

Postpartum Involution and Cancer: An Opportunity for Targeted Breast Cancer Prevention and Treatments?

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ABSTRACT

Childbirth at any age confers a transient increased risk for breast cancer in the first decade postpartum and this window of adverse effect extends over two decades in women with late-age first childbirth (>35 years of age). Crossover to the protective effect of pregnancy is dependent on age at first pregnancy, with young mothers receiving the most benefit. Furthermore, breast cancer diagnosis during the 5- to 10-year postpartum window associates with high risk for subsequent metastatic disease. Notably, lactation has been shown to be protective against breast cancer incidence overall, with varying degrees of protection by race, multiparity, and lifetime duration of lactation. An effect for lactation on breast cancer outcome after diagnosis has not been described. We discuss the

most recent data and mechanistic insights underlying these epidemiologic findings. Postpartum involution of the breast has been identified as a key mediator of the increased risk for metastasis in women diagnosed within 5–10 years of a completed pregnancy. During breast involution, immune avoidance, increased lymphatic network, extracellular matrix remodeling, and increased seeding to the liver and lymph node work as interconnected pathways, leading to the adverse effect of a postpartum diagnosis. We also discuss a novel mechanism underlying the protective effect of breastfeeding. Collectively, these mechanistic insights offer potential therapeutic avenues for the prevention and/or improved treatment of postpartum breast cancer.

Breast Cancer and Pregnancy

Cancer is an increasing complication of pregnancy worldwide, in part due to the advancing age of childbearing women (1–3). Cancer diagnosis during pregnancy is overall a relatively rare event, affecting about 1 in 1,000 pregnancies and representing 0.1% or less of all cancers (4). Globally, the most common cancers diagnosed during pregnancy follow the patterns of prevalent cancers in the underlying population. In Western countries, breast, thyroid, and gynecologic cancers, as well as melanoma and lymphomas are the most common (3, 5, 6). In Asia, the rate of gastric cancer is much higher, and melanoma not reported (7, 8). Great progress has been made in advancing the ability to safely treat pregnant women with excellent guidelines and reviews available across many cancers (1, 6–10). Of the cancers that affect woman during the childbearing life window, only breast cancer and melanoma have been implicated as being increased in frequency, specifically among postpartum women, in comparison

with age-matched peers (11). Breast cancer is globally the most frequent cancer diagnosed during pregnancy and in the postpartum years, and therefore the most studied. However, the impact of pregnancy on breast cancer is substantially more than the complexity of managing those diagnosed during pregnancy and, to date, it is only breast cancer where parity status has been shown to influence prognosis. This review will focus on the complex and varied interactions between pregnancy and breast cancer with emphasis on breast cancer metastasis, and the unique biology underlying these interactions as observed in rodent models.

Breast cancer in women of childbearing age is a significant global problem, as there is disproportionately increased mortality of young women with breast cancer (YWBC), a problem exasperated in the lowest socioeconomic countries (11). YWBC, variously defined by patient age of ≤ 35 –45 years, has increased risk for metastasis and death, with nearly twice the mortality in comparison with older women (12–15). Survival outcomes in YWBC have lagged overall improvements in the field, with the discrepancy increasing steadily since the 1970s (16). Moreover, the incidence of distant metastases is increasing by approximately 2% annually exclusively in YWBC (17, 18). These adverse outcomes are often cited as because of delayed diagnosis and advanced disease presentation in the absence of screening for women under 40 (12, 19). However, in a large recent study of early stage I–II disease, young age was an independent negative prognostic factor after adjustment for clinical, pathologic, and treatment-related variables (15). Another factor cited has been the greater proportion of aggressive biologic subtypes in YWBC, those that lack hormone receptor expression, including triple-negative and Her 2–overexpressing cancers (TNBC and Her 2, respectively; refs. 12, 13, 16, 17). Yet, a large retrospective YWBC study reported significantly increased two-fold risk of death with estrogen receptor–positive cancer (ER⁺), while risk was only modestly increased for TNBC, and was not significant in HER2⁺ (20). In fact, the association with negative prognosis is the strongest in YWBC with early stage ER⁺ tumors otherwise expected to have excellent outcome (12, 20, 21). Overall, risk factors for YWBC are not well understood, and only 10%–15% of YWBC is due to an inherited pathologic gene variant, such as the *BRCA* genes, *p53*, or *PTEN* (22); lifestyle factors, such as oral contraceptive use, also

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contribute (23). Thus, while young age at diagnosis is an independent risk factor for relapse and death (12, 15, 16, 20, 21), current advances in the field find that heritable germline mutations do not account for the vast majority of YWBC cases, nor find that poor outcomes are accounted for by increases in poor prognostic tumor characteristics.

