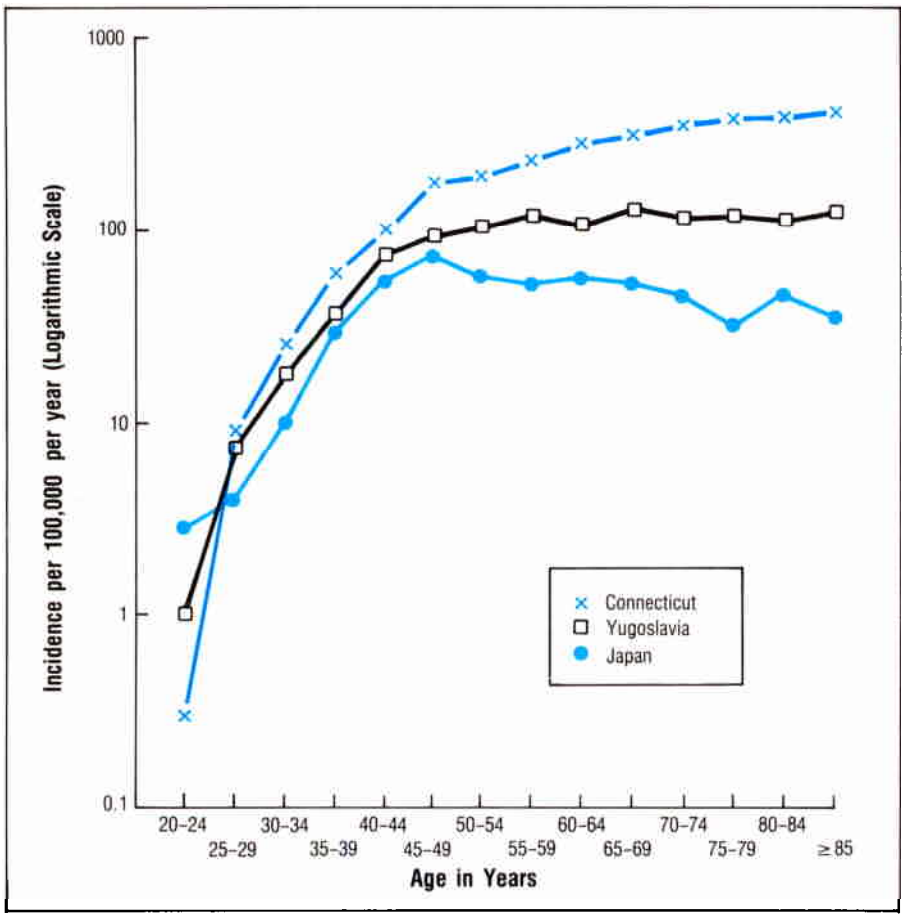

Fig. 2. Age-specific incidence rates for breast cancer in three localities: Connecticut, USA, 1978–1982; Slovenia, Yugoslavia, 1978–1981; Miyagi Prefecture, Japan, 1978–1981. Data from the International Agency for Research on Cancer and the International Association of Cancer Registries.[5]

0.5 compared with women with no pregnancies.[9–12] This protective effect of parity has been noted mainly for breast cancer diagnosed in women of about age 50 and older; some studies have reported that the risk of breast cancer at younger ages is increased among parous as compared with nulliparous women.[9–12] Some evidence suggests that the increase in risk lasts about 10 years after the last pregnancy.[10]

Until recently, most investigators found that lactation did not have an effect on the risk of breast cancer that was independent of the effects of parity and early age at first birth. However some recent studies,[12–15] although not all,[16,17] have found that as the number of months of breast-feeding increases, the risk of breast cancer decreases, particularly for premenopausal women.

The earlier the age at menarche, with its associated earlier onset of "regular" menstrual cycles, the higher the risk of breast cancer.[10,18] Also, the later the age at menopause, the higher a woman's risk.[10]

Bilateral oophorectomy before age 40 confers a lifelong reduction in risk which has been estimated to be about 50 percent.[19] The increased risks associated with early age at menarche and late age at menopause suggest that the total number of years of menstrual activity is of etiologic importance.[18] It is also possible that early age at menarche and late age at menopause are independent risk factors for breast cancer.

