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Association between breastfeeding, mammographic density, and breast cancer risk: a review

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Abstract

Background Mammographic density has been associated with breast cancer risk, and is modulated by established breast cancer risk factors, such as reproductive and hormonal history, as well as lifestyle. Recent epidemiological and biological findings underscore the recognized benefits of breastfeeding in reducing breast cancer risk, especially for aggressive subtypes. Current research exploring the association among mammographic density, breastfeeding, and breast cancer is sparse.

Main findings Changes occur in the breasts during pregnancy in preparation for lactation, characterized by the proliferation of mammary gland tissues and the development of mammary alveoli. During lactation, the alveoli fill with milk, and subsequent weaning triggers the involution and remodeling of these tissues. Breastfeeding influences the breast microenvironment, potentially altering mammographic density. When breastfeeding is not initiated after birth, or is abruptly discontinued shortly after, the breast tissue undergoes forced and abrupt involution. Conversely, when breastfeeding is sustained over an extended period and concludes gradually, the breast tissue undergoes slow remodeling process known as gradual involution. Breast tissue undergoing abrupt involution displays denser stroma, altered collagen composition, heightened inflammation and proliferation, along with increased expression of estrogen receptor α (ERα) and progesterone receptor. Furthermore, elevated levels of pregnancy-associated plasma protein-A (PAPP-A) surpass those of its inhibitors during abrupt involution, enhancing insulin-like growth factor (IGF) signaling and collagen deposition. Prolactin and small molecules in breast milk may also modulate DNA methylation levels. Drawing insights from contemporary epidemiological and molecular biology studies, our review sheds light on how breastfeeding impacts mammographic density and explores its role in influencing breast cancer.

Conclusion This review highlights a clear protective link between breastfeeding and reduced breast cancer risk via changes in mammographic density. Future research should investigate the effects of breastfeeding on mammographic density and breast cancer risk among various ethnic groups and elucidate the molecular

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mechanisms underlying these associations. Such comprehensive research will enhance our understanding and facilitate the development of targeted breast cancer prevention and treatment strategies.

Keywords Breast cancer, Mammographic density, Breastfeeding, Risk factors

Background

According to global cancer statistics, female breast cancer has emerged as the most diagnosed cancer worldwide, ranking as the foremost contributor to cancer incidence [1]. Several countries have implemented regular breast cancer screening programs, utilizing mammography to enhance the early detection of this disease. Over the past few decades, there has been more focus on identifying various risk factors associated with breast cancer, including specific gene mutations, mammographic density, reproductive factors, lifestyle choices, dietary habits, environmental exposures, and more [2] (Fig. 1). High mammographic density, among the risk factors associated with breast cancer, is notably recognized as an independent one that increases breast carcinogenesis [3–5] and which can diminish the sensitivity of mammography in screening procedures [6–8]. It also stands out for being non-static in the span of a woman's life, owing to its changeable nature which can be influenced by established breast cancer risk factors, such as reproductive and hormonal history, as well as lifestyle [9–12].

In recent decades, breastfeeding has become a topic of increasing concern, drawing particular interest in its implications and optimal duration. Recent epidemiological and biological research has underscored the acknowledged benefits of breastfeeding in mitigating the risk of breast cancer, notably of its more aggressive subtypes [13–15]. Currently, research exploring the association among mammographic density, breastfeeding, and breast cancer is still relatively sparse. Our review aims to analyze and synthesize the existing epidemiological studies on the association among mammographic density, breastfeeding, and breast cancer. In addition, we endeavor to elucidate the multifaceted dynamics of how mammographic density, influenced by breastfeeding, impacts breast cancer risk. Furthermore, we seek to highlight gaps in current knowledge and suggest directions for future research, particularly in understanding the mechanisms underlying these associations.

