Breast Cancer RESEARCH

VIEWPOINT

# Pregnancy offers new insights into mechanisms of breast cancer risk and resistance

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**Abstract**

Pregnancy induces long-lasting changes in gene expression that are associated with a reduction in breast cancer risk. Although several mechanisms have been proposed to mediate the reduction in breast cancer risk among parous women, recent studies focus attention on progenitor cells as major targets. The results suggest new biomarkers that may improve risk prediction and provide endpoints for assessment of clinical responses to prophylactic therapies.

## Viewpoint

An increased prevalence of breast cancer among Roman Catholic nuns in Italy was observed in the 1600 s, providing early links between reproductive factors and breast cancer risk. Epidemiological studies in the 1970s identified pregnancy as a key factor in reducing the risk of breast cancer. This was evident in a variety of species and reproduced in rodent experiments. This is not a simple relationship, because the incidence of breast cancer is increased transiently during the period immediately after pregnancy in women [1], but the overall effect is that lifetime risk is reduced by up to 50% [2]. Furthermore, the protective mechanisms are robust, rendering the breast epithelium resistant to the carcinogenic effects of ionizing radiation [3] and alkylating agents [4].

Studies in rodents suggest four mechanisms to explain the protection afforded by pregnancy: (a) systemic changes in endocrine factors [5], (b) differentiation of the mammary epithelium- and stroma-reducing proliferative responses [5], (c) sensitization of pro-apoptotic pathways, especially those mediated by p53 [6,7], and (d) restriction of the progenitor cell population [8]. Transcriptional profiling of mammary tissues revealed stable changes in parous rodents [9]. However, genome-wide transcriptional profiling experiments using human breast tissues containing both epithelial and stromal components yielded variable results. Host factors such as age, obesity, and genetic diversity greatly influence gene expression patterns [10,11] and may obscure changes in the pathway subset that are responsible for the protective effects of parity. Alternatively, the mechanisms in women may differ from those in mice.

A new study by Choudhury and colleagues [12] addressed this complexity by examining gene expression profiles in subsets of breast epithelium representing luminal ($CD24^+$), myoepithelial ($CD24^{low}/CD10^+$), and progenitor ($CD24^{low}/CD10^{low}/CD44^+$) cells and stromal fibroblasts. Among these cell populations, parity had the greatest effect on gene expression patterns in the $CD44^+$ progenitors. The persistent effects of parity were paralleled by changes in DNA methylation, suggesting an epigenetic mechanism. The effect of parity was surprisingly robust given the limited number and diversity of patients (three nulliparous and three parous, the latter including both an African-American and a Caucasian). These results mirror experiments in mice in the lab of Meier-Abt and colleagues [13], who found that gene expression patterns altered most dramatically in the mammary stem cell population. This was corroborated by functional testing of the progenitor activity *in vitro* and by transplantation *in vivo*. Therefore, restriction of the progenitor cell population is a common effect of pregnancy in both mice and women.

The association between breast cancer risk and stem cells has been more difficult to demonstrate. Choudhury and colleagues [12] compared expression profiles of $CD44^+$ progenitor cells from high-risk individuals who were carriers of mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2* and found patterns to be most similar to nulliparous women regardless of parity. This suggests that parity is less protective in these

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individuals. However, epidemiological studies have been divided on this point, and the majority of recent studies demonstrated a reduction in risk among parous *BRCA1/2* carriers which was similar to that of the general population [14]. The apparent discrepancy may be due to disruptions in cell lineages in the high-risk patients. Using cell sorting, Lim and colleagues [15] found that the breast stem cell population was reduced among the 10 *BRCA1* patients analyzed compared with the 30 normal controls. However, the progenitor population committed to the luminal epithelial lineage was increased [15]. Subsequent experiments demonstrated that the hormone receptor-negative luminal progenitors are the 'cells of origin' for breast cancers in *BRCA1* patients [15,16]. Therefore, alterations in cell lineages in *BRCA1/2* mutation carriers may contribute to the clustering observed by Choudhury and colleagues. As parity has been suggested to engage multiple pathways, it is likely that there are compensatory pathways that confer protection even when the equilibrium of the cell lineages is disrupted.

The broader goal is to develop biomarkers that identify individuals who are at elevated risk and that guide selection of prophylactic therapies. The decrease in cells expressing nuclear p27 (encoded by *CDKN2a*) among parous women, especially the decrease in hormone-responsive cells that are positive for both p27 and estrogen receptor-alpha ($p27^+/ER^+$), is intriguing [12]. The results suggest that quiescent 'hormone-sensing' cells are biomarkers of progenitor cell dynamics. The role of the $ER^+$ cells in sensing hormone exposures and regulating progenitor cells was also observed in mice [13]. In these studies, pregnancy reduced secretion of Wnt4, which limited the population of progenitor cells. Both decreases in Wnt signaling and increases in apoptosis were among the pathways altered significantly among $CD44^+$ cells from parous women [12].

These data reveal biomarkers of progenitor cell dynamics that can be applied to assess breast cancer risk and provide surrogate endpoints in trials assessing efficacy of chemopreventive therapies designed to restrain progenitor populations. Selective stimulation of the hormone-sensing cells to restrict Wnt expression or enhance expression of Wnt antagonists, such as secreted frizzled-related proteins, offers novel targets for chemoprevention.

#### Abbreviation
ER: Estrogen receptor.

#### Competing interests
The authors declare that they have no competing interests.

#### Authors' contributions
DJJ and KAD provided content related to the overall effects of parity. GM-J provided clinical perspectives especially related to the effects of pregnancy in *BRCA1/2* patients. GMC evaluated the histopathology and potential for clinical impact. Funding related to this topic was provided by the National Cancer Institute (R01ES015739 to DJJ) and the Avon Foundation (02-2009-011 and 02-2011-028 to DJJ, GM-J, and GMC). All authors read and approved the final manuscript.

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Published: 24 Sep 2013

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10.1186/bcr3482
**Cite this article as:** Jerry *et al.*: Pregnancy offers new insights into mechanisms of breast cancer risk and resistance. *Breast Cancer Research* 2013, 15:312