Evidence is inconsistent as to whether a history of induced or spontaneous abortion at any time during the reproductive years[20] or specifically prior to a woman's first full-term pregnancy[20–23] is associated with an increased risk of breast cancer. Studies concerned with abortions are complicated by the difficulty in distinguishing between induced or spontaneous abortions during ascertainment of the reproductive history by questionnaire. Also inconsistent have been the results of studies to determine whether women diagnosed with infertility from a hormonal abnormality[24–27] or women with irregular anovulatory menstrual cycles[18,28] have an altered risk for breast cancer.

Other reproductive characteristics have recently been reported from individual studies to be risk factors, but at present corroborating evidence is lacking. Late age at last birth,[29,30] wide spacing of births,[29] and late age at any birth[29,30] may increase breast cancer risk independent of late age at first birth. One group of investigators noted a reduced risk of breast cancer among women with multiple births as the last birth[31] and among women who experienced hypertension during pregnancy;[32] both conditions are related to elevated levels of serum alphafetoprotein during pregnancy. Finally, an increase in breast cancer risk may occur among women born to older mothers.[33,34]

Endogenous Hormones

The association of various reproductive and menstrual characteristics with breast cancer risk in humans, as well as findings from animal studies, strongly suggest that endogenous hormones are etiologically involved.[35] Despite the large body of epidemiologic and laboratory research in this area, precisely which hormones are important and the underlying biologic mechanisms through which they operate remain obscure.[35–37] The circulating hormones and metabolites that have been considered include serum or urinary levels of estrone, estradiol, estriol, androstenedione, testosterone, dehydroepiandrosterone, progesterone, sex-hormone-binding globulin, and prolactin as well as blood levels of certain thyroid hormones.[38–44a]

In studying the possible etiologic role of these hormones and metabolites, issues such as the storage of serum samples, the measurement of certain hormones such as the biologically active component of prolactin, and the detection of biologically meaningful interactions among hormones need to be considered. Also, reliance on a single measurement as a valid indicator of exposure, as is done in most studies, may not be feasible.[45] Whether there are specific time periods of a woman's life, such as in utero, adolescence, pregnancy, or the perimenopausal years, during which these hormones have their major influence on breast cancer risk needs further attention. Currently, the possible etiologic role of nonprotein-bound and albumin-bound estradiol is of great interest.[35] Biologically active prolactin is also the subject of considerable research.[37]

The American Cancer Society's current estimate is that one in nine women will develop breast cancer at some time during their lives.

One group of investigators[46,47] has suggested that studies of hormone levels in serum need to be supplemented by measurements of hormone levels in breast fluid, since breast fluid estrogen levels may be five to 45 times higher than serum levels. It has been reported that women with benign breast disorders have elevated levels of estradiol in their breast fluid[46] and that parous or lactating women have low

levels.[47] Concentrations of breast fluid cholesterol and its oxidation products, cholesterol epoxides, which have been reported to be mutagenic, carcinogenic, and cytotoxic, have been associated with certain breast cancer risk factors, including biopsy-confirmed proliferative epithelial disorders.[48,49]

Exogenous Hormones

Oral Contraceptives

Many epidemiologic studies have found that oral contraceptive use does not affect the risk of breast cancer in the majority of women regardless of the dose, brand, or type of estrogen or progestin.[50] Some studies, however, have identified subgroups of oral contraceptive users who have an increased risk of breast cancer. Such subgroups include women with several years of oral contraceptive use before age 25 and/or before the first full-term pregnancy;[51–55] women who use oral contraceptives at age 45 or older;[56,57] women with a history of biopsy-confirmed benign breast disorders;[58–60] nulliparous, premenopausal women with an early menarche;[61] women with only one child;[55] and women with a family history of breast cancer.[62,63] Taken together, these subgroups include a large number of women, but, fortunately, many studies do not find that women in most of these subgroups are at high risk.[60,62,64–69]

On average, the older the age at which a woman gives birth to her first child, the greater her risk of breast cancer.

