Review

Models of Breast Cancer Show That Risk Is Set by Events of Early Life: Prevention Efforts Must Shift Focus

Graham A. Colditz and A. Lindsay Frazier

Channing Laboratory, Brigham and Women's Hospital [G. A. C.]; Harvard Medical School [G. A. C., A. L. F.]; and Center for Cancer Prevention, Harvard School of Public Health [G. A. C.]; and Pediatric Oncology, Dana-Farber Cancer Institute [A. L. F.], Boston, Massachusetts 02115

Abstract

We have recently published a mathematical model of the etiology of breast cancer based on the data from the Nurses Health Study that extends the Pike model of breast cancer (see Appendix). The most salient feature of the model is that it identifies the years before the first birth of a child as the most crucial in establishing future risk of breast cancer. The extended model includes several additional details of reproductive risk factors, allowing us to quantify the relative importance of the each of the reproductive risk factors and to estimate the effect of changes in key determinants of breast cancer. In this review, we present the evidence from both animal studies and epidemiological research that corroborate the critical importance of the exposures that occur before first birth. We argue that research and preventive interventions should now focus on youth. Population-wide prevention strategies are necessary because the inherited genetic risk for breast cancer accounts for no more than 10–15% of all breast cancer cases, leaving 85% of cases diagnosed among women who are not in this high-risk subgroup of the population. An example of a population-based intervention would be the promotion of increased physical activity among young girls that could result in the delay of menarche. An example of additional research that focuses on the importance of early life exposures would be an analysis of the relation between diet and other lifestyle factors during adolescence and the subsequent risk of breast cancer and studies of precursor lesions (atypical hyperplasia). Shifting the focus of breast cancer prevention to this age group is urgently needed.

Important Aspects of the NHS Extended Model of Breast Cancer

Key determinants of the risk of breast cancer for women are the timing of the reproductive events in her life: age at menarche, age at first birth, number of children, and age at menopause. The relation between reproductive risk factors have been synthesized into an hypothesized sequence for breast carcinogenesis by de Waard and Trichopoulos (1). The mathematical model of breast cancer published by Pike et al. (2) was based on the observed age-incidence curve and the known relations among age at menarche, first birth, and menopause; parity; and the risk of breast cancer. However, it did not include terms for the spacing of pregnancies, nor did it easily accommodate pregnancies after age 40 years. To analyze the importance of these events, we fitted an extension of the Pike et al. (2–4) model of breast cancer incidence to the Nurses’ Health Study data from follow-up of 1976 to 1988 (5; see Appendix).

When we fit the Pike model to an independent prospective data set (the prospective Nurses’ Health Study and added a term to summarize the spacing of births, we observed that closer spacing of births was significantly related to reduced risk of breast cancer. Another feature of our extended Pike et al. (2) model of breast cancer incidence is a term for an increase in risk associated with the first pregnancy. This term was significant only for the first pregnancy not for subsequent pregnancies (5). Thus, the breast is presumably protected against the effects of cell proliferation (and the high hormone levels) during second and subsequent pregnancies by the terminal differentiation that occurs during first pregnancy. The increase in risk with first pregnancy has been observed in a subsequent analysis of prospective data from Sweden (6) and analysis from an international case-control study (7).

Pike coined the phrase “breast tissue aging” to signify the effects of the different variables in his model in determining risk of breast cancer. In molecular terms, breast tissue aging is the accumulation of molecular damage in the pathway to breast cancer. In our extension of the Pike model, the time between menarche and first birth had the highest rate of breast tissue aging, consistent with our hypothesis that this time period was the time when the breast tissue was most vulnerable to mutagenesis. We also observed in our model that the increase in risk of breast cancer associated with first pregnancy is followed by a 20% decrease in the rate of breast tissue aging. This transient increase followed by a decrease in risk of breast cancer explains the “cross-over” effect seen in certain subgroups of women who initially a group has higher rates but, usually around the age of menopause, the rates drop below that of the other subgroup. For instance, using incidence data from New York state, Janerich and Hoff (8) showed a cross-over in breast cancer mortality between single and married women at age 42, such that married women had higher incidence than did unmarried women before this age and lower incidence of breast cancer mortality after this age. A similar cross-over of incidence has been reported between black and white women in the United States (9, 10), consistent with the distribution of age at first birth by race. Over many decades, black women in the United States have had higher rates of pregnancy and an earlier age at first birth than white women (11). Whereas others have argued that the cross-over effect is a result of differential exposure to carcinogens (10), the model predicts these patterns of incidence based solely on the reproductive variables.
Support from Animal Models of the Importance of the Prepregnancy Period to Risk of Breast Cancer

