REVIEW ARTICLES

MEDICAL PROGRESS

BREAST CANCER

(First of Three Parts)

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BREAST cancer is a major public health problem of great interest and importance to physicians in a variety of specialties. Since this topic was last reviewed in the *Journal*,[1] the incidence of the disease has increased dramatically, heightening concern among physicians and women in general. In addition, long-term results are now available from clinical trials initiated in the 1970s and 1980s to evaluate the usefulness of early detection with mammography and physical examination, breast-conserving treatment with limited breast surgery and irradiation, and adjuvant systemic therapy with hormonal therapy and chemotherapy. Furthermore, in the light of newly gained knowledge, new strategies for addressing this problem have been proposed.

In this review, we describe the recent trends in incidence and mortality and the epidemiologic features that may be responsible for the rise in incidence. We summarize the evidence evaluating the strategies for diagnosis and therapy initiated in the 1970s and 1980s, including their benefits and costs. Finally, we describe the prospects for prevention and for more specific treatments based on evolving biologic knowledge.

TRENDS IN INCIDENCE AND MORTALITY

Breast cancer is a major affliction of women in affluent countries. On the basis of incidence rates for 1983 through 1987 and mortality rates for 1987 in the United States,[2,3] 12 percent of all women will be given a diagnosis of breast cancer and 3.5 percent will die of the disease. The impact of breast cancer is magnified because women are at risk from their middle to later years. The incidence rates increase rapidly during the fourth decade and become substantial before the age of 50, thus creating a long-lasting source of concern for women and a need for vigilance. After menopause, the incidence rates continue to increase with age, but less dramatically than before. Breast cancer is the leading cause of death among American women who are 40 to 55 years of age.[3] In less affluent parts of the world and in the Far East, the same pattern of increase with age is seen,[4] but the absolute rates are much lower at each age. In Japan, for example, the overall incidence of breast cancer has been only about one fifth that in the United States.[5]

The rates of breast cancer have been steadily increasing in the United States since formal tracking of cases through registries began in the 1930s (Fig. 1). Between 1940 and 1982, the age-standardized incidence rose by an average of 1.2 percent per year in Connecticut, which has the oldest cancer registry in continuous operation.[6] Improvements in the thoroughness of the registry, whose coverage became virtually complete in the early 1970s,[7] are unlikely to account for more than 25 percent of the increase that occurred before 1982. Between 1982 and 1986, the incidence in the United States rose more sharply, at 4 percent per year.[6] The time trends seen in Connecticut appear to reflect the experience in other parts of the United States, for which only recent data are available. Increases have occurred among all age groups since 1935, although the magnitude of the increase has been greatest among older women.[8] Age-adjusted incidence rates of breast cancer have increased in parallel among black and white women in the United States since 1975; rates among postmenopausal black women remain about 15 percent lower than those among postmenopausal white women, but the rates among premenopausal black women are now slightly higher than those among white women.[2] As in the United States, long-term increases in the incidence of breast cancer are being observed worldwide, in both industrialized and developing countries.[9,10]

The age-adjusted mortality rates for breast cancer, in contrast to the incidence rates, have been remarkably stable in the United States (Fig. 1). However, the time trends appear to vary depending on the age at diagnosis; since 1950 mortality rates have increased by about 15 percent among women over the age of 55 and declined by about the same amount among those younger than 45.[11] The declining mortality among younger women appears to be best characterized as applying to women born after about 1935 in Connecticut and after about 1950 nationwide.[12] Since 1975 the mortality rates among black women have increased substantially and are now slightly higher than those for white women.[13] The relative constancy of the overall mortality rate, despite increases in incidence, could be the result of more complete reporting of incident cases, increases in a more benign form of disease, earlier detection, or advances in treatment. These factors,

