According to Milanese et al. (1), there is an inverse association between lobular involution and parity. Although the persistence of lobular structures caused by subsequent pregnancies could be associated with increased risk of breast cancer, multiparity is generally associated with a reduced risk of breast cancer. The authors hypothesized that “the breast cancer risk modification associated with parity is independent of involution status” (1).

In postlactational involution, the mammary gland regresses to its prepregnant state—fibroblasts secrete proteases that degrade the extracellular matrix proteins, with the consequent release of bioactive matrix fragments that can promote tumor growth, motility, and invasion (2). In contrast, the molecular mechanism of age-related involution has not been characterized by detailed microarray-based surveys. In the study by Milanese et al., the degree of involution for each specimen was categorized by histologic findings according to the extent of lobular involution in the background breast.

A possible biologic mechanism through which failure to undergo involution could influence a patient’s breast cancer risk is that stem cells or early progenitors (i.e., the prime targets of intrinsic and/or extrinsic mutagenic stresses) may become quiescent (3). The lobules found in the breast of postmenopausal women, who had an early full-term pregnancy, appear to be composed of epithelial cells that are refractory to transformation (i.e., stem cells or early progenitors) (4). This refractoriness has been associated with the absence of a proliferative response in the parous epithelium when confronted with the carcinogen, compared with the nulliparous gland (5). Parity-induced epithelial cells are pluripotent, committed to secretory cell fate, contribute to the development of secretory lobules after successive pregnancies, and can self-renew over multiple transplant generations (6).

A reduction in the reproductive life span of these multipotent mammary epithelial stem cells in situ results in a statistically significant association with reduced susceptibility to mouse mammary tumor virus–induced mammary tumorigenesis (5). Expression of activated transforming growth factor β1 by the parity-induced epithelial cells during pregnancy or tissue remodeling in the absence of lactation severely curtails the self-renewing activity of these cells in transplants but not their capacity to proliferate and produce epithelial progeny with diverse fates in the mammary epithelium of multiparous female mice when left in situ (6).

We think that the involution status could be, in part, dependent of parity because, after successive pregnancies, stem and/or progenitor cells accumulate in the mammary glands of multiparous female mice (6). The risk of carcinogenesis in mammary glands might be associated with transformation of these cells by deregulation of self-renewal pathways. In transplants from triple transgenic multiparous female mice, whey acidic protein promoter–transforming growth factor β1–positive parity-induced epithelial cells cannot proliferate expansively or self-renew. Finally, because full-term pregnancies after age 35 years are associated with an increased risk of breast cancer (7), we agree with Milanese et al. that further data on a woman’s age at each pregnancy would be helpful in more precisely evaluating the relationships of parity, involution, and breast cancer risk.

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FRANCESCO COGNETTI
Response

We appreciate the interest of Ferretti et al. in the complex arena of age-related lobular involution, parity, and breast cancer risk. In our cohort of women with benign breast disease, we found that pregnancies were associated with persistence of lobular structures. In the cohort overall, persistence of lobules (i.e., no involution) was associated with an increased risk of breast cancer. We concluded that “breast cancer risk modification associated with parity is independent of involution status.” We realize that our definition of involution is a histologic one. Ferretti et al. rightly point out that protection from breast cancer may also be conferred at the cellular or molecular level and may not be registered histologically as involution. And we certainly concur.

In Table 1, we provide data regarding the effect of involution in parous women in our cohort specifically. We observed a stepwise reduction in risk of breast cancer with progressive degrees of involution. Thus, even in breast tissue from parous women, which is already at reduced risk of breast cancer, completing the process of involution appears to be associated with further risk reduction.

The mechanism(s) by which pregnancy exerts a protective effect on breast tissue remains unknown (1–3). The most widely cited explanation is that parity induces terminal differentiation of stem cells and/or early progenitors in the mammary gland, rendering them resistant to transforming stimuli (4). However, this hypothesis is based on chemically induced rodent models of mammary cancer. Not all subscribe to this model (1), and it has not been studied in humans. Interestingly, transgenic rodent models that express oncogenes driven by hormone-responsive promoters develop pregnancy-induced mammary cancers (5). Clinical data show that, although pregnancy is associated with a lower lifetime risk of breast cancer, it is associated with an increased risk during pregnancy and for the next several years (6). These trends also vary by age(s) at pregnancy and the interval between pregnancies. We certainly concur with Ferretti et al. that the intersection of parity and age-related involution in humans provides fertile ground for new ideas in risk reduction.

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TIA R. MILANESE
CELINÉ M. VACHON
ROBERT A. VIERKANT

Table 1. Parity, lobular involution, and risk of breast cancer*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of women</th>
<th>No. of person-years</th>
<th>No. of observed events</th>
<th>No. of expected events</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All parous women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of involution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>893</td>
<td>19200</td>
<td>94</td>
<td>48.2</td>
<td>1.95 (1.57 to 2.38)</td>
</tr>
<tr>
<td>Partial</td>
<td>2780</td>
<td>52014</td>
<td>227</td>
<td>174.6</td>
<td>1.30 (1.14 to 1.48)</td>
</tr>
<tr>
<td>Complete</td>
<td>836</td>
<td>13584</td>
<td>36</td>
<td>57.4</td>
<td>0.62 (0.44 to 0.87)</td>
</tr>
</tbody>
</table>

* Analyses accounted for the effects of age and calendar period.

References


Notes

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Response

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