Of greatest concern has been the possible increase in the risk of breast cancer occurring among the subgroup of women under age 45 who have used oral contraceptives for relatively long periods of time at an early age (or before their first full-term pregnancy). This association has been observed by several investigators (Table 1),[51–55] although not all,[60,62,69–71] and has been most consistently found for breast cancer diagnosed before age 35, which of course constitutes only a small proportion of all cases. In view of the well-designed studies both supporting and not supporting this association and the large number of women potentially affected, further evaluation of this association is of major importance. Also, as these young women age, there is concern that the risk for breast cancer at older ages may also be altered.

Depot-medroxyprogesterone Acetate

Most studies have shown no relationship between use of the injectable contraceptive depot-medroxyprogesterone acetate (DMPA) and breast cancer risk.[67,72,73]

Estrogen-Replacement Therapy

Studies concerned with whether an elevation in risk for breast cancer occurs among women who use estrogen-replacement therapy have produced conflicting results,[74–83a] and the elapse of additional time may be the main hope of resolving this controversy. Several studies have shown no association, but some recent ones[76,77] have suggested that use for 20 years or more may be associated with relative risks of around 1.5 to 2.0 (Table 2). A few studies[74,82,83] have suggested slightly increased risks with high doses of estrogen, while another[83a] has reported that recent use is associated with a small increase in risk. One recent study from Sweden[84] noted a positive association when progestin and estrogen were used in combination; the number of subjects, however, was much too small for firm conclusions to be drawn. Thus, most current evidence suggests either no effect on breast cancer risk from estrogen-replacement therapy or an elevation in risk of less than twofold with very long-term use or relatively high doses. Additional studies that include large numbers of women who have used estrogen for 15 years or more are needed, and studies of the effect of progestin when used in conjunction with estrogen are of high priority. Any effect of estrogen-replacement therapy on breast cancer risk would have to be considered in conjunction with the therapy's

TABLE 1
ADJUSTED RELATIVE RISK FOR BREAST CANCER, WOMEN AGE 35 OR YOUNGER, BY TOTAL DURATION OF ORAL CONTRACEPTIVE USE, UNITED KINGDOM NATIONAL CASE-CONTROL STUDY

Months of Use	Adjusted* Relative Risk
0	1.0
1–48	0.9
49–96	1.4
≥97	1.7**

*Adjusted for age at menarche, nulliparity, age at first full-term pregnancy, breastfeeding (ever/never), and family history of breast cancer (mother or sister).

**Test for trend: $p < 0.001$

Data from UK National Case-Control Study Group[53]

TABLE 2
ADJUSTED RELATIVE RISK OF BREAST CANCER BY YEARS OF USE OF ESTROGEN-REPLACEMENT THERAPY
Breast Cancer Detection Demonstration Project Case-Control Study

Years of Use	Adjusted* Relative Risk	95% Confidence Limits
0	1.0	—
<5	0.9	0.8 - 1.0
5–9	1.1	0.9 - 1.3
10–14	1.3	0.9 - 1.6
15–19	1.2	0.9 - 1.8
≥20	1.5	0.9 - 2.3

*Adjusted for age, type of menopause, and interval since oophorectomy.

Data from Brinton et al[76]

established protective effect against osteoporotic fractures and increased risk for endometrial cancer, and probable decreased risk for coronary artery disease.

Diethylstilbestrol

Several studies[85–88] have reported that use of diethylstilbestrol (DES) during pregnancy is associated with an increased risk for breast cancer; overall estimates of a relative risk of about 1.5 have generally been found. In some studies, it was not possible to separate the effect of DES from the reason for which DES was prescribed (prevention of spontaneous abortion, in most instances), but the general consistency of the results and the presence of a dose-response relationship are suggestive of a causal association. Although DES is no longer used to prevent spontaneous abortion, the possible association between DES and breast cancer suggests that exposure to certain agents over a short but critical time period, such as while breast tissue is growing rapidly during pregnancy, may increase the risk for breast cancer.

In postmenopausal women, body weight and various indicators of weight to height are positively associated with breast cancer risk.

Body Build

In postmenopausal women, body weight and various indicators of weight for height are positively associated with breast cancer risk.[89–91] This association is biologically plausible, since heavy postmenopausal women have both higher rates of conversion of androstenedione to estrogen in adipose tissue and lower levels of sex-hormone-binding globulin than do thinner women.[92] One study[93] has reported that the earlier the age at menopause, the stronger the association between weight and obesity, suggesting that longer exposure to this hormonal milieu results in a higher risk. On the other hand, thinner women appear to have a higher risk of premenopausal breast cancer,[89,90] although the possibility that this association results from easier detection of tumors in thinner women has not been ruled out.