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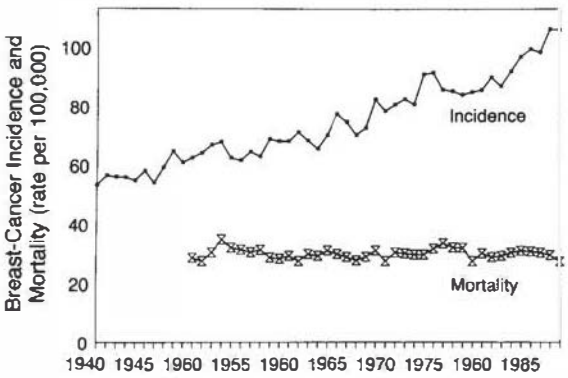

Figure 1. Age-Standardized Incidence of Breast Cancer and Mortality Rates in Connecticut from 1940 to 1988.
The data are from the Surveillance, Epidemiology, and End-Results Program (Miller B: personal communication).

all of which appear to be contributing to the divergence of incidence and mortality, are discussed subsequently.

Whether the increase in the incidence of breast cancer has been the result of more widespread use of screening mammography has been examined in several analyses. The initiation of a screening program will temporarily increase the incidence by advancing the time of diagnosis, as was noted nationally in 1974 through 1976 (Fig. 1). If screening is not repeated, a deficit of incident cases will ensue; if screening is performed regularly, a new steady-state incidence will be achieved at a rate close to that which will occur without screening. The number of breast cancers diagnosed in screening programs that would not eventually be recognized clinically appears to be small; there is minimal underdetection of breast cancer in autopsy series,[12] no excess incidence in a 10-year period was seen in a randomized screening trial,[14] and little increase was seen among women undergoing mammography for routine screening in a national program for the detection of breast cancer.[15] In an Oregon prepaid health plan, only 9 percent of cases diagnosed in 1985 were initially detected by screening mammography, and it was estimated that screening could account for no more than 5 percent of incident cases.[16] However, most of the increase between 1960 and 1985 was accounted for by tumors with estrogen receptors, suggesting a hormonal influence and the possibility that the increase may be due to a more benign form of breast cancer. In the United States as a whole, the annual rate of screening mammography among women over the age of 50 years did not appear to exceed 15 percent in 1984.[17] Because screening causes at most a transient rise in incidence and because its use was not widespread at least through the early 1980s, it can explain little of the long-term increase in the incidence of breast cancer.

The upsurge in the incidence of breast cancer that began in the early 1980s is almost entirely due to an increase in tumors measuring less than 2 cm in diameter; the incidence rate of tumors measuring 2 cm or more has not changed appreciably.[6] In addition, the proportion of cases diagnosed while the tumor is in situ or localized increased substantially,[6] after having been stable during the 1970s.[11] These findings as well as an improved two-year survival rate are compatible with the concomitant substantial increase in the use of screening mammography.[6] To the extent that the recent acceleration in the incidence of breast cancer represents the transient rise expected in the early stages of a screening program, it will eventually result in the prevention of deaths due to breast cancer during this decade. However, the incidence of larger tumors and those with regional or distant metastases at diagnosis has not decreased,[6] which would be expected if a screening program was implemented and the true incidence was constant. This indicates that the underlying long-term increase in the incidence of breast cancer has continued through the 1980s and suggests that no major decline in mortality rates should be expected in the near future. Stable mortality rates in the face of an apparent true increase in incidence suggest that the earlier detection of cases in more recent years, and possible improvements in treatment, have improved survival sufficiently to offset the rising incidence.

Although the very recent surge may be due largely to the increased use of mammographic screening, the much larger increase over the past half century appears to be real. Breast cancer is clearly continuing to increase, especially among postmenopausal women, and will require even greater attention on the part of researchers and clinicians. In particular, specific factors that explain the long-term increase should be sought.

