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GUEST EDITORIAL

A model for breast cancer risk based on stem-cell theory

A Countercurrents Series[a] with S.A. Narod MD

Recent studies of cells in culture and of mice models support the notion that the mammary stem cell is a precursor to the breast cancer cell [1–4]. Those observations prompt an examination of beliefs about the causes of breast cancer and a consideration of novel avenues for prevention.

The conventional model integrates genes and the environment. In the conventional model, a cancer cell accumulates, through inheritance or somatic mutation over multiple cell divisions, a number of critical gene mutations (and passenger mutations), leading to a dominant clone of cells with a competitive growth advantage that eventually acquire the other hallmarks of malignancy such as independent growth, invasiveness, and metastatic potential. Environmental factors that damage DNA increase the mutation rate, thereby increasing the incidence of cancer. In support of this conventional model, some authors have proposed that estrogens act as mutagens through catechol intermediates [5]. But several long-standing observations are not easily explained:

- Menarche at age 11 influences the risk of breast cancer at age 50 [6].
- There appears be no association between smoking and breast cancer despite the delivery of ample doses of carcinogens to the breast [7] (and researchers have been unable to identify other environmental carcinogens).
- The risk ratio for contralateral breast cancer in young women with breast cancer is very high (for example, about 25 in those who develop the disease at age 30), which is far too high to be explained by genes or the environment [8]. And there is a surprising degree of histologic concordance for bilateral cancers [9].
- Hormone replacement therapy (HRT) increases breast cancer risk slowly over many years, but the risk disappears within 2 years of cessation [10,11].

Among the intrinsic risk factors for breast cancer, perhaps the most interesting are age of menarche and breastfeeding. Reducing the age of menarche by 1 year, say from age 11 to age 10, increases the annual risk of breast cancer in a 40-year old woman by about 10% for the next 10 years [6]. How is this gap of 30 years from exposure to impact bridged? It is insufficient merely to say that early menarche acts by increasing lifetime exposure to estrogen without accounting for the prolonged latent period. Each year of breastfeeding decreases the risk of breast cancer by about 4% [12]. Given that the average woman ovulates for about 40 years, the degree of protection for both risk factors is greater than would be expected if the effects of late menarche and breastfeeding operated through a proportionate reduction in the number of ovulatory cycles.

I know of only 3 bona fide environmental breast carcinogens: ionizing radiation [13], HRT [10,11], and alcohol [14]. Of those three, only radiation is clearly mutagenic, and the period of highest sensitivity is between menarche and age 18. There is much less evidence that exposure to radiation or other potential environmental carcinogens after age 18 affects breast cancer risk. Exposure to HRT increases the risk of breast cancer in a dose-dependent way, and at any age, the relative risk is proportional to the past duration of exposure. After cessation, the risk dissipates within 2 years [10]. It is not known if the effect of alcohol dissipates rapidly after cessation.

Perhaps basic science and epidemiology can be integrated into an updated model based on evolving stem-cell theory. The hypothetical risk model proposed here is based on two relevant cell populations: mammary stem cells and cancer cells. The cancer cell comes about through mutation of the mammary stem cell (or an intermediate progenitor cell). In this model, risk factors can be divided into three types:

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1. Those that increase or decrease the pool of mammary stem cells.
2. Those that influence the mutation rate (passage from stem cell to cancer cell).
3. Those that influence the growth of established cancers.

Consider a theoretical and dynamic population of mammary stem cells with the following properties: the size of mammary stem-cell pool remains very small until menarche. The pool then expands continuously from menarche until age 18 (that is, the time at which breast development stops). In the nulliparous woman, the stem-cell pool remains constant until menopause through slow cell division. Episodes of breast-feeding differentiate a proportion of the stem cells and thereby deplete the pool. After menopause, the size of the stem-cell pool steadily declines. Assume further that the breast cancer risk is proportionate to the size of the stem cell pool. It then follows that a factor that increases the size of the pool increases the breast cancer risk, and that a factor that decreases the size of the pool decreases the risk.

Under this model, the size of the stem-cell pool at the end of breast development would depend on the age of menarche. Breast cancer risk later in life would be proportionate to the time elapsed from menarche to age 18. The breast cancer risk would be more or less set at age 18, but would be decreased by episodes of breastfeeding. Hormone replacement therapy—in particular progesterone—maintains the size of the stem-cell pool by abrogating the natural decline associated with menopause. The relative increase in the breast cancer risk associated with HRT reflects the difference in stem-cell numbers in women who do and do not take HRT, and with increasing time on HRT, the absolute difference increases. The acute effect on breast cancer risk of the removal of HRT is likely primarily a result of the removal of a source of estrogen for an estrogen-dependent tumour—that is, HRT is a type 3 risk factor among the types as earlier described.