Childbearing is a natural life window that overlaps with risk for breast cancer diagnosis in women ages 20–45 and 80% of all YWBC will occur in parous women, with 50% of YWBC arising in young mothers within 10 years of their last childbirth (24). The completion of a prior childbirth is one of the more common, yet poorly recognized, risk factors for YWBC, in part because the interaction between pregnancy and breast cancer is complex. Because we and others find parity status impacts breast cancer incidence and outcomes in women diagnosed ≤ 45 years of age (24–26), we define YWBC as cases diagnosed at age 45 and under. Thus defined, YWBC accounts for approximately 13% of all breast cancer in developing countries and higher percentages in lower economic countries (27, 28). Worldwide estimates of postpartum breast cancer (PPBC) range from approximately 150,000 to 350,000 cases annually, based on global breast cancer (27, 28) or childbirth rates (24), respectively (see Worldwide Incidence of PPBC).

Pregnancy, both promotes and protects against breast cancer (29–31). All parous women are under a 10%–30% increased risk of developing breast cancer for at least a decade after childbirth in comparison with nulliparous young women, with older age at first birth increasing the magnitude of risk (31). Overtime, a crossover effect dissipates this risk and the prior childbirth subsequently protects against breast cancer if the woman began her childbearing before age 35 (30, 31). What factors other than parity also influence the incidence of breast cancer in postpartum women and YWBC remain under investigation. Increased breast density, radiographically identified as heterogeneously dense or extremely dense tissue on mammograms, elevates breast cancer risk four-fold or higher, and equally affects risk in women of all ages (32, 33). In women age 45 and under, higher breast density is seen with nulliparity and later onset of childbearing, which

are life factors known to increase breast cancer risk (34, 35). African-American women, who face a high incidence of YWBC, have higher breast density when multiple qualities of breast density are incorporated across age and parity group, as compared with white women (36). Further on in this review, mechanistic links between parity, lactation, and active collagen deposition within the breast are described. These data offer leads to an improved understanding of the role of breast density in PPBC, and highlight the need for additional studies.

Overall, the postpartum life window is underrecognized as a time of higher risk for early-onset breast cancer (Fig. 1). Moreover, cancers diagnosed during this window of increased risk also carry worse prognosis (24, 26, 30, 37–39). Women diagnosed and treated during their pregnancy have usual prognosis, based on stage and biology of the tumor (26, 30). Conversely, women diagnosed postpartum have significantly increased risk for metastatic recurrence (37–39), which is highest among women diagnosed within 5 years of last childbirth but extends to 10 years postpartum (37). Furthermore, the risk for metastasis is 3- to 5-fold higher for postpartum stage I/II cancers, regardless of ER status (37). Recognition of this extended risk window for both ER⁺ and ER⁻ cancers is critical with respect to understanding the underlying biology of PPBC, as well as for identifying YWBC patients at highest risk of recurrence. This later point is highlighted by the fact that when outcomes are grouped as pregnancy-associated breast cancers (pregnant cases plus 1- to 2-year postpartum cases) and compared with an unselected group of age-matched YWBC, the differences in outcome are obscured (24). Thus, the definition of PPBC matters, as it effects the interpretation of outcomes data and ultimately patient care.