Adolescent weight has also been negatively associated with premenopausal breast cancer.[90] Adult weight gain increases the risk of postmenopausal breast cancer,[89–91] while weight loss during adulthood may be protective.[89] The regional distribution of adipose tissue may be related to breast cancer risk independently of total weight; two studies[94,95] have reported an increase in risk among women with a higher ratio of central to peripheral fat deposition whereas another[96] found no association. Whether height increases breast cancer risk independently of weight is uncertain.[89,91,97]

Diet

Dietary fat has long been thought to play a role in the etiology of breast cancer. This suspicion stems from animal data,[98] marked international correlations between per capita fat "disappearance" data and breast cancer incidence and mortality rates,[99] migrant studies,[6] and temporal increases in breast cancer incidence paralleling higher rates of fat intake.[100] However, many other factors could explain these differences in breast cancer incidence rates over time and geographic area, and the applicability of animal studies to humans is uncertain. Thus, the results of these positive studies should be considered at most suggestive.

Most epidemiologic case-control and cohort studies, on the other hand, have found weak associations (either positive or negative) or no association between total fat, saturated fat, or animal fat intake in adulthood or childhood and subsequent breast cancer risk (Table 3).[101–112] The effect of diet on endogenous hormones that may be involved in breast cancer etiology has been considered in some studies, again with inconsistent or inconclusive results.[113–117] Studies considering dietary vitamin A, beta-carotene, and retinol;

TABLE 3
AGE-ADJUSTED RELATIVE RISK OF BREAST CANCER ACCORDING TO CALORIE-ADJUSTED INTAKE OF TOTAL FAT, NURSES HEALTH STUDY COHORT

Quantile of Fat Intake	Age-adjusted Relative Risk	95% Confidence Limits
1 (Low)	1.0	—
2	0.8	0.6 - 1.0
3	0.9	0.7 - 1.1
4	0.8	0.6 - 1.0
5 (High)	0.8	0.6 - 1.1

Data from Willett et al [101]

serum vitamin A, vitamin E, retinol, and retinol-binding protein; and plasma retinol and beta-carotene have also produced inconsistent results.[102,105,109,118–121] At most, individual studies show slight protective effects of one or the other of these micronutrients. A recent report[121a] that indole 3-carbinol, found in cruciferous vegetables, increases the extent of estradiol 2-hydroxylation merits further study. Epidemiologic studies[122,123] have failed to support the hypothesis[124] that low dietary selenium brings about an increased risk for breast cancer. It is possible that total caloric intake is the most important dietary characteristic.[125,126] Total calories could influence risk through its effect on obesity and age at menarche.

Designing epidemiologic studies to test dietary hypotheses is difficult. The extent of measurement error makes observational studies likely to be inconclusive. Since any effect of diet is probably small at most, randomized trials would have to be of such size that they would be almost prohibitively expensive. Not only are the roles of specific dietary constituents unclear, but the age at which they are likely to have an effect is unknown. One recent study in mice suggests that the fat content of the prenatal diet of the mother may be important.[127] A more detailed summary of the literature on diet and breast cancer has been published by Willett.[128]

Alcohol Consumption

A modest positive association between alcohol consumption and the risk of breast cancer has been observed in many epidemiologic studies (Table 4),[129–136] although not all.[112,137–142] Among the studies showing a positive association, results have been inconsistent as to whether the risk varies with the type of alcoholic beverage consumed and as to whether the elevation in risk is associated with moderate levels of intake (fewer than three drinks per week) or only with larger amounts. A few studies have found that the increase in risk may be associated with alcohol consumption specifically in early adulthood,[130,136] a finding that needs further evaluation.