Mammographic density and breast cancer risk

Mammographic density is defined as the proportion of fibroglandular tissue relative to fatty tissue within the breast. The fibroglandular tissue, comprised of "fibrous" (stromal) and "glandular" (lobular and ductal) components, which absorbs ionizing radiation, manifests as white areas, in mammography [6]. Hence, it is commonly referred to as "dense tissue". Breast cancer typically originates from the ductal and glandular components of the breast, which appear white on mammography. Consequently, dense tissue, due to its similar radiographic appearance, can obscure these cancers, effectively masking them from detection.

Two-dimensional digital mammography (DM) and digital breast tomosynthesis (DBT) are most commonly used technologies. To standardize clinical interpretations of imaging, the American College of Radiology introduced the Breast Imaging Reporting and Data System (BI-RADS), which comes up with four distinct risk categories of mammographic density. In the 5th edition, it delineated mammographic density categories as [16]: (a) Almost entirely fatty; (b) Scattered areas of fibroglandular density; (c) Heterogeneously dense, potentially obscuring the detection of small masses; and (d) Extremely dense, which lowers the sensitivity of mammography (Fig. 2).

Numerous epidemiological studies have demonstrated that high mammographic density is associated with an increased risk of breast cancer, with this evidence primarily derived from cohort and case-control studies [3–5, 17–20]. Initial case-control studies conducted by Wolfe et al. [21] and Boyd et al. [22] revealed that women with the highest mammographic density category are more likely to develop breast cancer compared to those with low mammographic density category. This significant finding suggests that high mammographic density may serve as a surrogate marker of increased breast cancer risk. The association has been later confirmed by research conducted on various ethnic populations worldwide, under the guidance of a singular measurement of mammographic density, however, many studies assessing the correlation between mammographic density and the risk of breast cancer have relied on a singular measurement of mammographic density. This approach presents considerable variability in the interval between the diagnosis of breast cancer and the timing of the last negative mammogram [23].

Contribution of genetic factors to mammographic density

Given the substantial body of research establishing the heritable nature of mammographic density and its role as a significant risk factor for breast cancer [24–26], particularly among individuals with a family history, there's compelling evidence for the genetic influence on mammographic density [18, 25, 27, 28]. For instance, a cohort study involving 1,370 women from 258 independent families pinpointed the influence of a major autosomal gene on mammographic density, as demonstrated by separation analysis [25]. Furthermore, classic twin studies have