The susceptibility of the rat mammary gland to carcinogenesis is entirely dependent on the age of the rat and the corresponding stage of mammary gland development (12). In the rat, the mammary gland results from progressive branching of the main lactiferous duct. The bulbous ends of these branches are called TEBs. The TEBs are formed by day 21, which marks the beginning of menarche for the rodent. The TEBs are stimulated with each estrous cycle of the rat to divide and differentiate into ABs. Administration of a carcinogen during the time that TEBs are differentiating into ABs induces the greatest number of intraductal carcinomas. Once this process of differentiation has been completed, the incidence of tumors induced by the same dose of carcinogen decreases by >50%. The ABs coalesce into a collection called a lobule. During pregnancy, these lobules also undergo a massive amount of cell proliferation. The major morphological change is the sprouting of new ABs in each lobule. In the human, the mean number of alveolar buds per lobule is 11 before pregnancy, increasing to 80 AB/lobule by the end of pregnancy.

Each step in the progression from TEB to AB to virginal lobule to lactational lobule is accompanied by a lengthening of the average cell-cycling time. For instance, the length of the cell cycle of the TEB is 13 h; once the cell has differentiated into an AB, the cell cycle is prolonged to 34 h. The difference is due to longer time spent in G1. More time in G1 means more time for repair of DNA and less likelihood of propagation of transformed DNA. In the rat, the amount of repair can be measured by the removal of DNA adducts. TEBs remove fewer adducts than do ABs. The lack of adequate time for DNA repair is a biological explanation of the enhanced vulnerability of the TEB to carcinogenesis as compared to the AB or lobule.

Differentiation within the mammary gland is neither uniform nor synchronous. Even in the parous rat, it is possible to find TEBs that have not differentiated into ABs and lobules that have a low density of ABs comparable to the density found in the virginal breast. Each pregnancy "recruits" more of the remaining undifferentiated cells. In rats, administration of carcinogen immediately before pregnancy produces a high number of tumors; the presumption is that the short interval does not allow for adequate repair in the remaining undifferentiated cells that will undergo proliferation and differentiation due to the hormonal stimulus. However, administration of carcinogen after pregnancy and lactation induces very few tumors, presumably because of the protective effect of terminal differentiation. The implications for prevention are that the timing of the exposure is key to its carcinogenic potential. Furthermore, closer spacing of children may be protective because of decreasing the possible amount of time available for exposure to carcinogen before the proliferative effect of next pregnancy.

Irradiation and Breast Cancer. Girls who undergo irradiation of the chest at a young age have an increased risk of breast cancer. This observation has been replicated in a number of settings. Women who survived the atomic bomb in Hiroshima or Nagasaki, Japan, have an increased risk of breast cancer, dependent on both age and dose (13). Elevation in risk is seen with doses as low as 0.5 Gy. The excess relative risk increases with decreasing age; the excess relative risk was 5.3, 2.6, 1.2, 0.6, and 0.4, respectively, for women age 0–9, 10–19, 20–39, 40–49, and over 50 years at the time of the bombing. The dramatic relation of risk to age at exposure highlights the vulnerability of the developing breast to carcinogenic exposure.