A recent meta-analysis[143] has concluded that the literature favors a positive association between alcohol and breast cancer risk. Others, however, have pointed out that any conclusion is premature, given the varying quality of the investigations, the difference in control groups used, and the difficulty of assessing alcohol intake.[144,145]

Certain biologic mechanisms for an association between alcohol consumption and breast cancer have been suggested,

TABLE 4
ADJUSTED RELATIVE RISK FOR BREAST CANCER ACCORDING TO LEVEL OF DAILY ALCOHOL INTAKE, NURSES HEALTH STUDY COHORT

Alcohol Intake (g/day)*	Adjusted** Relative Risk	95% Confidence Limits
None	1.0	—
< 1.5	1.0	0.8 - 1.3
1.5 - 4.9	0.9	0.7 - 1.2
5.0 - 14.9	1.3	1.0 - 1.6
≥ 15.0	1.6	1.3 - 2.0

*Five grams of alcohol per day is roughly equivalent to three drinks per week.

**Adjusted for age, menopausal status, age at first birth, age at menarche, maternal history of breast cancer, and parity.

Data from Willett et al [133]

such as interference with cell-membrane permeability in breast tissue,[146] exposure to circulating cytotoxic products of ethanol,[147] and altered hepatic function.[148,149] However, none of these explanations is generally accepted, and it is possible that the increased risk is attributable to some other difference between women who do and do not drink rather than to the alcohol itself. Also, some other constituent of the drink could be responsible. Thus, it has yet to be determined whether the association between alcoholic beverage consumption and breast cancer is indeed causal.

Other Lifestyle Factors, Medications, Electric Power Use

Despite occasional reports[150] of an association between caffeine consumption and breast cancer risk, the vast majority of investigations have found no association.[151–153] A few studies have found cigarette smoking to have a weak protective effect,[154] while others have reported a slight positive association among certain subgroups of women;[140] most studies, however, have found no relationship between cigarette smoking and breast cancer.[137,140,155–157] Other exposures at some time purported to increase the risk for breast cancer but which are now largely negated by the weight of evidence include hair dyes, reserpine, and diazepam.[4,158] Also, the limited evidence available suggests that emotional stress and depression are not risk factors.[4]

Moderate levels of physical activity have been observed to reduce the risk of breast cancer in two studies,[159,160] but additional corroborating evidence is needed. Physical activity could affect breast cancer risk through its influence on endogenous hormones. One study[161] suggests that moderate physical activity at an early age decreases the frequency of ovulatory menstrual cycles, and another[162] indicates that luteal progesterone levels are decreased in young adults who undertake moderate physical activity. In addition, ammenorrheic runners have been observed to have decreased levels of estradiol.[163]

A woman's risk of breast cancer has been hypothesized to be increased by exposure to the magnetic fields produced by electric power.[164] Although a positive relationship between residential exposure to

magnetic fields and breast cancer was found in one study,[165] another reported no association.[166]

Benign Breast Conditions

Many studies have reported that women with benign breast conditions have a two- to threefold increase in risk of developing breast cancer. Current evidence suggests that the elevation in risk occurs primarily in women with proliferative lesions.[167–170] Atypical hyperplasia as seen on biopsy is associated with about a fivefold increase in risk of breast cancer, while hyperplasia characterized as moderate, florid, solid, or papillary, as well as papilloma with a fibrovascular core and sclerosing adenosis, confer relative risks of about 1.5 to 2.0.[167,169,171,172] Calcification in a biopsy specimen may also indicate an increase in risk.[167,169] Several studies are currently in progress that will further evaluate the risks associated with specific subtypes of benign breast disorders; results of these studies should be forthcoming soon.

Mammographic Parenchymal Patterns

Breast tissue seen on radiographs can be classified into four different categories: N1, essentially normal breast composed of fat; P1, mostly fat but with some prominent ducts occupying up to one fourth the volume of the breast; P2, similar to P1 but with prominent ducts occupying more than one quarter of the breast volume; and DY, extremely dense, dysplastic parenchyma, which usually denotes connective tissue hyperplasia.[173,174] Most studies show that the densest patterns, P2 and DY, are associated with a two- to threefold increase in the risk of breast cancer.[175,176] Numerous studies have examined the association between mammographic parenchymal patterns and selected breast cancer risk factors, but only age, parity, and body weight have been consistently shown to be inversely related to the proportion of dense patterns in breast tissue.[175] Interpretation of these findings is difficult, since breast cancer rates increase with age and postmenopausal body weight. More detailed discussions of the association between mammographic parenchymal patterns and breast cancer risk may be found elsewhere.[175,176]

