# Reproductive Events and Risk of Women's Cancers: From Parturition to Prevention

Mark E. Sherman[1], Miriam Levi[2], and Lauren R. Teras[3]

## ABSTRACT

Reproductive events beginning with pregnancy and ending with remodeling of the breast after cessation of breastfeeding alter breast structure and function and produce dramatic changes in systemic biology. In aggregate, these processes lower overall risk for breast, tubo-ovarian and endometrial cancers, albeit differentially by molecular subtypes of these tumors. Herein, we explore opportunities for research on protective mechanisms operative during this period of the life course, with the goal of encouraging studies to advance cancer prevention.

*See related article by Getz et al., p. 353*

Reproductive events that begin with pregnancy and end with restoration of the structure and function of the nongravid breast confer protection against breast, endometrial, and tubo-ovarian cancers (1). Increased understanding of the mechanisms that mediate these events offers untapped opportunities to advance cancer prevention. In a recent publication in The Journal, Getz and colleagues provisionally link breastfeeding to lower volumetric mammographic density, thus offering a possible explanation for part of the protective effect of lactation (2). Apropos this report, we offer a commentary in support of increasing research on this period of the life course to discover approaches for multi-site cancer prevention among women.

Although pregnancy and breastfeeding are inextricably linked, they exert different biologic effects on breast structure and gene expression. Collectively, reproductive events produce a net impact on systemic biology that reduces risks of several cancers and chronic diseases among mothers, and via the constituents of breastmilk, their children. We propose that reproductive events also contribute importantly to shaping the structural heterogeneity characteristic of the adult breast. Further, the associations of reproductive events with risk of breast cancer and other women's cancers (e.g., endometrial and tubo-ovarian) vary by histologic and molecular subtype, suggesting differences in the etiology of these tumors. For example, childbirth is associated with a transient rise in breast cancer incidence overall that peaks at 5 years, and then progressively declines over two decades for estrogen receptor (ER)-positive breast cancers but remains elevated for ER-negative breast cancers (3). Likewise, the protective effects of pregnancy and breastfeeding varies by tubo-ovarian histologic subtypes.

## Pregnancy

Pregnancy dramatically alters the structure and function of breast lobules, the site where milk is produced and where most breast cancer precursors arise (4). Specifically, pregnancy-related changes such as increases in sex-steroid hormones cause an expansion of lobular epithelium and induce milk production, in conjunction with depletion of adipose tissue. Delayed childbearing, which may increase cumulative mutational burden in stem/progenitor cells via repeated episodes of proliferation associated with uninterrupted menstrual cycling, heightens breast cancer risk. However, mutation load alone likely does not account for breast cancer risk because "normal appearing" breast epithelium contains numerous mutations (5). Given that breasts contain thousands of lobules, many of which may contain mutated cells, the development of breast cancer might be viewed as a rare event at the "per lobule" level. Increased understanding of processes that inhibit progression of mutated cells to form premalignant clones related to intrinsic cellular mechanisms (e.g., apoptosis and senescence), immune factors, and the stromal microenvironment may hold keys to improving risk prediction and prevention of breast cancer. Pregnancy-related increases in cortisol are proposed to exert anti-inflammatory and tolerogenic effects, which protect the fetus from immune attack, but also represent a form of immune suppression, which may partly explain why multiparity increases risk of cervical cancer, a disease caused by a persistent infection with carcinogenic human papillomaviruses.

## Breastfeeding

Breastfeeding guidelines are largely intended to optimize infant health, rather than to lower cancer risk among mothers. In the United States, women are urged to nurse exclusively for 6 months, with continuation for 1 year or more, but many

[1]Quantitative Health Sciences, Mayo Clinic College of Medicine and Science, Jacksonville, Florida. [2]Department of Obstetrics and Gynecology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota. [3]American Cancer Society, Atlanta, Georgia.

**Corresponding Author:** Mark E. Sherman, Quantitative Health Sciences, Mayo Clinic College of Medicine and Science, 4500 San Pablo Road, Jacksonville, FL 32224. Phone: 904-953-0771; E-mail: Sherman.Mark@Mayo.edu

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women stop nursing involuntarily. While a meta-analysis suggests that long-duration exclusive breastfeeding confers the greatest breast cancer protection (6), analysis of complex relationships among duration, frequency, exclusivity, and other factors are limited by inaccurate recall. Use of phone apps could enable collection of more accurate breastfeeding data in real-time, revealing important relationships with cancer risk at multiple organ sites.