Tumor Promotion during Postpartum Breast Involution

The fact that a postpartum diagnosis in young women strongly associates with worse outcomes has led to the concept that a prometastatic biology is present in the postpartum breast (31). A unique breast biology specific to postpartum women that may account for the increased risk of metastasis is mammary gland involution (40). Mammary tissue expands approximately 10-fold during pregnancy in preparation for lactation; then, mammary gland involution occurs when milk production ends, either after birth in the absence of nursing, or after weaning (41). In adult rodents and women, postpartum mammary gland involution is reported as the most dramatic example of physiologic tissue remodeling to occur in the adult, as 80%–90% of the alveolar mammary epithelium is removed by programmed cell death (42, 43). Direct support for the hypothesis that postpartum mammary gland involution is tumor promotional comes from pre-clinical studies. Using xenograft and isogenic tumor transplant models, the normal tissue microenvironment of the actively involuting mammary gland has been demonstrated to increase breast cancer tumor take and metastasis compared with the mammary microenvironment of the nulliparous or parous host (44–46).

There are several mechanisms observed in the involuting gland that may drive metastasis. The death of the alveolar mammary epithelium is coordinated with inflammation (47, 48), lymphangiogenesis (44), fibroblast activation (49), and collagen 1, fibronectin, and tenascin-C-rich matrix deposition (49, 50), all stromal attributes that mirror wound-healing and are causal to cancer outcomes. Importantly, the findings of a similar protumor, breast involution program being present in the breast tissue of young, recently pregnant women offers a plausible link between involution and PPBC outcomes (41, 44). The potential mechanisms by which the transient event of normal

Worldwide Incidence of PPBC

Metrics related to reproductive history are not commonly included in breast cancer clinical datasets, such that the number of breast cancers that meet the definition of postpartum breast cancer (PPBC) is currently derived from best estimates. One approach to estimate global burden of PPBC is to utilize data obtained from developed countries, which show that approximately 13% of all breast cancers are young women with breast cancer (27, 28) and that approximately 50% of these cases have likely completed a pregnancy within 10 years of their diagnosis (29). This approach results in a global estimation of approximately 130,000 PPBC cases per year. An alternative approach is to determine the incidence of PPBC cases per completed pregnancy (again relying on data from developed countries) and then determining global burden based on number of pregnancies worldwide. Best estimates for PPBC cases in the United States for 2015 were approximately 13,000. On the basis of 4.5 million U.S. pregnancies/year, this would predict a PPBC incidence of 0.0028% (one in every ~350 pregnancies). With approximately 130,000,000 live births globally per year, this estimation approach predicts 364,200 cases of PPBC worldwide (<https://www.un.org/en/development/desa/population>).