Risk Factors

Large variations in the rates of breast cancer among countries[5] and over time within countries[10] and large increases in the rates of breast cancer among populations migrating from nations with a low incidence to those with a high incidence[18] indicate the existence of major nongenetic determinants of breast cancer and the potential for prevention. The elucidation of specific risk factors for breast cancer is important to understand the observed variation among and within countries, to identify women who could benefit from intensified surveillance or prophylactic treatment, to select subjects for participation in intervention studies, and to modify factors that will ultimately reduce risk.

The strength of a risk factor is typically indicated by its relative risk — the incidence among persons possessing a characteristic in question divided by the incidence among otherwise similar persons without the characteristic. The relation of a risk factor to the disease, however, can be complex for a number of reasons. Many risk factors are measured as continuous variables (for example, the age at which breast cancer was diagnosed in a relative and the ages of women at

menarche, the birth of the first child, and menopause), and their relative risks can be quite arbitrary, depending on the segments along the continuum that are compared. To evaluate the potential causes of breast cancer and the reasons for the international differences, comparisons of extremes are often of interest, such as an age of 11 years at menarche as compared with an age of 16 years. From a clinical perspective, however, the group with the highest risk on the basis of any particular factor is usually of primary interest; the relative risk for this group as compared with that for the rest of the population will typically be much smaller than when it is compared with the group with the lowest risk. Furthermore, the risk for an individual woman cannot be determined by multiplying the relative risk by the average risk for the population because the general population includes persons with and without the risk factor. In addition, the occurrence of an elevated risk in association with a given factor does not necessarily imply causation; however, this information may still be useful for prediction.

Table 1. Established and Probable Risk Factors for Breast Cancer.

Risk Factor	Comparison Category	Risk Category	Typical Relative Risk	Study
Family history of breast cancer	No 1st-degree relatives affected	Mother affected before the age of 60	2.0	Nurses' Health Study*
		Mother affected after the age of 60	1.4	Nurses' Health Study*
		Two 1st-degree relatives affected	4–6	Gail et al.[19]
Age at menarche	16 yr	11 yr	1.3	Kampert et al.[20]
		12 yr	1.3	
		13 yr	1.3	
		14 yr	1.3	
		15 yr	1.1	
Age at birth of 1st child	Before 20 yr	20–24 yr	1.3	White[21]
		25–29 yr	1.6	
		≥30 yr	1.9	
		Nulliparous	1.9	
Age at menopause	45–54 yr	After 55 yr	1.5	Trichopoulos et al.[22]
		Before 45 yr	0.7	
		Oophorectomy before 35 yr	0.4	
Benign breast disease	No biopsy or aspiration	Any benign disease	1.5	Willett et al.[23]
		Proliferation only	2.0	Dupont and Page[24]
		Atypical hyperplasia	4.0	Dupont and Page[24]
Radiation	No special exposure	Atomic bomb (100 rad)	3.0	Boice and Monson[25]
		Repeated fluoroscopy	1.5–2.0	McGregor et al.[26]
Obesity	10th percentile	90th percentile:		Tretli[27]
		Age, 30–49 yr	0.8	
		Age, ≥50 yr	1.2	
Height	10th percentile	90th percentile:		Tretli[27]
		Age, 30–49 yr	1.3	
		Age, ≥50 yr	1.4	
Oral contraceptive use	Never used	Current use†	1.5	Romieu et al.[28]
		Past use†	1.0	
Postmenopausal estrogen-replacement therapy	Never used	Current use all ages	1.4	Colditz et al.[29]
		Age, <55 yr	1.2	
		Age, 50–59 yr	1.5	
		Age, ≥60 yr	2.1	
		Past use	1.0	
Alcohol use	Nondrinker	1 drink/day	1.4	Longnecker et al.[30]
		2 drinks/day	1.7	
		3 drinks/day	2.0	

*Unpublished prospective data were obtained from Graham Colditz (personal communication).
†Relative risks may be higher for women given a diagnosis of breast cancer before the age of 40.