Multiple Primary Neoplasms

Women with a history of primary breast cancer have a three- to fourfold increase in risk for primary cancer in the contralateral breast.[177] The risk for a second primary in the breast is especially high in women with a positive family history of breast cancer,[178–180] but findings regarding other factors that might affect the risk of a second primary, including prior radiation treatment for cancer, reproductive factors, and body build, have been inconsistent.[181–184] Women with a history of endometrial or ovarian cancer have a relative risk of about 1.3 to 1.4 of developing a second primary cancer in the breast.[185]

With the exception of age, country of birth, and a history of breast cancer in both a mother and a sister, all of the relative risks for breast cancer reported to date are of a relatively modest magnitude.

Familial Aggregation and Heredity

Women with a first-degree relative who has had breast cancer have a risk for breast cancer two to three times the risk of the general population. It used to be thought that the risk was especially high if the relative had breast cancer diagnosed at a young age or if the relative had bilateral disease, but the evidence is no longer consistent in this regard.[186–189] Studies continue to show that women who have both an affected mother and sister have a very high risk for breast cancer; one recent study[190] reported the risk for breast cancer to be 50 percent by 65 years of age in women with an affected mother and sister.

The recent finding[191] that families with ataxia-telangiectasia, an autosomal recessive syndrome, have an excess risk of breast cancer provides further evidence of a hereditary component in at least some families. The extent to which the familial aggregation of most breast cancer is attributable to hereditary or environmental factors is not fully known. Through complex segregation analysis of nuclear families of cases identified through two population-based tumor registries, Newman et al[192] found evidence of autosomal dominant transmission of a susceptibility allele with high penetrance in four percent of families. Identification of high-risk families with evidence of susceptibility genes should help in the identification and mapping of such genes. This in turn should lead to a better understanding of the role of heredity and its interaction with environmental risk factors.

The studies in women exposed to radiation, DES, and oral contraceptives suggest that the timing of some exposures may be critical, since the effects of these agents may be limited to specific time periods of rapid breast development.

Estrogen Receptors

Studies seeking to determine associations of risk factors with the estrogen-receptor status of the tumor have been reviewed in detail by Stanford et al.[193] The proportion of estrogen-receptor positive tumors increases with age, is higher in whites than in blacks, and may be higher in postmenopausal than in premenopausal women. Otherwise, no breast cancer risk factors have consistently been found to be associated with estrogen-receptor status or concentration. In addition, whether the estrogen-receptor status of a diagnosed tumor is in any way influenced by exposures before the tumor developed or during the early stages of tumor development, and whether the receptor status of a tumor reflects the receptor status of the cells from which the tumor arose, are unknown. Likewise, it is not known whether the estrogen-receptor status of normal cells affects the likelihood of cancer following exposure to a carcinogenic agent.

Radiation

It has long been recognized that relatively high doses of ionizing radiation can cause breast cancer. Evidence comes from studies of atomic bomb survivors in Japan, women who were treated with high-dose x-rays for acute postpartum mastitis, and women who received multiple chest fluoroscopies in the course of pneumothorax treatment for tuberculosis.[194] These data indicate that the risk from multiple exposures at relatively low dosages is similar to the risk of one large dose of similar magnitude.[195]

Previously, susceptibility of the breast to the carcinogenic effect of radiation was believed to be greatest between ages 10 and 20 when breast tissue is rapidly developing, with little increase in risk associated with exposure before age 10 or after age 40. After age 40, radiation still appears to have only a small effect on breast cancer risk.[196,197] However, it is now known[198–200] that women who were below age 10, including during infancy,[201,202] at the time of exposure also have an increased risk, but the excess risk was not apparent until the women had reached the ages at which breast cancer normally occurs. The increased risk associated with exposure to radiation persists for at least 35 years and may well remain throughout life.[196] Although a linear dose-response relationship has generally been reported, no empirical data exist for estimating the risk associated with very low levels of exposure.

