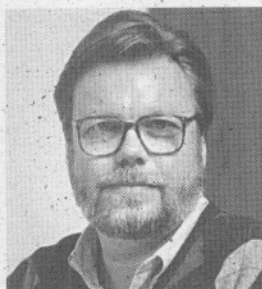




Risk in Perspective

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

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"...we...review...the published epidemiologic literature on risk factors for breast cancer...examining the degree to which experts in the field have come to agreement"

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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

Table 1.

Breast Cancer Risk Factors

Established (well agreed upon by field)	Probable (less well established)	Possible (suggested factors, but weak or inconsistent evidence)
Gender	No Breastfeeding	Dietary Factors
Age	Few Children	Smoking
Socioeconomic Status	Pregnancy at Late Age	Abortion
Never Married	Regular Menstrual Cycle	Electromagnetic Fields
Ethnicity	Current Use of Oral Contraceptives	Environmental Estrogens
Urban Residence	High Alcohol Consumption	Experience as Fetus
Family History	Sedentary Life-style	Multiple Birth Mother
Early Age at First Period		Low-Dose Radiation
Late Age at Menopause		Breast Implants
No Children		Aspirin Use (protective)
First Child at Late Age		
Long Use of Estrogen Replacement Therapy		
High-Dose Radiation		
Obesity		
Being Tall		

coronary heart disease and reduced osteoporosis are accompanied by some increase in breast cancer risk.

The only environmental agent among established risk factors for breast cancer is *high doses of ionizing radiation*. Risk is only well established for high doses, such as received in radiation therapy or certain defunct occupations. Ordinary diagnostic X-rays, mammograms, modern occupational exposures (such as those to radiologic technicians) and similar low doses are considered only a possible breast cancer risk, with most studies showing no effect or only a weak, questionable risk increase.

Obesity has a complex influence on breast cancer risk. Thin premenopausal women seem to have a somewhat higher risk than heavy women, but among postmenopausal women, obesity increases risk, and weight gain may exacerbate the effect. Interestingly, recent research has largely disproved the former hypothesis that high-fat diet in itself is a breast cancer risk factor. (There are other health benefits from avoiding a high-fat diet, however.) Also, *tall* women appear to be at somewhat increased breast cancer risk, for reasons that are not clear but may be related to childhood nutrition or general hormonal activity.

Probable Factors

We saw that having no children is an established breast cancer risk factor. Among women who do have children, it appears that having *fewer children* rather than more lessens the protective effect. Undergoing a full-term *pregnancy at a late age* may somewhat decrease

the protection afforded by earlier children, however. *Failure to breastfeed* infants may raise risks (although studies are somewhat inconsistent in findings), probably due to a lessening of differentiation of breast cells. These factors are basically elaborations of the main, established factors having to do with childbearing. Similarly, *short menstrual cycles*, and *regular* (as opposed to irregular) *menstrual cycles* appear to increase risk by adding to the lifetime number of cycles.

Oral contraceptives act by manipulating the monthly hormonal cycle, and they may prolong or enhance the monthly phase of stimulation of cell division in breast tissue. Because these are plausibly connected to breast cancer, the question has been intensively studied. The story is complex because the formulations of birth control pills, and the population of women who use them, have changed over the years. Many studies show a small (15-30%) increase in risk in women during *current use of oral contraceptives*, a risk that seems to disappear after cessation of use (within 5 years).

High alcohol consumption seems to cause a modest increase in breast cancer risk, but the amount of consumption associated with an increase is inconsistent among studies, although most suggestions are that effects begin to show for consumption of over 1-2 drinks/day. A *sedentary life-style* has also been associated with some increase in risk, perhaps acting through the effects of physical activity on metabolism, body weight, or (in the case of intense exercise regimens) on reducing menstrual cycling. Highly active girls may delay the onset of menstruation.

