Lobular Involution: the Physiological Prevention of Breast Cancer

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It truly is a remarkable event when traditional pathologic observations lead to new ideas about the prevention of cancer. In this issue of the Journal, Milanese et al. (1), through a histologic review of breast biopsy specimens, show that the extent of age-related lobular involution is strongly associated with a reduced risk of breast cancer. Breast cancer risk decreased with increasing extent of involution in both high-risk and low-risk subgroups defined by age, epithelial atypia, reproductive history, and family history of breast cancer.

Beginning in the premenopausal period, lobular involution is a physiologic process that occurs over many years whereby the parenchymal elements in the breast progressively atrophy and disappear (2,3). The study reported by Milanese et al. represents a unique application of the Mayo Benign Breast Disease Cohort to investigate prospectively involution as a risk factor for breast cancer. It is the first study, to our knowledge, to substantiate a hypothesis that is based on pathologic and epidemiologic considerations that delayed involution is a major risk factor for breast cancer (4,5).

As for an explanation of the effect of lobular involution on breast cancer risk, it has been suggested that a reduction in mammary gland tissue that results from involution should lead to a reduction in breast cancer because a progressively smaller amount of epithelial tissue is available for malignant transformation (1,5). The result of involution, therefore, can be considered physiologically analogous to a partial prophylactic mastectomy, with a corresponding reduction in breast cancer risk.

Although a reduction in mammary tissue is a plausible explanation, the underlying issue is one of aging or, more precisely, the failure of breast tissue to age normally. The aging process in the breast is under control of various hormones and does not follow the pattern seen in other organs or tissues. Pathologists have long commented on the possibility that persistent atypical lobules might be precursors of invasive breast cancer (6,7). It seems paradoxical that an organ that normally undergoes complete or near complete physiologic atrophy would be a site in which cancer rates steadily increase with age. The continuing increase in breast cancer risk with age is likely associated with the persistence of glandular epithelium beyond the time of normal involution, reflecting an abnormal delay of the aging process in the breast (4,5)

Except for morphologic observations concerning age of onset and progression with age, practically nothing is known about the process of involution. Even less is known about factors that control involution or that delay or accelerate the process. In this context, it is unknown whether the rate of involution is genetically determined and whether known breast cancer risk or environmental factors alter the rate of involution.

Evidence indicates that some risk factors for breast cancer may interfere or affect the process of involution. In the Mayo study, women with benign proliferative breast disease were substantially less likely to have complete involution than were women with benign nonproliferative disease, and women with a strong family history of breast cancer had slightly less advanced involution than women without such history (1). Late age of menopause, which increases the risk of breast cancer, is likely to result in delayed involution because of persistence of estrogen activity (8). Women whose first full-term pregnancy occurs after age 35 years have an elevated risk for breast cancer compared with nulliparous women or with women whose first pregnancy was at a much younger age (9,10). After the commencement of involution, late pregnancy with its concomitant increase in the proliferation of the ductal–alveolar epithelium is likely to interrupt the normal process of involution, which typically begins between 30 and 40 years of age. Oophorectomy, which protects against breast cancer (11), leads to the same type of atrophy of breast parenchyma in young women as that seen in older women (12). The reduction in risk may be due to the acceleration of involution induced by oophorectomy.

One of the most striking findings in the study of Milanese et al., however, is the degree to which the strong association between extent of involution and breast cancer risk was independent of all known breast cancer risk factors that were investigated (1). This observation suggests that factors unrelated to known risk factors are responsible for the protective effect of involution. For this reason, a greater understanding of the biologic basis for involution will be required to elucidate the mechanisms of the protective effect of lobular involution on breast cancer risk.

The observations reported by the Mayo group may find practical applications for risk prediction (1). It may be useful for pathologists to report the extent of involution in addition to any epithelial changes found in breast biopsy specimens that do not contain cancer. It will be important to determine the extent to which mammographic breast density serves as a surrogate for the extent of involution. By taking extent of involution into account, it should be possible to increase the predictive ability of breast cancer risk models.

Results of the Mayo study provide a new paradigm for breast cancer research and prevention. Age has always seemed the opponent because of the increasing risk of breast cancer with age,
but age may now become an ally. The challenge will be to unravel the natural history of involution and the normal process of aging in the breast. Eventually, involution could become a useful surrogate endpoint for research in breast cancer prevention. A possible approach to prevention may be to develop strategies that achieve complete involution as early as possible after childbearing is completed.

REFERENCES


NOTE

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