Current evidence suggests a small effect of diagnostic radiography on breast cancer risk, such that less than one percent of breast cancer cases probably result from diagnostic radiography.[203] The risk for breast cancer is reduced among patients

TABLE 5
ESTABLISHED RISK FACTORS FOR BREAST CANCER IN FEMALES

Risk Factor	High-Risk Group	Low-Risk Group	Magnitude of Differential
Age	Old	Young	♦♦♦
Country of birth	North America Northern Europe	Asia, Africa	♦♦♦
Socioeconomic status	High	Low	♦♦
Marital status	Never married	Ever married	♦
Place of residence	Urban	Rural	♦
Place of residence	Northern US	Southern US	♦
Race ≥45 years <40 years	White Black	Black White	♦ ♦
Nulliparity	Yes	No	♦
Age at first full-term pregnancy	≥30 years	<20 years	♦♦
Oophorectomy premenopausally	No	Yes	♦♦
Age at menopause	Late	Early	♦
Age at menarche	Early	Late	♦
Weight, postmenopausal women	Heavy	Thin	♦
History of cancer in one breast	Yes	No	♦♦
History of benign proliferative lesion	Yes	No	♦♦
Any first-degree relative with history of breast cancer	Yes	No	♦♦
Mother and sister with history of breast cancer	Yes	No	♦♦♦
History of primary cancer in endometrium or ovary	Yes	No	♦
Mammographic parenchymal patterns	Dysplastic parenchyma	Normal parenchyma	♦♦
Radiation to chest	Large doses	Minimal exposure	♦♦

♦♦♦ denotes relative risk of greater than 4.0
♦♦ denotes relative risk of 2.0 to 4.0
♦ denotes relative risk of 1.1 to 1.9

Modified from Kelsey[205] and Berkowitz and Kelsey[4]

treated by radiation therapy for cancer of the cervix, almost certainly because of exposure of ovarian cells to the radiation,[204] while radiation therapy for breast cancer may increase the risk of contralateral primaries.[177,184]

Summary and Conclusions

Table 5 presents risk factors for breast cancer generally regarded as established, together with their approximate relative risks.[4,205] With the exception of age, country of birth, and a history of breast cancer in both a mother and a sister, all of the relative risks reported to date are of a relatively modest magnitude. Thus, new risk factors need to be identified and knowledge of existing risk factors refined.

Factors for which the evidence of an etiologic role has mounted over the past several years, but which are not yet considered to be established, include the protective effects of parity and lactation in certain age groups and the increased risks associated with alcohol consumption and with DES exposure during pregnancy. In addition, physical activity has emerged as a factor worthy of further study. Some evidence suggests that use of oral contraceptives for several years at an early age modestly increases the risk for breast cancer diagnosed before age 35 and perhaps age 45. Use of estrogen-replacement therapy for 20 years or more has been found by a few studies to increase the risk for breast cancer in the postmenopausal years; further studies of very long-term users are needed. Also, other risks and benefits of these hormones need to be taken into account when women decide whether to use them.

Surprisingly elusive has been the etiologic role of endogenous hormones, especially in view of the large number of studies that have been concerned with them. A better understanding of the role of endogenous hormones should help explain the mechanisms of action of known and suspected risk factors.

Areas of high priority for further research thus include establishing with more certainty whether the risk for breast cancer is increased in any subgroups of women who use oral contraceptives and estrogen-replacement therapy and determining the etiologic roles of specific endogenous hormones. The possible risks associated with alcohol consumption and lack of physical activity need to be studied more thoroughly, and ideas about new potential risk factors are needed. Although epidemiologic studies will continue to be concerned with diet, enthusiasm for its etiologic role in women has been considerably dampened by the lack of association in many of the studies reported to date.

The studies in women exposed to radiation, DES, and oral contraceptives suggest that the timing of some exposures may be critical, since the effects of these agents may mostly be limited to specific time periods of rapid breast development. The effect of radiation and the possible effects of estrogen-replacement therapy and oral contraceptives remind us that there may be a long period of latency before carcinogenic effects are seen. Also, it is hoped that susceptibility genes will be identified and lead to further progress in our understanding of genetic-environmental interactions.

Finally, with the exception of obesity, none of the established risk factors readily lead to opportunities for primary prevention. Some of the emerging risk factors may be more amenable to risk modification, and it is hoped that risk factors identified in the future will also lead to preventive measures. In the meantime, it is important for effective means of secondary prevention such as mammography to be more widely implemented and for potentially valuable and less expensive methods such as breast self-examination to be made more effective.

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