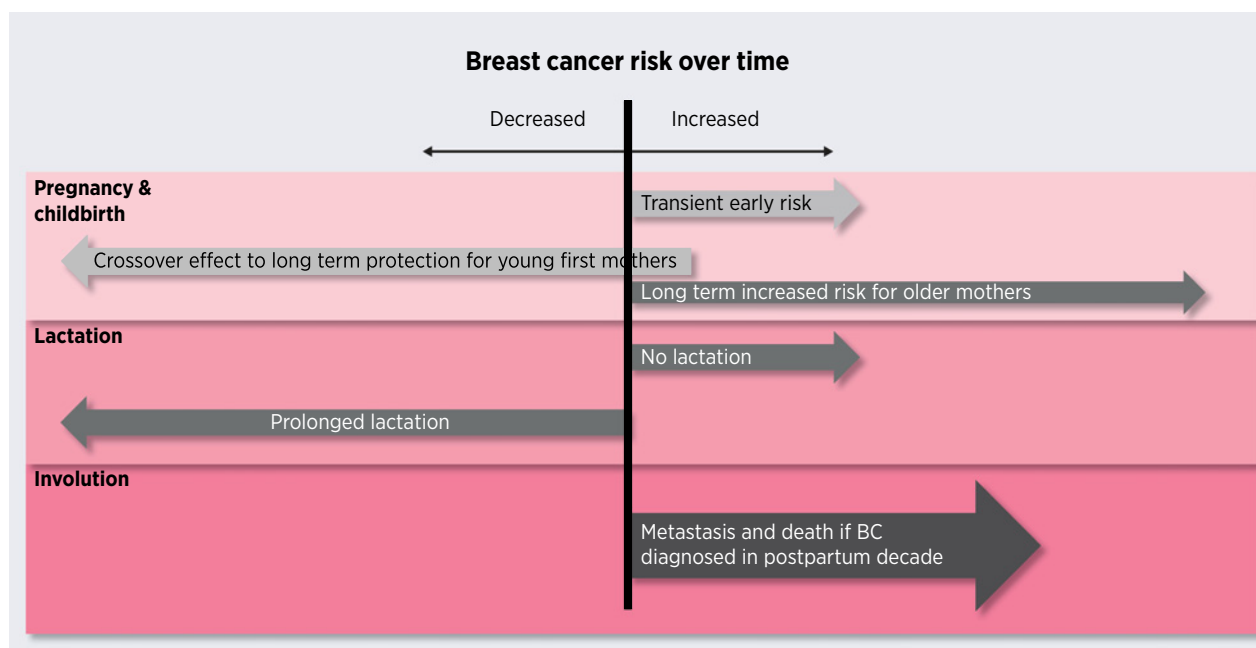


Figure 1.

Graphical presentation of the associations between pregnancy and lactation with breast cancer risk and outcome. While pregnancy confers long-term protection in young first mothers, all mothers experience a transient early risk for breast cancer, which extends long term in older mothers. In addition, in those who do not lactate, this risk is also increased and there is evidence that prolonged lactation can also decrease long-term risk for breast cancer. Finally, if breast cancer is diagnosed in the postpartum decade, there is an increased risk for metastasis and death from breast cancer compared with nulliparous or older women, which is not seen among cases diagnosed during pregnancy. BC, breast cancer.

mammary gland involution impacts long-term outcomes in postpartum patients is likely multifactorial. Rodent models of PPBC reveal that occult tumor cells are “released” into the activated mammary stromal compartment during weaning-induced alveolar collapse, where they access the vasculature, disseminate, and set up micro-metastases in distant organs (44, 45). In addition, expansion of the lymphatic vasculature occurs during involution allowing for increased tumor cell trafficking in the lymph vessels and seeding of the lymph node (44, 51). This involution-specific mammary lymphangiogenesis is consistent with the observed increased lymph node involvement in patients with PPBC compared with age-matched nulliparous patients (26, 44).

There is also a distinct visceral pattern of metastasis in PPBC that suggests circulating tumor cells released from the involuting mammary gland have additional metastatic advantages. In postpartum patients, an approximately 3-fold increase in liver metastasis but not lung, brain, or bone is reported (52). This metastatic pattern is consistent with a uniquely hospitable “soil” in the liver of postpartum women. This novel hypothesis is supported by rodent studies, where the postpartum liver is found to support breast cancer metastasis. The basis of this liver-specific metastatic preference appears to be due to a functional link between the mammary gland and liver that is established to support lactation. Specifically, in preparation for lactation and throughout lactation, the rodent liver doubles in size and increases anabolic metabolism (52). Upon weaning, the liver undergoes a regression process that displays the hallmarks of mammary gland involution: parenchymal (hepatocyte) apoptosis, catabolic metabolism, ECM remodeling including deposition of collagen I, tenascin-C, and fibronectin, and immune cell influx suggestive of immune tolerance (52). Intraportal tumor cell delivery (53) to the involuting liver

leads to increased metastatic outgrowth compared with livers of nulliparous murine hosts, data consistent with the establishment of a prometastatic liver niche following weaning (52). While the molecular mechanisms that mediate the functional coordination between the lactating mammary gland and liver are unknown, and evidence for post-weaning liver involution in women not reported, continued investigation into site-specific metastasis patterns in YWBC and PPBC is warranted.

In rodent models, involution and PPBCs are also marked by an immune phenotype typically associated with immune tolerance and T-cell exhaustion. Specifically, within the lymphoid lineage, Th17, Th2, and Treg-skewed T cells are elevated (48, 54, 55), with functional evidence for active suppression of T-cell proliferation limited to the involution window (48). Within the myeloid lineage, there are observed enrichments in CD11b⁺/F480⁺ myeloid-derived suppressor cells (48) and M2-skewed macrophages, which likely suppress T-cell activation through secretion of IL10, a Th1 inhibitory cytokine, and by depleting arginine from the tissue microenvironment (54, 47). These macrophages exhibit characteristics that are similar to tumor-associated macrophages, which have been identified to promote tumor cell invasion and extravasation (56, 57). In addition, the involuting gland is enriched for mammary macrophages similar to the recently identified tumor-associated podoplanin-expressing macrophages or PoEM (58). Within tumors, PoEMs promote metastasis via production of collagen and loosening of the lymphatic vasculature, allowing for tumor cells to enter the lymphatics (58). Histologic evidence confirms the presence of increased lymphatic-associated macrophages in patients with PPBC (51). Molecular analysis of the lymphatic vessels and macrophages during involution and in models of PPBC has also revealed expression of programmed death ligand-1 (PD-L1), similar to