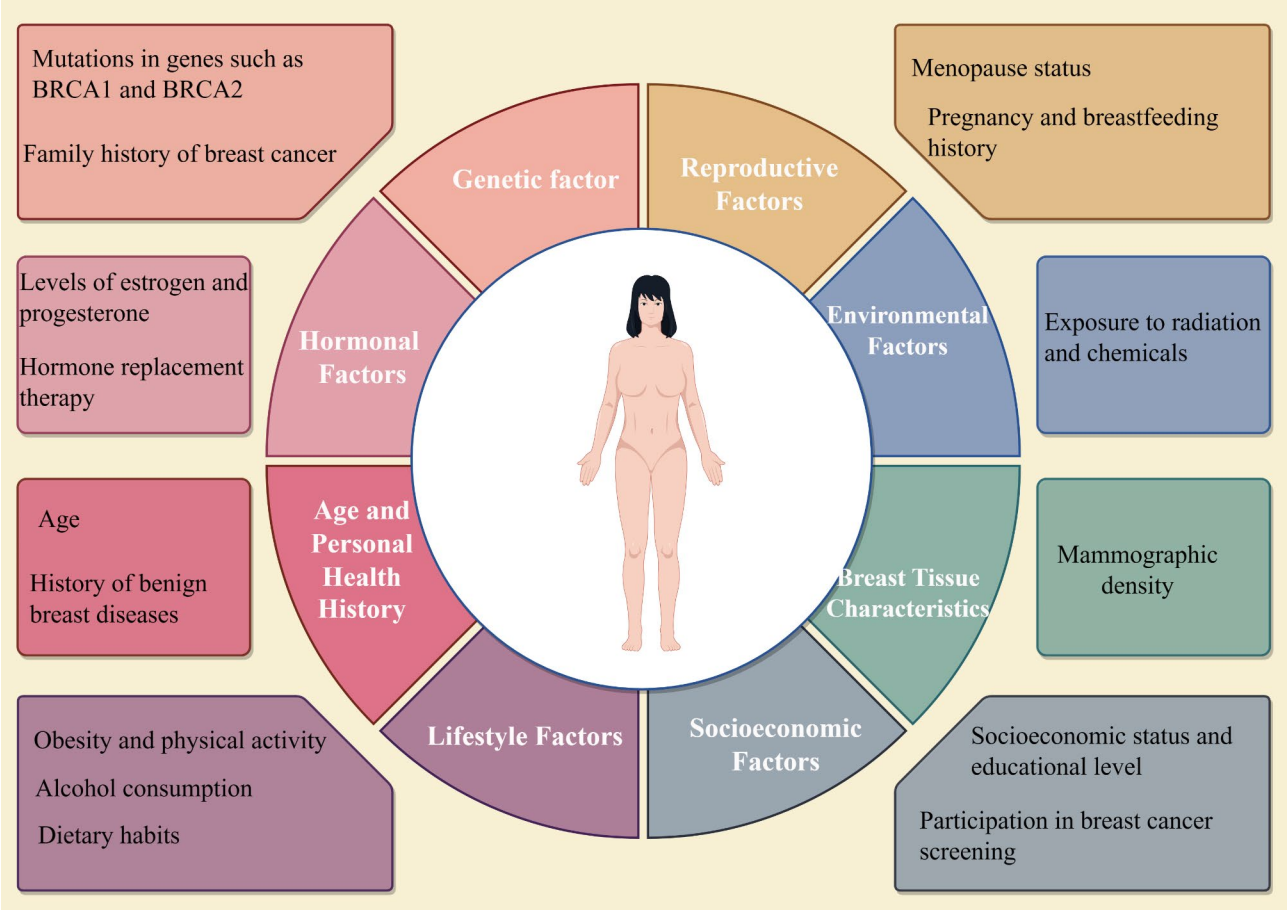

Fig. 1 The risk factors associated with breast cancer. Note: The figure was drawn by using Figdraw

delineated the substantial genetic contribution to variations in mammographic density, revealing heritability estimates ranging from 60 to 75% [26]. The significant heritability of mammographic density underscores the necessity of research into the shared genetic loci that influence both mammographic density and breast cancer [29–32]. This necessitates a deeper exploration into the mechanistic pathways linking these genetic loci with breast cancer risk, offering a fertile ground for advancing our understanding and potentially uncovering new therapeutic targets.

In-depth whole-genome array analysis further revealed how specific genetic variations influence breast cancer risk by modulating mammographic density. For instance, the down-regulation of *UGT* genes due to exposure to female sex hormones is directly associated with high mammographic density, which could further increase the risk of breast cancer [33]. This discovery not only enriches the comprehension of the hormonal-genetic interplay affecting mammographic density but also prompts further investigation into the preventive strategies that could mitigate these risks. Further study has discovered that tumors in different mammographic densities exhibit distinct genetic characteristics, such as an increased frequency of TP53 mutations and the extent of genomic alterations, revealing how mammographic density is linked to breast cancer risk through genetic pathways [34]. Furthermore, research has shown that single-nucleotide polymorphisms (SNPs) are associated with mammographic density, indicating that these genetic variations may influence breast cancer risk by altering mammographic density [35, 36]. A meta-analysis [37] of 68 studies identified key genetic modifiers for mammographic density such as *ESR1* and *IGF1*, suggesting their potential as biomarkers for risk assessment. Additionally, a study linking polygenic risk scores (PRS) with mammographic density underscores the genetic basis of breast cancer risk [24]. These findings underscore the importance of further exploring the genetic basis of mammographic density for the early identification of breast cancer risk and the development of personalized screening strategies.

