



Risk in Perspective

BREAST CANCER RISK FACTORS: WHAT DO WE KNOW AND HOW WELL DO WE KNOW IT?

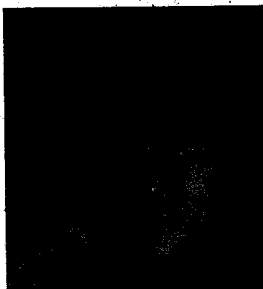
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Breast cancer is a leading cause of cancer death among American women. Recent years have seen a large increase in public awareness of breast cancer issues, including research on potential causes and risk factors, mammography screening, and treatment options. The good news is that breast cancer mortality has begun to decline. According to the National Cancer Institute, the age-adjusted rate fell about 5% from 1989 to 1993, with the improvement being more marked for younger than older women and for White compared to Black women. Most scientists ascribe much of the improvement to a combination of greater awareness, wider mammography screening, and improved anticancer drugs, leading to more successful treatment.

This good news must be tempered, however, by the fact that the breast cancer incidence rate (the rate of diagnosis of new cases) is still high and has (until recently) been steadily increasing. Much of this increase is explained by the aging of the American population—as with most cancers, breast cancer is largely a disease of older ages, and as older women increase as a proportion of the population, the diseases that afflict them increase as well. Another major factor is the great expansion of mammographic screening in recent years, leading to earlier and more complete diagnosis of tumors that otherwise would have been found only later, temporarily increasing the apparent incidence rate. Yet even accounting for these factors, most analysts agree that there has been some modest but real increase in the true age-adjusted rate of new breast cancers in past decades. (Just this month, however, the National Cancer Institute reported that over the last five years,

overall incidence of breast cancer has no longer been rising.)

Breast cancer rates differ markedly among ethnic groups and among different regions of the world. Women who emigrate from regions with low breast cancer rates (e.g., Japan) to areas with higher rates (e.g., the United States) begin to take on the breast cancer rates of their new countries, with the effect being most pronounced in their daughters and granddaughters. This suggests that breast cancer rates are modifiable by some factors having to do with life-style, diet, or the environment. If these factors can be identified, the reasons for changes in breast cancer rates over time may become understandable. More importantly, new avenues of breast cancer prevention may be revealed, pointing to measures that we can take individually and collectively to try to reduce this major threat to women's health.

In this issue of **RISK IN PERSPECTIVE**, we summarize some results of our review of the published epidemiologic literature on risk factors for breast cancer. This review is aimed at identifying the list of factors that have been suggested, but also at examining the degree to which experts in the field have come to agreement about the nature, magnitude, and importance of the influence of the factor on breast cancer risk.

Established, Probable, and Possible Factors

Table 1 lists risk factors for breast cancer that have at least some level of support from epidemiologic studies. We have divided them into three categories showing our judgment about how well established they are, based on our review of the literature. *Established* factors are those that

have been generally recognized in the literature, with ample corroboration, little contradiction, and little dissent among experts. *Probable* factors are those for which more studies show the effect than do not, but the findings are not felt to be certain because of some contradictions or the inability to rule out with confidence alternative explanations. These are factors that most epidemiologists would agree have evidence that, while suggesting an effect, is not yet conclusive. *Possible* factors are those for which some positive results exist, but these findings have not generally been corroborated and significant questions remain about whether there is any effect. Most experts would judge these factors to be hypothetical. The three categories we have used represent degrees along a continuum, and the specific placements are the result of our judgments. We also wish to emphasize that the magnitude of the effects—how much each factor may alter breast cancer risks—is a separate judgment that is not addressed here. Also, we have not tried to name every risk factor studied, focusing on those that affect most women.

Established Factors

The first factor, *gender*, may seem surprising, but in fact men get breast cancer too, just at much lower rates (100-fold less) than women, reflecting their rudimentary amount of breast tissue. Hence, all subsequent discussion will refer to women only. *Age* is also a well known influence on risk; from small levels until about the age of 40, women's risks roughly double each decade until menopause and then increase somewhat more slowly, reaching a peak in the late 70's. More than 80% of U.S. breast cancers are detected after the age of 50.

Higher *socioeconomic status* is associated with greater risk, probably because of its association with other factors related to childbearing habits and physical activity. The magnitude varies among studies, but upper middle-class or highly educated women may have up to twice the age-specific risk of lower class or poorly educated ones. Similarly, *non-married* women have higher risks, probably due to childbearing differences.

Ethnicity has complex effects. Asian women have low rates, but Asian-American women have rates approaching those of other Americans. Among Americans, women of Ashkenazi Jewish descent have somewhat elevated risk, apparently because of a higher frequency of inherited abnormal breast cancer genes than in other populations. Young Black women have somewhat higher rates than do Whites, but after age 40 the pattern reverses. Since the rates are higher at later ages, the result is that White women have higher overall rates. Native Americans have particularly low rates, Hispanic women moderately low rates, and Native Hawaiians quite high rates. It is hard to judge how much of these patterns is due to

ethnicity *per se* and how much is due to the differences that these groups have in other risk factors.

Family history—breast cancer in near female relatives—is an important risk factor because it may indicate an inherited breast cancer gene variant in the family, and partially because family members are likely to share life-style features that may affect risk. (Only a few percent of breast cancers are explained by inheritance of faulty genes, however.)

It has been estimated that each 2-year delay in the *age at menarche* (first menstrual period) reduces breast cancer risk by about 10%. The average age at onset of menstruation has declined over the decades in developed countries, the average age in the U.S. having dropped about 4 months per decade for the last 120 years. This factor appears to explain a good deal of the international differences in breast cancer rates, and perhaps the rising incidence in the U.S. What has caused the progressive drop in age at first period is not completely clear, but most evidence points to better nutrition and less rigorous physical activity in young girls compared to previous decades.

Just as early onset of menstruation increases breast cancer risk, so does late cessation, i.e., *age at menopause*. One study has shown that for every 5-year delay of menopause, breast cancer risk increases 17%, but most of this increased risk occurs after age 65. It appears that the underlying effect is actually the overall number of menstrual cycles a woman experiences in her life, which increases with her early puberty or late menopause. During each cycle, hormonal changes cause some cells in the breast tissue to divide, and it appears that each such episode entails some small increased risk that one such cell may be transformed into the seed of a tumor. In fact, many of the risk factors for breast cancer can be understood in terms of their effects on the tendency of breast cells to divide and/or to differentiate (i.e., to undergo permanent biochemical changes leading to mature, functional cells that no longer divide).

Pregnancy and lactation promote breast cell differentiation, which tends to remove cells from the pool of those susceptible to carcinogenic transformation. Thus having *no children* increases breast cancer risk, as does having the first full-term pregnancy at a late age. Although detailed tradeoffs are hard to calculate, it seems that after about 35 years of age, the increased risk due to a late first child slightly outweighs the risk from having no children at all.

The ovaries cease production of estrogen at menopause, and increasing numbers of women are undergoing postmenopausal *estrogen replacement therapy* to ease menopausal symptoms. When continued for a long period (10 or more years) such therapy may have a variety of effects, some positive and some negative. A clear reduction in the risk of