what is observed during peripheral tolerance (59–62). Because PD-L1 engagement of its receptor PD-1 inhibits T-cell responses through activation of proapoptotic signaling, these data suggest that lymphatic-mediated immune avoidance (63–65) is one mechanism by which involution promotes PPBC. Consistent with this, murine PPBC tumors are particularly sensitive to anti-PD-1 therapy, which resulted in regression of the lymphatics and decreased T-cell exhaustion (59). Collectively, these data provide several plausible mechanisms for increased metastases in postpartum patients that include immune avoidance, increased tumor cell escape from the primary site, increased lymphatic network for dissemination and maintenance of immune avoidance, and increased seeding in the liver, all of which may be targetable with clinically available therapies.

In addition to involution creating favorable stromal microenvironments for the expansion and spread of tumor cells, a second mechanism by which involution might durably promote breast cancer and poor outcomes is through tumor cell imprinting. Several lines of evidence suggest that tumor cells and mammary epithelial cells are permanently altered after a pregnancy/lactation/involution cycle. First, parity induced mammary stem cell populations, with similarities to tumor cells, are maintained after pregnancy and expand with multiparity in rodents (66, 67). Second, mRNA analysis of normal mammary tissues from parous women within 10 years postpartum reveals stable changes in gene expression associated with inflammation, ECM, and hormone receptor signaling (68, 69). Multiple studies have also identified programs of postpartum involution that are mirrored in tumor cells and in the tumor microenvironment after involution (70). Specifically, collagen, COX2, SEMA7A, and lymphangiogenesis are described in involuting mouse mammary tissue, in normal adjacent mammary tissue from postpartum patients, and in PPBC tumors in murine models (44, 46, 51, 47, 71). Importantly, NSAID inhibition reveals that COX2 activity is required for metastasis in murine postpartum hosts; additionally, NSAIDs reverse aspects of gland desmoplasia, lymphangiogenesis, and T-cell suppression, including reestablishment of Th1 cytokine production and T-cell accumulation at the border of postpartum tumors (45, 55). Finally, SEMA7A promotes multiple aspects of tumor progression during involution including lymphangiogenesis, mesenchymal phenotypes, as well as tumor cell invasion and survival (51, 72). Moreover, knockdown of SEMA7A reduces collagen deposition and COX2 expression in preclinical models of PPBC (73) and knockdown of COX2 similarly results in downregulation of SEMA7A (72), suggesting a relationship between these two signaling molecules. Thus, both COX2 and SEMA7A represent additional avenues that can be explored for the prevention and treatment of PPBC.