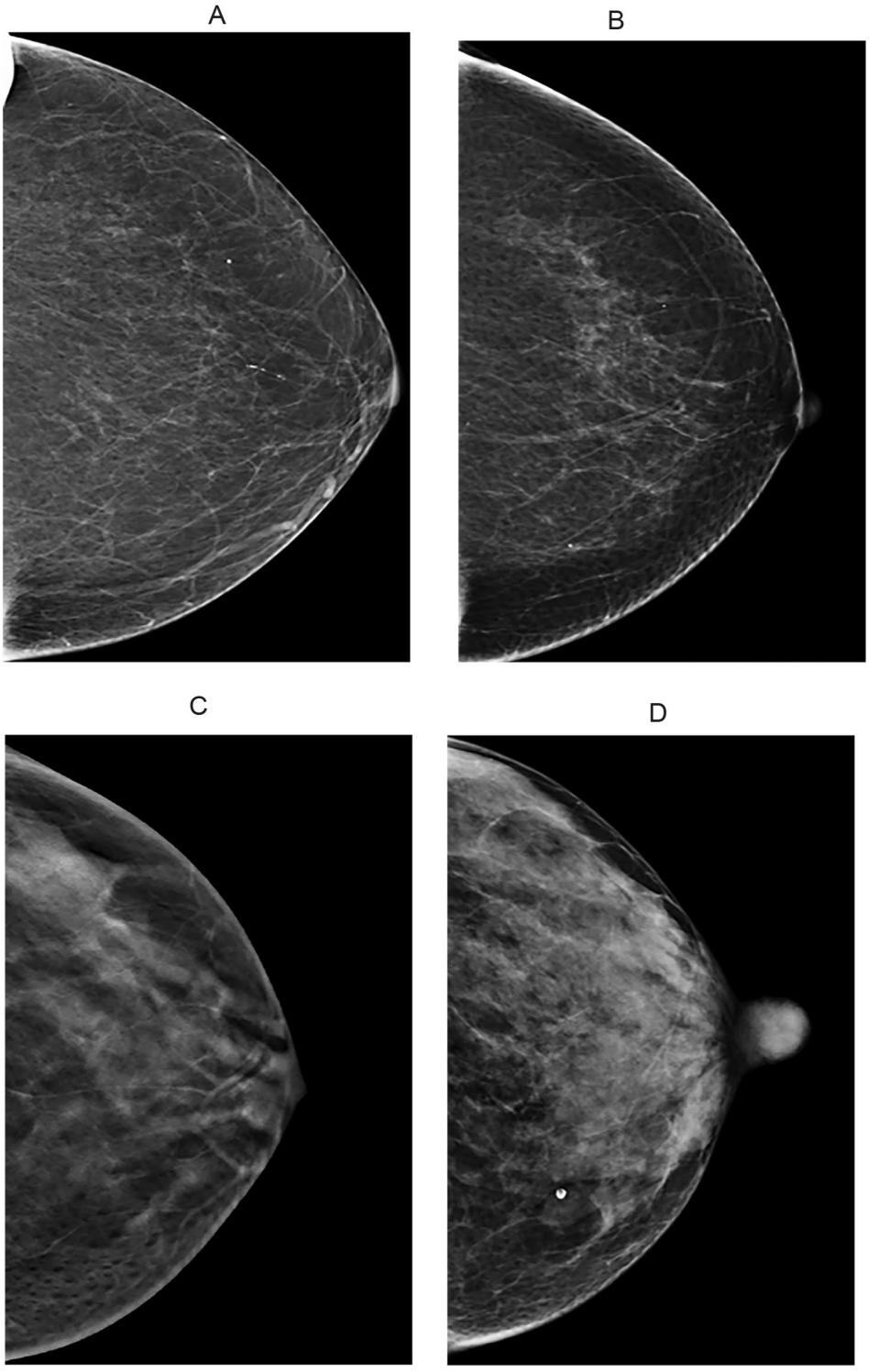

Fig. 2 The images represent different categories of mammographic density: **(A)** almost entirely fatty; **(B)** scattered areas of fibroglandular density; **(C)** heterogeneously dense; **(D)** extremely dense. Source: Images courtesy of Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital & Institute