Although risk of breast cancer among survivors of the atomic bomb is obviously the most extreme example of the relation between radiation and risk, several other examples of excessive radiation and increased risk of breast cancer have been documented. The recurring theme is that younger age at exposure confers greater risk of breast cancer. Girls with tuberculosis treated with repeated fluoroscopy, (14) girls diagnosed with Hodgkin’s disease treated at a young age with ionizing radiation (15), and infants with "enlarged" thymuses who underwent irradiation (16) all have an increased risk of breast cancer dependent on age at exposure.

These examples of the risk of breast cancer after radiation underscore unequivocally the importance of the age at which the exposure occurs. However, the amount of radiation in each case far exceeds the amount received by a normal individual during a lifetime. These examples, therefore, although illustrative, do not provide insight into preventive measures available at the population level.

Alcohol Consumption at an Early Age and Risk of Breast Cancer. Multiple studies have linked the consumption of alcohol to breast cancer (17). The risk shows a dose-response relationship. The Nurses’ Health Study has examined the effect of alcohol consumption among women who were otherwise without risk factors for the development of breast cancer (had a full-term pregnancy by age 26 years and no history of benign breast disease or family history of breast cancer). For women who drank 15 g of alcohol/day (>1 drink) the relative risk of breast disease or family history of breast cancer). For women who start to drink before age 25 years, had a relative risk of breast cancer of 1.8 (adjusted for reproductive history, family history, and age) compared to women whose first exposure to alcohol occurred after age 25 years (21). Hiatt et al. (22) used the alcohol data collected on 68,674 women during routine health care to study the 303 women who subsequently developed breast cancer. The women were asked to estimate the time in their lives when they drank "the most." Women who reported drinking the most before age 30 years had nearly twice the relative risk (2.6) when compared to women who reported drinking more in later periods of their lives (1.4). In a third case-control study, consumption between ages 18–35 years conferred a greater relative risk (RR = 2.2)

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Exposures during Adolescence and Early Adulthood Determine the Risk of Breast Cancer for Women

Age at the time of exposure has been shown to be pivotal in determining the subsequent risk of breast cancer. In studies linking breast cancer with irradiation, alcohol consumption, and cigarette smoking, the younger the age at exposure, the greater the risk.

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than drinking after age 35 years (RR = 1.8; Ref. 23). Obviously, these findings need to be corroborated, but the consistent implication that drinking at a young age adversely affects the risk of breast cancer warrants serious attention by those interested in prevention. If onset of drinking could be delayed, risk of breast cancer could potentially be markedly reduced. Additionally, if we could identify factors that counteracted the effect of alcohol (e.g., a high consumption of a certain vitamin), we might also be able to affect incidence. Only if there is recognition of the importance of this “window” of vulnerability before first pregnancy will these suggestions become part of the research agenda.

Smoking and Breast Cancer. Current smoking as an adult has not been related to the incidence of breast cancer in numerous studies. Most studies show either no association or, at most, a small increase in relative risk. However, several studies that have examined age at commencement of smoking have demonstrated an elevation in risk for early initiators. In three studies, the elevation in risk was modest (RR = 1.3; Refs. 24–26); however, in a fourth study, the association between early smoking and risk of breast cancer was more pronounced. Among women who were heavy smokers (>25 cigarettes/day), those who started to smoke before the age of 16 years had a 70–80% greater risk of breast cancer (odds ratios of 1.7 among cases in Canada and 1.8 among cases in the United States; Ref. 27).

Why Are Age at Menarche and Age at First Birth So Important in Determining Risk?

A plausible explanation for the effect of age at menarche and other reproductive risk factors is that genetic errors before first pregnancy are propagated by the proliferation of pregnancy and that the differentiation of breast duct cells during pregnancy and altered rates of cell turnover after the first pregnancy are, thereafter, protective against additional genetic insult. The time-dependent susceptibility of the breast to carcinogens and the impact of pregnancy on risk are consistent with this concept.

