Early-onset breast cancer: what do we know about the risk factors?

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

If a woman develops invasive breast cancer in the left breast at age 30, the probability of her developing breast cancer in the right breast by age 40 is about 5% (0.5% per year) [1]. The risk of primary breast cancer rises monotonically with age, but the risk of contralateral breast cancer decreases throughout life. The cumulative risk of breast cancer to age 40 in Canada is only about 1 in 250 (1 in 500 for the right breast and 1 in 500 for the left breast) [2]. If the two rates are compared, the result is a relative risk of 25 for breast cancer before age 40, given a prior instance of breast cancer. That risk is similar in magnitude to the risk of breast cancer attributable to a mutation in *BRCA1, BRCA2,* or *TP53*. The only other risk factor of similar size is probably that for mantle cell lymphoma secondary to radiation for Hodgkin disease in adolescence [3].

How can such a high relative risk of contralateral breast cancer be explained?

Conventional explanations are not helpful. Some authors have proposed that a common toxic environment, a disrupted internal hormonal milieu, or genetic susceptibility is at fault [4]. But no known environmental risk factors for breast cancer can explain a risk ratio anything close to this. To date, studies of occupation, diet, and environmental contamination have led to few insights about breast cancer—and it is unlikely that a risk factor of this magnitude would go unnoticed.

Hormones don't qualify either: Variation in any or all of the known reproductive and nonreproductive hormones predict premenopausal breast cancer only to a very small extent. The same goes for oral contraceptives and for hormone replacement therapy.

What about genes? It is true that mutations in *BRCA1* and *BRCA2* are associated with very high risks of contralateral breast cancer [5], but that association 0accounts for only a fraction of early-onset breast cancer cases [6], and mutations in other highly penetrant genes are even rarer. Moreover, single-nucleotide polymorphisms in low-penetrance genes, although abundant and much in the public eye, cannot arrange themselves in a way to generate a relative risk of 25.

There is another piece of the puzzle to align. Contralateral breast cancers tend to resemble each other [4,7]. Studies to date on contralateral breast cancer have included only a few markers (such as grade, stage, and histology subtype), but even with those few markers, it is clear that the degree of concordance is greater than might be expected by chance. For example, in a study by Huo and colleagues [4], a very strong association in estrogen receptor status was noted in synchronous breast tumors (odds ratio: 26). Our group also previously demonstrated a similar association in bilateral breast cancer in women with a *BRCA* mutation [7]. But these tumours are also often enough discordant to rule out the possibility that most second cancers are metastases. Any explanation of cause must take into account this degree of similarity.

And so it seems likely that some women have breasts that are prone to cancer for reasons unknown. And that a given woman is prone to develop one subtype over another. Mammographic density gives us a clue: It is a host risk factor both for primary breast cancer [8] and for breast cancer recurrence [9]—and it reflects the composition of normal breast tissue. That observation suggests that, as proposed by Finak *et al.* [10], certain stromal proteins, when overexpressed, help to account for primary breast cancer. The same group also identified a stromal gene expression signature that predicted outcome in breast cancer patients independent of features related to the tumour itself [11].

The tendency for a breast to develop a cancer may reflect on the relative abundance of its various cellular components or cancer precursors, either because the population of normal stem cells is large or because some replicating cells have started down the pathway to cancer. Perhaps both breasts become overpopulated

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with high-risk cells at the first stages of development (and if so, then breast cancer might share other features with other developmental diseases). Or else a systemic factor acting later in life causes the proportions of precursor cells to expand simultaneously.

Studies by Joshi *et al.* [12] and by Asselin–Labat *et al.* [13] in manipulating breast stem-cell populations with progestogens and other hormonal factors are interesting in this regard. Schramek and colleagues suggest that the osteoclast differentiation factor RANKL (receptor activator of nuclear factor κB ligand) may be the intermediary between progesterone exposure and the breast stem cell population [14]. Identification of the relevant cell types and the factors that account for their rise and fall may open avenues for chemoprevention.

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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Correspondence to: Steven A. Narod, Women's College Research Institute, Women's College Hospital and the Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario M5G 1N8. ***E-mail:*** steven.narod@wchospital.ca