Contribution of environmental factors to mammographic density

Mammographic density is known to be influenced by reproductive history, lifestyle choices, and exogenous hormones [10, 38–41], indicating that it may serve as a marker of exposure to environmental factors that predispose women to breast cancer. Pike et al. [42] has proposed a model of breast cancer incidence that shifts focus from chronological age to the concept of "breast tissue exposure". This model identifies the exposure of breast tissue to hormonal and reproductive factors as critical determinants, affecting the tissue's susceptibility to carcinogens. Generally, mammographic density either remains stable or decreases incrementally with time. An increase in mammographic density, however, may signify proliferative changes that surpass the effects of aging. Changes in mammographic density can reflect the hormonal environment of a woman, as well as the reproductive factors that are associated with breast cancer risk.

Puberty is a critical period for breast development, during which endocrine and paracrine factors stimulate the growth of epithelial, stromal, and adipose tissues in the breast [43, 44]. The relative proportions of these different cell types determine mammographic density and influence the risk of breast cancer. Epidemiological studies have found that timing of puberty, onset of pubertal breast development, onset of menstrual cycling, and pubertal tempo, were associated with adult mammographic density [45–50]. For example, Schoemaker et al. [46] found that earlier pubertal onset was associated with lower adult mammographic density. Another prospective cohort study found that a slower pubertal tempo was associated with higher mammographic density in young women [45]. Some studies have found that later age at menarche was positively associated with mammographic density [47–50], while others found no relationship between age at menarche and mammographic density [11, 51, 52]. Additionally, fatty deposition and glandular involution post-menopause can significantly influence changes in mammographic density [53–55]. Many epidemiological studies have used subgroup analyses, stratifying populations by menopausal status to adjust for potential confounding factors.

Some studies have explored the inverse relationship between body mass index (BMI) and mammographic density, indicating that higher BMI is often associated with lower mammographic density [11, 56–60]. This trend persists when examining the impact of pubertal adiposity, as measured by BMI, on mammographic density in adult women [47, 48, 61]. Epidemiological studies have also evaluated the association between mammographic density and other risk factors, such as alcohol consumption, smoking, diet, and physical exercise; however, the results were not always consistent [62–67]. The variability in findings across different studies highlights the intricate interplay of genetic and environmental factors that contribute to mammographic density and, by extension, breast cancer risk.

Breast tissue composition associated with mammographic density

Breast tissue comprises mammary epithelial cells, where breast cancer mostly originates, as well as stroma, including mammary fibroblasts, collagen, immune cells, and the extracellular matrix (ECM), and adipose tissue [68, 69]. The relative abundance of these components determines mammographic density that appears on the mammography. The intricate interplay between the epithelium, stroma, and ECM may play a role in elevating mammographic density and, consequently, breast cancer risk.

Epithelium and stroma

Some studies, utilizing surgical biopsies or mastectomy specimens for histological comparison with mammographically determined mammographic density, have found that increased amounts of epithelium and/or stroma are associated with higher mammographic density [70–74]. The structural and signaling scaffold provided by the stroma not only encapsulates epithelial structures but also fosters their optimal development and functionality, mediating this through paracrine growth factors [75]. Increased stromal density directly regulates the three-dimensional mechanical microenvironment of mammary epithelial cells, influencing proliferation and phenotype [76]. However, not all studies found an increase in cell proliferation in denser breast tissues, indicating that other factors might be at play [74, 77, 78]. In a study analyzing samples from women undergoing prophylactic mastectomy, tissues with high mammographic density exhibited increased collagen deposition and organization compared to those with low mammographic density [74]. Additionally, another study confirmed that high mammographic density is associated with a higher proportion of stromal composition, particularly increased collagen density and fibrosis extent [79]. These findings underscore the role of the breast's extracellular matrix in modulating tissue stiffness and potentially facilitating a pro-carcinogenic microenvironment. Interactions within the breast microenvironment influence each component, and changes induced by various factors in any component can directly or indirectly alter the microenvironment, thereby influencing the risk of breast cancer.