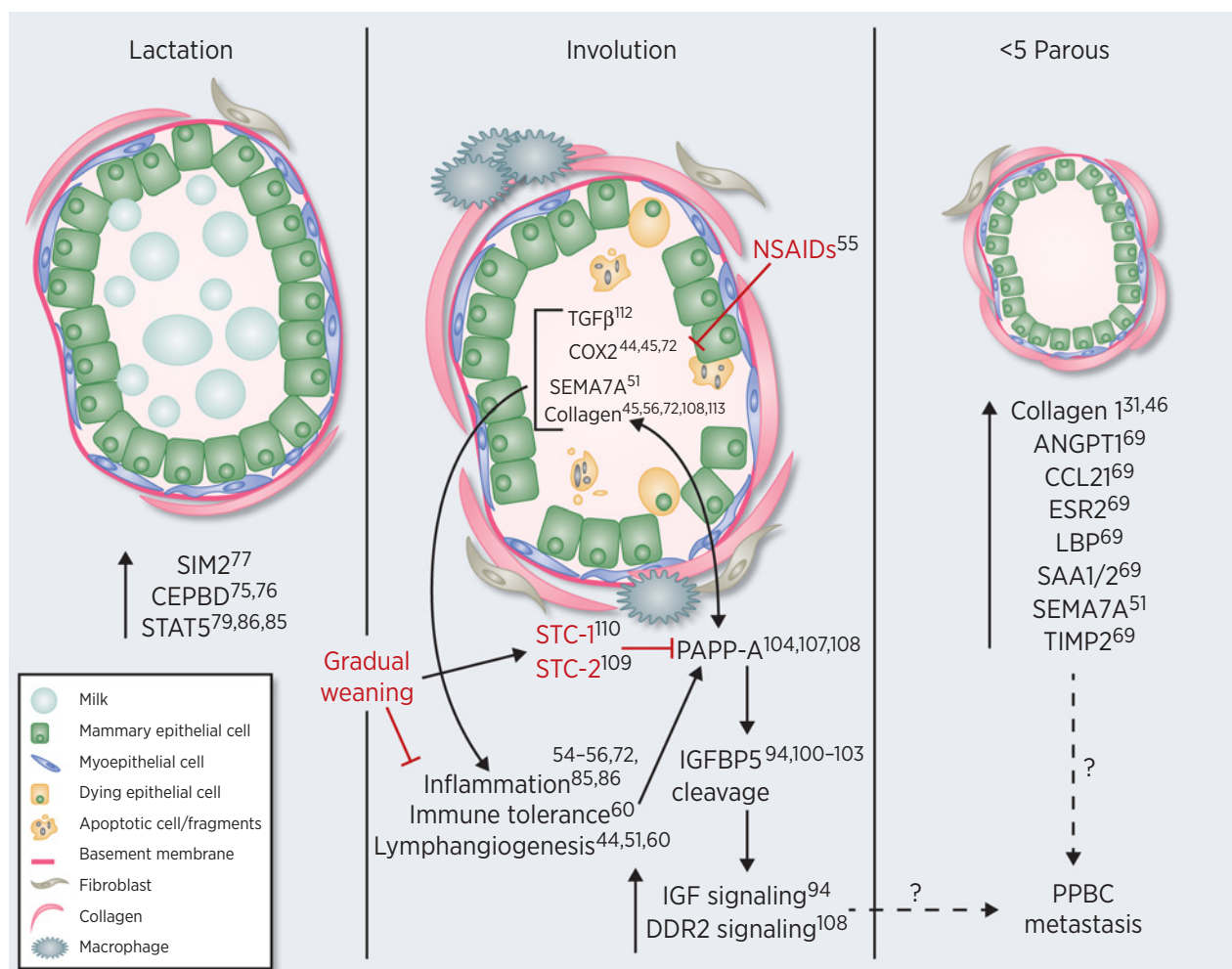
While evidence for tumor cell imprinting in PPBC is still emerging, the study of transcriptional regulators of normal mammary gland involution may also offer insights. Transcriptional regulators with known pro- and antitumor activities orchestrate the balance between epithelial cell survival and death during involution. For example, CEBPD, a member of the C/EBP transcription factor family, is an important regulator of involution (74, 75). In *CEBPD* gene-knockout studies in mice, CEBPD was found to support proapoptotic signaling of involution as well as stromal remodeling, particularly via upregulation of matrix metalloproteinases (74, 75). Conversely, SIM2s, a transcription factor with known tumor suppressive activities, is required for lactogenic differentiation. Continued expression of SIM2s delays involution by decreasing Stat3 and NF- κ B signaling (76), two proapoptotic signaling pathways critical for involution (77–81). Interestingly, SIM2s was recently shown to downregulate COX2 and loss of SIM2s promotes mammary tumorigenesis via upregulation of epithelial–mesenchymal transition and invasion (82, 83). Importantly, inhibition and knockdown of COX2 reduces invasion and restores SIM2 expression in breast cancer cells and xenografts (82, 83). An intriguing prospect is that PPBC will be imprinted by the transcriptional programs of involution, such as CEBPD gain and SIM2s loss, which may identify additional novel pathways of vulnerability in PPBC. Indirect evidence for this hypothesis has been reported, as gene signatures associated with normal mammary gland involution (84, 85) correlate with aggressive triple-negative and inflammatory breast cancers and predict worse breast cancer-specific survival in breast cancer overall (86, 87).