Implications for Prevention

From menarche to first birth, the log incidence of breast cancer increases at a rate of approximately 7%/year. The rate decreases after each birth except the first. With first birth, there is an increase in risk, followed by a decrease after 10 or more years. This adverse effect of first pregnancy is related to the delay between menarche and first birth, with an increase in log incidence of approximately 1.5%/year elapsed between menarche and first birth, a finding consistent with animal models of mammary carcinogenesis. The main effects of reproductive events are accumulated up to the age at menopause, whereupon the rate of increase in breast cancer drops to a significantly lower rate.

Options for prevention that offer the greatest potential to reduce the societal burden of breast cancer thus may focus on one of two approaches: (a) decreasing the period from menarche to first birth; or (b) preventing the accumulation of DNA damage during this interval, perhaps through dietary factors. The alternatives to dietary and lifestyle changes [i.e., manipulation of hormone levels to reduce cell division (28) or administration of human chorionic gonadotrophin or other hormones to induce differentiation of mammary epithelium (29)] do not appear to be acceptable to women or feasible at the population level. We emphasize population level interventions because 85% of breast cancer occurs among women without a strong genetic predisposition. Screening for carriers of the brca1 gene that predisposes to breast cancer will only identify 15% of women who will develop breast cancer (46). The cost of screening will be enormous; a conservative estimate of the cost of the test alone, not accounting for the requisite counseling, teaching, and treatment, put a price tag of $90 million on a program to screen all potential carriers (30). Technology at this price may not be affordable in the United States, much less in other less developed countries that are just beginning to witness the rise in incidence of breast cancer due to delayed childbearing and decreases in parity.

A reduced interval from menarche to first birth may be obtained either by delaying menarche or by reducing the age at first birth. Both of these events are strongly influenced by social factors. Age at menarche has decreased from an average of 16 years of age to <13 years of age over the past 130 years (31), a trend reflecting improved nutrition, decreased childhood infections, and decreased levels of physical activity during this century. Concurrent with this change, median age at first birth among white women has risen in the United States and other developed countries since the second World War from approximately 23 to 27 years of age. As age at first birth has risen, the average number of children has decreased (32).

In contrast, we note that China and many developing countries have birth rate estimates from 30 years ago (i.e., 1960 estimate) of 6.5 births/woman (33). Such a reproductive rate is not associated with late age at first birth. We also know that the average age at menarche in China was about 17 even through the 1960s (34). If we use the model to fit menarche at 16, age at first birth at 19, and 6 births spaced a year apart and hold age at menopause constant at 50 years, we estimate a rate of breast cancer for a 65-year-old Chinese woman that is 93.6/100,000 women. For the birth cohort of United States women born during 1921–1925, the median age at first birth was 23 years, with a mean of 3 children spaced 3 years apart (35). On the basis of these characteristics, and holding age at menopause at 50 years, we predict the rate of breast cancer for a 65-year-old United States woman to be 279/100,000 women, approximately three times the rate for Chinese women.

The importance of reproductive risk factors is emphasized by the ability of the model to describe a 3-fold difference between developed and developing countries. However, this is an underestimate of the true difference because we do not account for height in the model. Height is known to correlate with the international rates of breast cancer (36) and is a strong predictor of risk among postmenopausal women. Height has increased over the past century. Childhood nutrition and reduced frequency of childhood infections may play an important role in these secular changes.

Our model overpredicts rates for Chinese women by assuming a height comparable to that of United States women for whom the model was derived. However, the mean height of United States women is 10 cm greater than that of Chinese women. Prospective data from postmenopausal women in the Nurses’ Health study show that a 10-cm decrease in mean height is associated with a relative risk of 0.84 (with control for age at menarche, parity, and menopause). Therefore, we may expect that the rates for Chinese women should be reduced by some 15% or more to reflect the lower mean height. Such adjustment would give a relative rate of “Western” women to Chinese women of approximately 3.5 (279 per 100,000/79.6 per 100,000).