A number of variables that predict the occurrence of breast cancer and their typical relative risks are described briefly in Table 1. As can be appreciated, the established risk factors for breast cancer — a family history of breast cancer, early menarche, late age at first childbirth, late age at menopause, history of benign breast disease, and exposure to ionizing radiation — are generally associated with only weak or moderate elevations in risk. The exceptions occur in uncommon subgroups of these variables; for example, a family history of breast cancer at a young age or a family history of bilateral disease.[31,32]

A family history of breast cancer, particularly when the diagnosis was made in the mother or a sister at a young age, can be an important risk factor for breast cancer.[33] As compared with the risk among women having no first-degree relatives with breast cancer, overall the relative risk is on the order of 1.5 to 2 for women who have one first-degree relative with breast cancer[34] and may be as high as 4 to 6 for those with two affected first-degree relatives.[19] The risks are heightened if the cancer was bilateral.[31,32] For a woman with a sister who had bilateral breast cancer before the age of 50, the lifetime cumulative risk of breast cancer appears to be greater than 50 percent, and it is even higher if the sister was affected before the age of 40.[31] The excess relative risk declines with the age of the relative at the time of diagnosis.[33,35] For a woman whose mother had unilateral breast cancer after the age of 60, the excess relative risk is only about 40 percent greater than that associated with having no first-degree relatives with breast cancer (Nurses' Health Study: unpublished data). An intensive search for DNA markers of familial risk is ongoing and will be described later.

Early menarche is a well-established but weak risk factor.[20] The relative risk is approximately 1.2 for women in whom menarche occurred before the age of 12 as compared with women in whom it occurred at the age of at least 14.[17] However, this variable may account for a substantial part of the international differences, because the contrasts are more substantial; in China the average age at menarche is 17 years,[36] as compared with 12.8 years in the United States.[37]

Nulliparity and a late age at first birth both increase the lifetime incidence of breast cancer.[21,38] The risk of breast cancer among women who have their first child after the age of 30 is about twice as high as that among those who have their first child before the age of 20;

women who have their first child after the age of 35 have a slightly higher risk than nulliparous women.[38] An earlier age at the birth of a second child further reduces the risk of breast cancer.[39] After an adjustment for the ages of the women at the births of their children, the number of births has at most a small influence on the risk of breast cancer.[39,40] Although pregnancy before the age of 30 reduces the lifetime risk of breast cancer, recent evidence suggests a more complex pattern of a transiently increased risk relative to that for a nulliparous woman that lasts for one to two decades, followed by a risk that is lower than that for a nulliparous woman later in life.

A late age at menopause increases the risk of breast cancer; the incidence is doubled among women with natural menopause after the age of 55 as compared with those in whom it occurs before the age of 45.[22,41] In the extreme, women with bilateral oophorectomy before the age of 35 had one third the risk of women with natural menopause in studies conducted before hormone-replacement therapy became standard practice.[41]

A history of benign breast disease has long been known to increase the risk of breast cancer slightly. However, the term "benign breast disease" covers a heterogeneous group of histopathologic entities and needs to be defined specifically.[24,42] As compared with women without a history of breast biopsy or aspiration, women who have lesions with any proliferative epithelial changes have twice the risk of breast cancer and those with atypical hyperplasia about four times the risk.[24,42] Lesions without proliferative changes are associated with little or no excess risk. Four to 10 percent of benign biopsy specimens show atypical hyperplasia.[24,42]

Exposure to ionizing radiation, particularly between puberty and the age of 30, can substantially increase the risk of breast cancer.[25,26] However, exposure to clinically important levels is rare.