Fibroblasts

Fibroblasts, the predominant cell type in the mammary stroma, play a crucial role in the production and turnover regulation of collagen and other ECM components [69].

In regions of high mammographic density, fibroblasts may secrete soluble factors that trigger the proliferation of epithelial cells [75, 80]. Subsequently, these overstimulated epithelial cells may experience phenotypic alterations and release factors that re-activate fibroblasts, creating a dynamic feedback loop that further stimulates fibroblast activity [75]. Continuous activation of fibroblasts can lead to the excessive accumulation of these components, resulting in fibrosis [69]. This process can be modulated by signals from immune cells present in the mammary stroma [34, 81]. Research has consistently shown that, compared to low mammographic density, high mammographic density is associated with a more pro-inflammatory environment [34, 81, 82]. The chronic pro-inflammatory milieu in dense breast tissue could serve as a priming ground for oncogenic mutations, facilitating the transition from hyperplasia to malignancy.

Collagen

Collagen, a key fibrous protein within the ECM, is now recognized not just for its structural role but also for its dynamic involvement in breast cancer pathogenesis. The established correlation between collagen's abundance and alignment in tissues with high mammographic density underscores the intricate relationship between the ECM composition and tumorigenesis [83]. Provenzano et al. [76] utilized a bi-transgenic tumor model featuring increased stromal collagen in mouse mammary tissue to assess the impact of collagen density. Their findings revealed that heightened collagen levels in mouse mammary tissue significantly accelerated tumor formation and led to a markedly more invasive phenotype. Further analysis utilizing second harmonic generation imaging on breast biopsies, discovered that as the severity of diagnosis increased, collagen fibers tended to be less dense, shorter, straighter, thinner, and more aligned with each other [83]. The increased deposition of fibrillar collagen has been demonstrated to lead to enhanced matrix stiffness and disrupt physiological mammary morphogenesis [84].

Targeting the mechanical properties of the ECM may offer new avenues for cancer treatment. A study provided direct 3D experimental evidence showing that ECM alignment and density could expedite breast cancer progression by fostering fibroblast induction and inhibiting T-cell activation [85]. This insight of the ECM's capacity in modulating the immune response highlights an underexplored avenue for the potential treatment role of ECM organization and density in breast cancer. Lysyl oxidase (LOX), a crucial mediator of collagen crosslinking, emerges as a potential therapeutic target due to its significant contribution to stromal stiffening and its pivotal role in maintaining ECM integrity [86]. The activity of LOX is essential for reinforcing the tensile strength of the ECM, which suggests that modulating LOX activity could alter the tumor microenvironment and potentially inhibit tumor progression [87].

Within this dynamic mechanical microenvironment, epithelial cells are significantly influenced by the dense collagenous stroma. At the molecular level, the identification of key pathways regulating epithelial-stromal interactions, particularly those mediated by focal adhesion kinase (FAK), opens up new possibilities for targeting cell adhesion and migration in cancer therapy [88]. FAK, a widely expressed non-receptor protein tyrosine kinase, is pivotal in regulating cell proliferation and gene expression via Extracellular-Signal Regulated Kinase (ERK)-mediated pathways [88]. It initiates cytoskeletal rearrangements and cellular shape changes, promoting actomyosin stress fiber formation [89]. Additionally, FAK influences cell motility and migration by loosening focal adhesions and upregulating MMP-9, contributing to the invasive phenotype of breast cancer [90]. In conclusion, while these findings advance our understanding of collagen's role in breast cancer, they also beckon further research into how these mechanisms can be harnessed for clinical benefit. Future studies should aim to explore the translational potential of targeting ECM components and their regulatory pathways, such as LOX and FAK, to develop novel therapeutic strategies against breast cancer.