To prevent breast cancer in our postindustrial society, social forces must now be brought to bear on the structures and social norms that support the current incidence rates. Epidemi-
ological data indicate that increased physical activity among preadolescent and adolescent girls is associated with delay in onset of menses (37) and also may be related to reduced risk of premenopausal breast cancer (38). On a positive note, recent trends in the United Kingdom (39) and the United States (40) suggest a plateauing and a slight increase in the age at menarche, perhaps reflecting greater participation by girls in sports over the past 40 years.

We must now consider seriously the influences that determine age at menarche and explore options for interventions that will delay onset of menses. A 1-year increase in age at menarche would lead to a 9% decrease in a population-wide risk of breast cancer at age 70 years.

Alternatives to delay in age at menarche may include introduction of dietary factors such as antioxidants and folate that would protect the breast against accumulation of molecular damage during the interval of high cell turnover between menarche and first birth. Factors, such as vitamin A, that appear protective in older age (Ref. 40; perhaps by promoting tumor differentiation) may also help at this younger age. Alternatively, folate, which protects against hypomethylation of DNA and is important in the pathway to colon cancer (41), may also protect the mammary glands during cell replication. However, data to address this protective role of diet are not currently available, and retrospective recall of adolescent dietary habits in a case-control study would greatly increase the risk of recall bias (42). Perhaps prospective studies could use atypical hyperplasia as an outcome measure for evidence that diet and other lifestyle factors inhibit the initiation of carcinogenesis. Research must postulate or identify other dietary factors that may protect the breast at this time of greatest vulnerability.

The age of initiation of smoking and alcohol consumption may play a key role in breast carcinogenesis if indeed adolescent exposures are the key determinants of risk. Interventions that delay uptake of these behaviors could greatly reduce risk of breast cancer (and many other diseases). Interestingly, because smoking lowers blood levels of antioxidants (43), an association between cigarette smoking and risk of breast cancer (and many other diseases). Interestingly, because smoking lowers blood levels of antioxidants (43), an association between cigarette smoking and risk of breast cancer may indirectly support the role of dietary interventions in this age group.

Our postindustrial Western society has evolved such that the political economy of health now measures breast cancer as a major social burden. A high proportion of women work in full-time jobs and many delay childbirth while pursuing professional education. To effect prevention at a population level, we require three key components: (a) a scientific basis for the intervention; (b) the political will; and (c) a social strategy (44). Research on the etiology and prevention of breast cancer is urgently needed to refine our understanding of childhood and adolescent exposures. These exposures, the most important in terms of lifetime breast cancer risk, are the least well described.

Although a growing level of political will to address the primary prevention of breast cancer is in place and the knowledge of the etiology is well advanced, social strategies have not yet been developed and tested. As the scientific base of understanding of childhood and adolescent exposures grows, we must explore the options that suggest new interventions. Earlier childbearing cannot be advocated without changes in the social and economic policies that will delay onset of menses. A 1-year increase in age at menarche would lead to a 9% decrease in a population-wide risk of breast cancer at age 70 years.

Other interventions may focus on increasing physical activity during childhood to delay menarche or reducing alcohol intake and smoking uptake among adolescents and young adults. Only with a focused effort will we move toward the prevention of breast cancer in Western society. This must be our highest priority in breast cancer prevention research.

Appendix

Revised model of breast cancer incidence for multiple births (5).

\[ \text{In (incidence)} = a + b_1(t_m - t_0) + b_4(t - t_m) + b_17\sum(t - ti)b \]
\[ + b_6(t_i - t_0) + b_19\sum(t - ti)(t - t_0)m \]

where \( t_0 \) = age at menarche, \( t_i = \text{age at first birth}, t_0 = \text{age at ith birth}, t_m = \text{age at menopause}, t = \text{current age}, \text{and } m = 1 \) if postmenopausal and 0 if premenopausal.

Values for the model are: \( a = -8.7911; b_1 = 0.0723; b_4 = 0.0425; b_6 = 0.015468; b_17 = -0.003033; \) and \( b_19 = -0.00031435 \).

References

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