FURTHER READING

"Breast Cancer," special issue of *Epidemiology Review*, Vol. 15, No. 1, 1993. (edited by Jennifer L. Kelsey)

Hunter DJ, Hankinson SE, Laden F, Colditz GA, Manson JE, Willett WC, Speizer FE, Wolff MS. Plasma organochlorine levels and the risk of breast cancer. *New England Journal of Medicine*, Vol. 337, No. 18, pp. 1253-8, 1997 Oct 30.

Harvard Report on Cancer Prevention, Vol. 1: *Causes of Human Cancer*. Supplement issue of *Cancer Causes & Control*, Vol. 7, November 1996.

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Possible Factors

The list of possible risk factors is long (longer than shown in Table 1) because it can include any hypothesized factor, even ones with weak or equivocal evidence or evidence that has been contradicted. *Smoking*, which affects many kinds of cancer in addition to lung cancer, has generally been shown to have no effect on breast cancer. Although a few studies hint at some involvement, others seem to show small effects on endocrine physiology that would be slightly protective. *Abortion* as a risk factor has been a controversial hypothesis; most studies show no significant effect, but some see a pattern of positive (although statistically insignificant) tendencies, although it is difficult to collect reliable data, with breast cancer patients more readily admitting to past abortions than tumor-free women.

A notable item among the possible factors is exposure to environmental estrogens. These are environmental chemicals that are suspected of mimicking the body's own natural sex hormone molecules and disrupting their signaling function, perhaps affecting the risks of hormonally influenced developmental disorders and cancers such as breast cancer. A 1993 study by Mary Wolff and colleagues appeared to show higher blood concentrations of the pesticide DDT and its metabolic breakdown products (which at sufficient concentrations can act as estrogen mimics) in breast cancer patients than in matched control women. More recent, larger studies have failed to show any association. While the association of breast cancer risk with exposure to environmental chemicals remains much discussed, to date there is no body of evidence showing any consistent association of breast cancer with any such exposures or with body burdens of environmental contaminants.

Do Established Risk Factors Explain Incidence Trends?

The international differences in breast cancer rates, and the changing rates of migrants from areas of low risk to areas of high risk, suggest that some aspects of lifestyle, diet, or environmental exposure affect breast cancer risk. The increasing incidence in the U.S. over time (until recently) raises the question of what changing factors could be responsible. We cannot know the cause of every case of breast can-

cer, but we can examine known influences on risk and ask whether geographic and temporal changes in these factors are sufficient to explain the patterns observed.

Differences in established risk factors, especially in childbearing patterns, socioeconomic status, and differences in the age at onset of menstruation—factors that vary internationally and over time in the U.S.—can largely explain the patterns seen. The National Cancer Institute has proposed that 40% of U.S. breast cancer cases are attributable to three well established factors: women having no children or only having them later in their childbearing years, high income level, and having a family history of breast cancer. Regional differences in breast cancer rates across the U.S. largely disappear when variation in these factors is taken into account. The increasing incidence over the last decades seems likely to be due principally to changes in childbearing patterns, with more women having fewer children later in life, the rising standard of living, and the progressive decrease in the age at which girls reach puberty. This is not to say that other factors might not be at play, but hypotheses about the causes of contemporary changes in breast cancer rates must be evaluated in light of the concurrent effects of risk factors that are already well understood.

What Can a Woman Do to Reduce Her Risk?

Many of the factors that affect breast cancer risk are not easy or (like childbearing patterns and socioeconomic status) reasonable to modify as a way of modifying one's individual risk profile. Women can avoid gaining weight, especially in later years, maintain a program of physical activity throughout life, and avoid excessive alcohol consumption. A healthful, balanced diet low in animal fat and with lots of fruits and vegetables is beneficial for many reasons. (Avoiding smoking is important, even though it is not thought to have much effect on breast cancer risk—one should not forget that lung cancer has surpassed breast cancer as the leading cancer killer in women.) The improving statistics on breast cancer mortality in the U.S. are due to better detection and treatment, so obtaining mammograms on the recommended schedule is important.