Other ECM components

The ECM is a complex and dynamic entity that, besides including collagen, encompasses other proteins such as laminin, fibronectin, proteoglycans (PGs), and proteases [91]. These components act as a structural scaffold, offering support for tissue assembly, maintenance, and integrity. Small leucine-rich proteoglycans (SLRPs), such as lumican, decorin, fibromodulin, and biglycan, play a crucial role as components of the ECM and are associated with increased tissue density [92–94]. Additionally, the accumulation of the matrix proteoglycan versican within the tumor stroma has been correlated with dense breast tissue and malignant transformation [95].

Immune system components

Several studies have showed that dense breast tissue was associated with a pro-inflammatory microenvironment that may promote cancer development [96–98]. Various immune cells, including macrophages, eosinophils, neutrophils, and lymphocytes (T and B cells), are integral to the mammary gland's development and transformation [99]. These cells contribute to inflammatory responses and shape the tumor microenvironment by secreting cytokines, enzymes, and chemokines (Table 1) [100–103].

Table 1 The function of various immune cells in breast microenvironment

Immune cells	Functions	First author/study (reference)
Macrophages	CC-chemokine ligand 2 (CCL2) is an inflammatory cytokine critical for recruiting macrophages to sites of injury. When expressed constitutively by the mouse mammary epithelium, CCL2 induces a state of chronic low-level inflammation that leads to an increased number of macrophages and enhanced stromal density.	Sun X [98]
Eosinophils	Eosinophils secrete eosinophil peroxidase, an enzyme that promotes fibroblast recruitment and establishment of collagen-rich ECM.	DeNichilo MO [99]
Cytokines	Cytokines linked to neutrophil signaling, such as granulocyte-monocyte colony-stimulating factor (GM-CSF), show elevated levels in collagen-dense tumors. This increase indicates an enhanced recruitment and activation of neutrophils within the dense collagen tumor microenvironment.	García-Mendoza MG [100]
Lymphocytes	High mammographic density tissue is characterized by increased infiltration of B cells and CD4 T cells, including activated T cells marked by PD-1 expression, as well as a pro-tumor Th2 polarization indicated by elevated secretion of IL-6 and IL-4. This pro-tumorigenic microenvironment potentially facilitates an escape from immune regulation, providing early tumor cell variants with a niche to evade immune surveillance and proliferate unchecked.	Huo CW [101]

There still remain many gaps in our understanding of the cellular and molecular mechanisms that underpin the strong association between mammographic density and breast cancer predisposition. The evidence points to a complex network of interactions that govern the relationship between mammographic density and cancer risk, implying that risk reduction strategies must account for the intricate composition of breast tissue and its microenvironment.

Breastfeeding and breast cancer risk

Breast tissue undergoes continuous transformation throughout an individual's lifetime. This includes the expansion and development of the mammary gland during puberty, cyclic proliferation and involution corresponding with menstrual cycles, glandular and ductal adaptations during lactation, and the deposition of fatty tissues coupled with further involution post-menopause [10]. Recent epidemiological findings underscore the recognized benefits of breastfeeding in reducing breast cancer risk, especially for aggressive subtypes [14, 104–109]. A collaborative reanalysis involving 47 epidemiological studies across 30 countries has demonstrated that the relative risk of breast cancer decreases by 4.3% for each year of breastfeeding [14]. This relationship holds true consistently across women from both developed and developing countries, spanning various ages and ethnic origins, and encompassing diverse childbearing patterns and personal characteristics. Specifically, breastfeeding has been shown to reduce the risk of triple-negative breast cancer (TNBC) by 20% and offers a risk reduction of 22–50% in carriers of BRCA1 mutations [107, 110–112]. Notably, a study including 4,000 Black women diagnosed with breast cancer, alongside 14,000 control participants, revealed a correlation between childbearing and an elevated risk of estrogen receptor negative (ER-) and TNBC. Crucially, this study also identified breastfeeding as a significant mitigating factor in reducing this heightened risk [113].