Obesity is not an important risk factor for breast cancer, and among premenopausal women it is actually associated with a reduced incidence.[27,43] Among postmenopausal women, it has a weak but clinically unimportant positive association with the incidence of breast cancer, but it has a stronger association with mortality from breast cancer, due in part to delayed diagnosis among more obese women[44] and to a worse prognosis that is independent of the stage of cancer.[45]

Other features have been associated with breast cancer, but they are not as firmly established as those noted above. Tallness is associated with an increased risk of breast cancer internationally[46] and in numerous case–control and cohort studies.[45,47-49] The use of oral contraceptives appears to increase the risk of breast cancer by about 50 percent, but the excess risk drops rapidly after the drug is stopped,[28,50] suggesting a late-stage tumor-promoting effect. However, issues related to their use early in reproductive life remain unsettled; in several recent case–control studies among women younger than 45 years,[51,52] the use of oral contraceptives for more than a few years was associated with increases in risk irrespective of when they were used. The use of postmenopausal estrogen supplements appears to increase the risk of breast cancer by about 40 percent among women who are actively taking them,[29] with little increase among those who are no longer taking them.[53] This increased risk among current users appears to be concentrated among older women, who also tend to take them for longer periods. Combining progesterone with estrogen replacement, which reduces the risk of endometrial cancer, does not appear to decrease the incidence of breast cancer, and may add to it.[54] Alcohol consumption, even at the level of about one drink per day, has been associated with a moderate increase in risk in most, but not all, case–control and cohort studies.[30,55] As for the more traditionally recognized risk factors described previously, the magnitude of associations between these less well-established variables and the risk of breast cancer is not strong.

Other potential risk factors have been studied, but the findings have been inconclusive. The fat composition of the diet has been thought to influence the risk of breast cancer, in great part because of the large differences in rates between countries.[10] However, only weak[56,57] or nonexistent[23,58,59] associations have been seen in case–control and cohort studies. In animals, mammary tumors appear to be most strongly promoted by linoleic acid (the primary dietary polyunsaturated fat) and inhibited by n–3 marine oils[60]; however, there is little evidence that these fats are related to breast cancer in humans. An inverse relation between breast cancer and the total intake of vitamin A has been observed in some studies,[61,62] but the validity of this finding is far from resolved. Lactation has been found to reduce the risk among premenopausal women in some studies,[63,64] but not in other large investigations.[65,66] Participation in varsity athletics was associated with reduced risk in one study,[67] but not in another.[68]

To convey the effect of various risk factors in combination, Gail and colleagues[19] have compiled detailed tables of estimates of the cumulative incidence of breast cancer among women at specific ages and according to the number of first-degree relatives with breast cancer, age at menarche, age at first live birth, and number of biopsies for benign breast disease. For example, the cumulative 30-year incidence of breast cancer for a 50-year-old woman would be approximately 20 percent if she had her menarche at the age of 11 years, had two first-degree relatives with breast cancer, and delivered her first child after the age of 30. If she had no first-degree relatives with breast cancer, her risk would be approximately 9 percent.

The accumulated data on risk factors for breast cancer suggest several biologic mechanisms. Genetic factors clearly contribute, and a search is now in progress for DNA mutations associated with this increased risk. Estrogenic stimulation increases the risk[69]; the elevated risk among users of estrogen supplements[29] supports this mechanism most directly, and the effects of age at menarche and menopause, obesity among post-

menopausal women, and the therapeutic effect of tamoxifen therapy[70] are also likely to be mediated by this mechanism. Studies of endogenous estrogen levels in relation to the risk of breast cancer are currently inconclusive because of the possibility that the levels may be influenced by the disease in case–control studies,[71,72] the limited size of prospective studies,[73,74] and the poor reproducibility of many serum hormone assays. Another mechanism is suggested by the finding that pregnancy early in life reduces the lifetime risk of breast cancer; the protective effect may result from pregnancy-induced differentiation of breast stem cells.[75] Finally, restriction of food intake early in life, which profoundly reduces the incidence of mammary tumors in animals,[60,76] may also be relevant to humans. This relation is reflected in the positive association between height and the risk of breast cancer,[45] and may underlie many of the differences in the rates among countries.[46,77]