It is reasonable to suppose that the numbers of stem cells in the two breasts of a given women at age 18 are similar. If risk is proportionate to the size of the stem-cell pool, it follows that the breast of a 30-year-old with breast cancer has more stem cells than the breast of the average woman. We expect that the number of stem cells in the two breasts at age 18 are similar, and therefore, a contralateral breast would, by virtue of a high number of stem cells, be at elevated risk. To explain the high degree of histologic concordance between bilateral cancers, recent findings suggesting that there are at least two kinds of breast stem cells (which might be precursors of different classes of breast cancer) might be relevant [4].

In the early stages of breast cancer, progesterone is probably more important than estrogen because the progesterone signal is central to stem-cell proliferation [15]. But once a tumour is established, estrogen becomes critical in maintaining the growth of cancers positive for the estrogen receptor [11]. Cancers may grow or regress under the stimulus or withdrawal of estrogen. It could be assumed that the mutation rate is fixed, that mutations arise through a stochastic process, and that the mutation rate is influenced by the environment to only a small extent. The notable exception is early irradiation of the expanding stem-cell pool. Also, some women may have intrinsically high mutation rates because of inherited genes that affect DNA repair. For example, mutations in *BRCA1* may increase the somatic mutation rate [16]. Foulkes suggests that *BRCA1* mutations may also shift the balance of stem cells from one pool to another [17].

The foregoing proposed model has several limitations. First, it is possible to estimate the age of onset of breast development more or less based on the age of menarche, but no biomarker or questionnaire item can be used to determine the end of breast development, and for simplicity, age 18 is chosen here. If women with delayed menarche have a commensurate prolonged period of breast development, then the model is weakened. Breast cancer is very rare in a woman's 20s, but this scarcity of cases might be a result of the time needed to acquire sufficient mutations. Furthermore, the breast stem-cell population expands during pregnancy [4], but parity protects against breast cancer [12]. Also, the model predicts that breast cancer risk declines or remains steady after menopause. That prediction holds true for much of the developing world, but not for Canada or the United States. However, late-emerging cancers might reflect the long latent period associated with the slow growth of an estrogen-receptor positive breast cancer. On a log–log curve, the increase in the incidence of breast cancer with age declines dramatically after menopause [18]. Also, the model is simplistic in that it assumes a single step from a breast stem cell to a breast cancer cell. The transition undoubtedly takes place through a number of steps and may involve intermediate progenitor cells and cancer stem cells. Also, I have not included exposures *in utero,* as was suggested years ago by Trichopoulos and colleagues [19,20] and as has been supported by recent findings about the effect of diethylstilbestrol in pregnancy [21].

The stem-cell model is difficult to test. In humans, such testing would not only require a valid and sensitive assay for quantifying minute numbers of stem cells, but would also depend on the accrual of a sufficient number of compliant women who are willing to participate in biopsy-based research. Much of the success achieved in gene-based studies rests on the fact that most researchers have very good access to blood (for the study of inherited mutations) and fairly good access to tumour tissue (to study somatic mutations). Specimens of normal breast tissue are not

easy to come by. The genetic theory of breast cancer has perhaps become dominant because of the availability of inexpensive and accurate technologies that allow for the reliable documentation of mutations.

What are the implications of the stem-cell model?

First, environmental carcinogens would likely contribute little to the burden of breast cancer, and the relevant ones would act in adolescence. The mutations that are acquired in stem cells that lead them to become cancer cells could be acquired stochastically—that is, at a fixed rate per mitosis. The mutation rates would be proportional to the number of dividing cells. There would be no need to invoke a growth advantage for cells with mutations if they occurred in a stem cell, because the mutant cell population would expand along with the parent clone. The stem-cell population is both dynamic and influenced by external factors.

The ideal preventive drug would be one that depletes the stem-cell population permanently. A short course of the ideal drug would have the potential to offer long-term protection against breast cancer. Candidate drugs include aromatase inhibitor [2], tamoxifen [22], or denosumab [which blocks the progeseterone/RANKL (receptor activator of nuclear factor κB ligand) pathway [15]]. Compared with identifying and eliminating elusive carcinogens, developing and researching this type of drug is more likely to be productive.

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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