There are several potential mechanisms by which breastfeeding may lower risk of breast cancer and other women's cancers. First, as with pregnancy, breastfeeding often leads to fewer menstrual cycles (i.e., anovulation), resulting in lower levels of circulating estrogen and other growth promoting hormones. Second, shedding of breast epithelium during lactation may eliminate mutated cells, and possibly carcinogens. Limited data also suggest that the composition of gut flora among mothers varies by breastfeeding patterns (e.g., exclusive versus nonexclusive) and this in turn may affect composition of breastmilk, thereby affecting both mother and child (7). The gut flora may also stimulate maturation of B lymphocytes into mature plasma cells that are hypothesized to traffic to the breast and secrete antibodies into breastmilk. Excessive use of antibiotics to treat presumed infectious mastitis, some of which may represent mechanical obstruction of ducts (i.e., a noninfectious inflammatory process), deserves further attention, as antibiotic use has been associated with elevated breast cancer risk (8) and could influence many aspects of women's health. Finally, breastfeeding may impact the process of involution of breast epithelium that restores the nongravid state of the breast.

## Weaning: Cessation of Breastfeeding and Postpartum Involution

After cessation of breastfeeding or without initiation, the breast undergoes postpartum involution (PPI), a process characterized by death of approximately 80% of breast epithelial cells, inflammation, and wound healing (4, 9). In preclinical models, PPI drives development of aggressive breast cancers, and can be inhibited with anti-inflammatory interventions (10); however, little is known about the effects of weaning, PPI, and subsequent remodeling on breast cancer risk among women. In preclinical models, abrupt weaning promotes epithelial proliferation, inflammation, fibrosis, and carcinogenesis (11). We propose that among women, PPI and remodeling may also contribute to fibro-inflammatory changes and microcalcifications, which collectively represent benign breast disease, which is itself associated with increased breast cancer risk. Systemic changes that occur during weaning have received limited attention and could have effects on gynecologic cancers and other health conditions.

Detailed studies of weaning patterns and cancer risk among women deserve further study. Validated methods to collect, process, and analyze breast fluid after weaning have not been developed, radiologic studies of the breast during this period are limited, and few studies have measured systemic markers of cancer risk during this period. Identification of women with prolonged or excessively intense inflammation or shedding of precancerous or cancerous cells by analysis of breast fluid post-weaning might aid in identifying candidates for early initiation of screening or prevention. Use of short-term anti-inflammatory approaches might offer net benefit by reducing fibrosis, calcifications, and breast cancer risk, but this hypothesis is untested in large human studies.

## Public Health Implications for High-Risk Individuals

Decisions about childbearing and breastfeeding among carriers of deleterious genetic variants (e.g., *BRCA1* or *BRCA2*) that confer risk of early onset breast and tubo-ovarian cancers are complex. Oral contraceptive use reduces risk of tubo-ovarian cancers but increases breast cancer risk. Breastfeeding is protective for both breast and tubo-ovarian cancers and may negate breast cancer risks related to oral contraceptive use (1); however, during pregnancy and lactation, women defer mammographic screening, and typically interrupt nursing when undergoing magnetic resonance imaging with contrast because gadolinium is secreted into breastmilk. Conventional ultrasound, although safe, has limited sensitivity for detecting breast cancer during this period. Development of novel radiologic methods and non-radiologic screening strategies to detect breast cancers in blood or breastmilk could enable women to breastfeed with less concern about foregoing screening. In low-resource settings, where premature and low birth-weight births are frequent, risks of vertical transmission of endemic infections may pose barriers to breastfeeding. Given that breastfeeding is particularly protective for triple-negative breast cancers, which has a high incidence in some parts of Africa, failure to breastfeed can negatively impact both mother and child (12). Research to develop evidence-based guidelines about breastfeeding practices and cancer prevention that incorporate health concerns of mothers and are compatible with women's diverse lifestyles worldwide is needed (**Fig. 1**).