Can the established risk factors for breast cancer account for the substantial increase in the incidence of breast cancer over the past 40 years? The age at menarche has declined from an average of about 17 years two centuries ago to an average of 12.8 years, but it has been stable in the United States since the 1940s.[37] Adult height has increased substantially over the past 150 years in the United States, but it also tended to stabilize sometime about 1940 among the middle and upper classes.[78,79] Thus, to the extent that the improvements in childhood nutrition reflected by the age at menarche and ultimate height adversely influence the risk of breast cancer, cohorts of women born before about 1940 will continue to have successively higher age-specific rates, but those born after this time should have little further increase.

Changes in the age at which women bear children explain little of the long-term increases in breast cancer, although recent delays in the time of first pregnancies could increase future rates by about 9 percent.[11,21] Widespread use of estrogen-replacement therapy has almost certainly contributed to the higher incidence among postmenopausal women. Some have claimed that increased fat consumption is a probable explanation for the rise in incidence,[10] but this assertion is based on data for fat production rather than intake; fat intake has actually been declining in the United States for the past 40 years.[80] Increased alcohol consumption by younger women may have contributed appreciably if the observed association with incidence is causal; alcohol consumption at the age of 18 was three times higher among Nurses' Health Study participants born between 1960 and 1964 than among those born 40 years earlier (unpublished data). Although an increase in the incidence of breast cancer would have been expected on the basis of changes in known and suspected risk factors, whether these factors can quantitatively account for the observed increase remains unclear.

The known risk factors for breast cancer do not collectively allow the identification of a small high-risk group that accounts for a large proportion of women with the disease. For example, in the Nurses' Health Study, women in whom menarche occurred before the age of 11, who had their first child after the age of 35, who had a history of benign breast disease, or who had a history of breast cancer in a first-degree relative composed 41 percent of the population and together had only a 54 percent greater incidence of breast cancer than did the remaining women (unpublished data). Furthermore, the excess incidence in the study population accounted for by these variables was only 18 percent. A small group of women, those with a mother or sister who has had bilateral breast cancer at a young age or multiple first-degree relatives with breast cancer at a young age, may have cumulative lifetime risks of 30 percent or more. These women warrant particularly careful follow-up by physicians experienced in breast disease, but they account for a small fraction of all breast cancers. Unfortunately, even women without identifiable risk factors have an appreciable lifetime risk of breast cancer (approximately 6 percent through the age of 80),[19] and they will benefit from regular screening for breast cancer.

From the standpoint of identifying risk factors to prevent breast cancer, our knowledge is even more disappointing. It is either impossible or culturally unacceptable to modify some of the clearly established risk factors. Although great strides have been made in the identification of lifestyle variables that are risk factors for cardiovascular disease and some forms of cancer, this paradigm may not necessarily apply to breast cancer. The search for modifiable risk factors has not been exhausted and must continue. However, to the extent that the high incidence of breast cancer in affluent countries is the result of rapid growth and early maturation of children resulting from historically unprecedented nutritional abundance and the control of infectious disease, the lifestyle changes needed to reduce the risk of breast cancer substantially may not be feasible. If this is the case, prevention may depend on artificial manipulation of hormones and growth regulators that underlie the known risk predictors, such as a woman's age at the birth of her first child and at menopause.

Screening

One potentially important strategy in reducing the mortality from breast cancer is earlier detection. Earlier diagnosis is hypothesized to result in treatment before the tumor metastasizes and thus to avert death due to the disease. The main methods for earlier detection of breast cancer have been mammography and physical examination performed by a trained health professional. Other potential methods of screening, such as self-examination of the breasts, have not yet been demonstrated to be of value,[81] and some methods, such as thermography and CT scanning, have been shown not to be of value. The ability of mammography to detect cancers well before they are apparent on physical examination has been indisputably established. The usefulness of mammography in recent years has been enhanced by technical advances

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