Mechanistic Insights into the Protective Effect of Lactation

Lactation is identified as an important factor affecting incidence of breast cancer in both YWBC and postmenopausal diagnosis. Breast-feeding has a significant protective effect against TNBCs in African-American women and BRCA1 mutation carriers, and overall breast-feeding reduces risk for white women and ER⁺ subtypes, particularly for a postmenopausal diagnosis (23, 37). A recent meta-analysis of 50,302 women from 47 independent studies revealed that extended lactation is protective against breast cancer, with risk reduction being dependent on cumulative lifetime duration, and independent of maternal age or multiparity. In this study, among the parous women with breast cancer, fewer had ever breastfed and for those who did, the average time of breastfeeding was shorter (9.8 months) when compared with parous women without breast cancer (15.6 months; ref. 88). Furthermore, from this study the authors suggested that extension of breastfeeding, by 12 months per child, may reduce the risk of breast cancer by more than half, since they reported a reduction from 6.3 breast cancer cases per 100 women to 2.7 breast cancer cases per 100 women (88). In addition, the length of lactation was found to be reduced in high-income countries relative to low-income countries, which may partially explain the increased incidence of postmenopausal breast cancer in high-income countries (27, 89). Therefore, understanding how lactation impacts risk of breast cancer, and whether it counters adverse effects of involution is critical.

Insulin-like growth factor 1 (IGF-I) protects mammary epithelial cells from apoptosis during lactation (90–92). IGF binding protein-5 (IGFBP5) prevents activation of IGF receptor by titrating away IGF-I and II (93). Thus, IGFBP5 was proposed as a mediator of involution, and IGFBP5-knockout mice exhibit delayed involution (94–97). Therefore, the effect of IGFBP5 on IGF signaling may be especially important during involution. In agreement with the importance of limiting IGF signaling in this setting, the protective effect of pregnancy is associated with reduced expression of IGF receptor (93). IGFBP5 is itself negatively regulated by the protease pappalysin-1 (PAPP-A; refs. 98–102), which is overexpressed in the vast majority of breast cancers (103), and decreased expression of IGFBP5 is associated with higher risk of developing breast cancer (104, 105). Analysis of transgenic mice with mammary-specific expression of PAPP-A revealed development of mammary tumors exclusively following pregnancy (106, 107). Importantly, the length of lactation drastically impacted the rate of PPBC in these mice (106). Transgenic females that had an abrupt cessation after 2 days of lactation developed PPBC; in contrast, females that fed their pups for extended periods of time did not (106). This observation suggests that extended lactation is protective against the oncogenic effect of PAPP-A. Mechanistically, glycoproteins Stanniocalcin-1 (STC1) and -2 (STC2) can act as inhibitors of PAPP-A (108, 109) and the protective effect of lactation is associated with the

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**Figure 2.**

Model of how lactation, postpartum involution, and epithelial cell imprinting of parity intersect to impact incidence and outcomes in PPBC. Physiologic involution (middle), which is mediated in part by protumorigenic TGF β , COX2, SEMA7A, and collagen-dependent signaling, shares numerous attributes with protumor wound healing, including immune cell infiltrate, immune tolerance, and lymphangiogenesis, resulting in involution being a risk window for poor prognostic breast cancer. Upregulation of molecules with known tumor suppressive functions are present during lactation (left) and abrupt cessation of lactation exacerbates involution-associated programs of inflammation, which contributes to abnormal expression of PAPP-A during involution. The increased deposition of collagen during involution acts to enhance the proteolytic activity of PAPP-A against IGFBP5, leading to increased IGF and collagen receptor DDR2 signaling and tumor promotion. In contrast, prolonged or gradual cessation of lactation promotes the accumulation of STC1 and 2, which act as inhibitors of PAPP-A, reducing tumor progression. Mammary epithelial cells are also imprinted by undergoing a reproductive cycle (right), which possibly accounts for the increased tumor risk and progression that are elevated for at least 10 years post childbirth. Image courtesy of Sarah E. Tarullo, PhD (University of Colorado, Aurora, CO).

expression of STC1 and STC2 (106). Furthermore, STCs are produced by the ovaries and can be detected at high levels in the serum only during pregnancy and lactation, but not during involution, suggesting a possible systemic role for STCs in tumor suppression during pregnancy and lactation (110).