## Future Directions

Despite investments in screening, early detection, and treatment, cancers of the breast, uterus, and ovaries aggregately accounted for over 373,000 new cases and 68,000 deaths in the United States in 2022 (13). Given that breastfeeding lowers risks of all of these cancers (1), even among high-risk mutation carriers, development of evidence-based guidelines that reflect the welfare of both infant and mother is critical. Extension of insights about the biology of normal versus dysregulated features of the pregnancy–lactation–PPI cycle might facilitate discovery of approaches to reduce fibro-inflammatory changes and microcalcifications in the breast, which impede radiologic detection of early breast cancers and prompt unnecessary biopsies. Efforts led by a small group of pioneers to discover pharmacologic approaches that mimic the preventive effects of

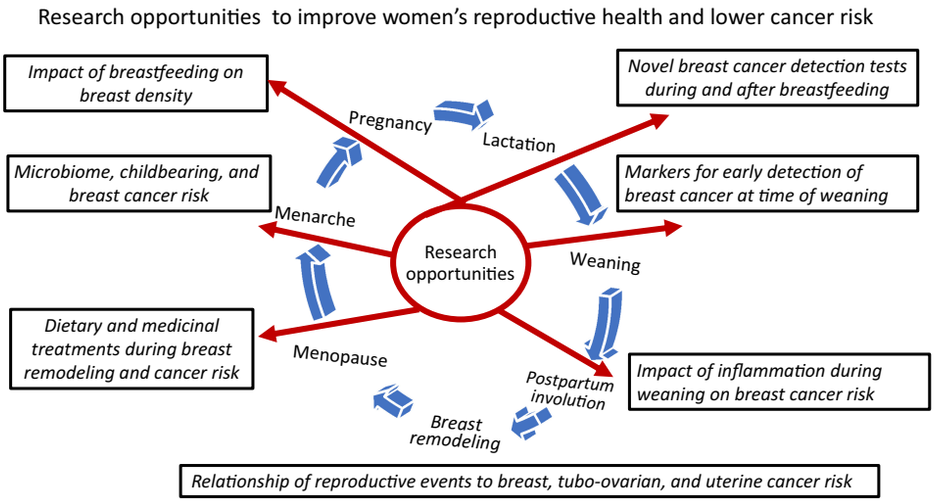


**Figure 1.**

The cycle of reproductive events offers a model of naturally occurring cancer prevention, which offers incompletely investigated opportunities to mirror these protective biological effects. While pregnancy induces expansion of breast epithelium it also imparts differentiation towards a secretory phenotype, thereby reducing the pool of undifferentiated cells susceptible to breast cancer development. In fact, several factors are known to pose greater breast cancer risk when exposure occurs prior to a first pregnancy (i.e., a proposed "window of susceptibility"). Given that the wound healing response during PPI is implicated in the pathogenesis of postpartum breast cancers, greater research is needed to understand the process of weaning and its impact on breast cancer risk. Processes that restore the breast to its nongravid state have not been well studied and offer the possibility to favorably shape the breast in a way that lowers breast cancer risk through influencing the stromal and immune microenvironments. Although breastfeeding is linked to lower risk of women's cancer, the underlying mechanisms are incompletely understood, and data related to breastfeeding exclusivity, duration and risk of specific cancer subtypes are not entirely consistent. Understanding how the systemic biology of lactating women is restored to a resting state may point to approaches to lower risk of endometrial and tubo-ovarian cancers, and potentially cancer of other organ sites, and to combat development of chronic diseases.

pregnancy have garnered more attention than funding, and have yet to come to fruition (14), and the effects of different patterns of weaning among women require further study. Finally, excessive weight retention after childbirth fuels the obesity epidemic, thereby increasing risks of multiple cancers and other chronic diseases. Studies to discover dietary interventions or probiotics that favorably modify the microbiome during the critical postpartum period of breast remodeling represents an under-explored avenue for achieving cancer prevention through modification of the breast microenvironment. The interval between childbearing and menopause is a time of cancer initiation; cancer diagnoses are comparatively rare. However, the long-term risk of reproductive cancers, which peaks in later years, may be altered by behaviors and events during this time in the life course. Given that women may be receptive to health messaging during this time, it provides a critical window to focus on cancer prevention. To advance this work, funding agencies could develop novel mechanisms that bring together cancer researchers with less familiar partners in obstetrical and pediatric specialties.

## Authors' Disclosures

No disclosures were reported.

## Authors' Contributions

**M.E. Sherman:** Conceptualization, writing–original draft, writing–review and editing. **M. Levi:** Conceptualization, writing–original draft, writing–review and editing. **L.R. Teras:** Conceptualization, writing–original draft.

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