Interestingly, a recent study reported that abrupt interruption of lactation in mice induces an increase in markers of inflammation. This finding is consistent with the role of PAPP-A in involution and the importance of the STCs to inhibit PAPP-A activity, because PAPP-A is known to be induced by inflammatory cytokines such as IL6, TNF α , IL1 β , IL4, and TGF β (111). Abrupt cessation of lactation was also associated with increased cellular proliferation and deposition of collagen as well as expansion of the luminal progenitor cells in the mammary gland compared with mice where cessation of lactation was

gradual (112). The latter observation in mice that abrupt cessation promoted the expression of estrogen and progesterone receptors is in agreement with the protective effect of breastfeeding against ER⁺ breast cancer in women (23, 37). The authors also reported ductal hyperplasia 4 months postpartum in mice where lactation was abruptly interrupted (112). It is currently unknown whether this holds true in humans. However, in human breasts undergoing gradual weaning, lobules undergoing apoptosis and tissue inflammation are observed adjacent to noninflamed lactational lobules (Supplementary Fig. S1; refs. 41, 113, 114). These observations suggest that, even with gradual weaning, tumor cells could be exposed to a protumor microenvironment, and therefore by extrapolation, appears that gradual weaning would not completely protect a woman's breast from the protumorigenic aspects of involution. Additional studies are necessary to

determine how gradual and abrupt cessation of weaning interact with involution and impact the breast tissue microenvironment, and subsequent breast cancer risk and outcomes.

Of note, increased deposition of collagen during involution induces COX2 expression, which drives PPBC metastasis (45) and the mammary glands of involuting PAPP-A transgenic mice following an abrupt cessation of lactation, exhibit an even higher level of collagen (106). In addition, PAPP-A is dependent on collagen for its activation (106), thereby offering a mechanism by which PAPP-A transgenic mice only develop mammary tumors following pregnancy, as passage through involution and increased collagen deposition during this phase is required for its activation. In a more recent study, PAPP-A was found to activate the collagen receptor DDR2 (107), which promotes metastasis via activation of the ERK–Snail axis (115). Thus, the activation of DDR2 by PAPP-A offers an additional mechanism by which PPBCs are associated with increased metastasis and worst outcomes. Consistent with this, deletion of DDR2 by CRISPR was shown to abolish the proinvasion effect of PAPP-A (107) and a PAPP-A/Snail/Collagen signature was found to identify patients at higher risk of metastasis (107). Collectively, these data suggest that lactation or extended lactation may be protective against breast cancer via suppression of PAPP-A and downregulation of collagen mediated protumorigenic signaling in the mammary gland.

Concluding Remarks

PPBC is a global health threat that affects approximately 150,000–350,000 young mothers annually, placing them at increased risk for metastasis and therefore death. Because lactation and postpartum

breast involution are both predictive for breast cancer, the postpartum life window is a free, readily available “biomarker” for assessments of PPBC risk and outcomes. The insights gleaned from mechanistic studies of lactation and involution offer important avenues in the future. Specifically, the roles of COX2, SEMA7A, and PAPP-A as putative oncogenes for PPBC, and the identification of lactation-induced SIM2s, STC-1, and STC-2 as inhibitors of PPBC-associated oncogenes, provide immediate leads for targeted prevention and treatment interventions (Fig. 2). To continue to advance PPBC prevention, additional programs to facilitate lactation globally are needed. Also, research efforts to identify women at high risk for PPBC will support future prevention trials. Finally, investigations into the unique molecular vulnerabilities of PPBC are anticipated to yield rich venues for targeted therapeutics. Combined, these strategies will address the unmet clinical needs of young women at risk for PPBC, a population in dire need of improved prevention and treatment strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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