Childbearing is generally linked to a long-term reduction in breast cancer risk; however, recent research indicates a nuanced pattern, particularly noting a transient increase in risk during the early postpartum period, specifically within the first 5–10 years following childbirth [114–116]. Key factors influencing this increased risk include maternal age at first childbirth, with older first-time mothers facing higher risks compared to younger ones [116], and the duration of breastfeeding [14, 117]. Extended breastfeeding, particularly beyond 12 months, is associated with substantial protective benefits against breast cancer [104, 105, 118]. This protective effect underscores the critical importance of breastfeeding duration in mitigating breast cancer risk. Additionally, women with no prior births (nulliparity) and those who delay childbearing are often found to have higher mammographic densities, further elevating their breast cancer risk [55, 115, 119]. The challenge is compounded by the lower frequency of mammographic screenings in young postpartum women, resulting in cancers that are typically self-detected, larger, and more advanced than those identified through routine screenings. To effectively manage and potentially mitigate these risks, it is crucial to adapt breast cancer screening strategies to accommodate the unique circumstances of young mothers, particularly during the vulnerable postpartum period. This adaptation may involve reassessing the timing and frequency of mammograms to ensure early detection and treatment of breast cancer in this high-risk group.

Overall, based on the epidemiological studies, breastfeeding exerts a protective effect against breast cancer, offering significant benefits for public health. Several mechanisms are proposed to explain how this effect comes about [120, 121]: Firstly, breastfeeding promotes

differentiation of breast cells for milk production, potentially reducing their vulnerability to carcinogenic transformation. Secondly, breastfeeding is associated with ovulatory cycles. The decrease in ovulation reduces the exposure to estrogen and other hormones that can promote breast cancer growth. Thirdly, during lactation, the shedding of breast epithelium may help to remove mutated cells and potentially eliminate carcinogens, thereby reducing the risk of cancer development. The concurrence of all these mechanisms represents the complex biological pathways through which lactation may confer protection against breast cancer and emphasize its role in cancer prevention strategies. It is thus imperative that breastfeeding should be promoted as a potentially impactful strategy in reducing breast cancer incidence.

Breastfeeding and mammographic density

The significant effect of breastfeeding and mammographic density on women's health, can be better understood in their relevance to breast cancer risk. Breastfeeding acts as a protective factor, whereas dense breast tissue is considered a risk factor. However, research on the association between the two has yielded inconsistent results, owing to the complex relationship between them and breast cancer risk which is liable to a combination of genetic, hormonal, and environmental factors. Furthermore, the underlying biological mechanisms whereby breastfeeding may influence mammographic density remain uncertain.

Epidemiological evidence

The epidemiological studies on the association between breastfeeding and mammographic density have led to inconsistent findings [11, 38, 54, 57, 122–128]. Some link breastfeeding with lower mammographic density [122, 125, 126, 128], particularly with prolonged duration, some suggest the opposite, associating it with higher mammographic density [11, 54], while others negate any significant relationship between the two [57, 124, 127]. These divergent conclusions can be attributed to an assortment of variables, one of them being menopausal status, that hinder a clear understanding of this association [38, 125, 128]. Another variable is the duration of breastfeeding which differs according to educational background and socioeconomic status. Reproductive history may also affect the results derived from related epidemiological studies by way of the number of pregnancies, the intervals between pregnancies, the duration of breastfeeding following each pregnancy, the duration of exclusive breastfeeding. All in all, the diversity of breastfeeding practices and reproductive patterns justifies the complexity of the problem but without showing the way out.

Biological mechanisms

The biological mechanisms through which breastfeeding impacts mammographic density remain elusive. The pregnancy-lactation-involution cycle represents a dynamic and multi-step process susceptible to many factors and involves significant changes in the breast tissue, starting with pregnancy, continuing through lactation, and concluding with the post-lactation involution. Each stage of this cycle could potentially affect breast tissue composition and consequently mammographic density. Breastfeeding significantly affects the physiological structure of the mammary glands, involving the proliferation of mammary gland tissues and the development of mammary alveoli during pregnancy, the filling of alveoli and milk secretion during lactation, and the involution of alveoli and remodeling of mammary tissues during weaning [121]. Moreover, the breast microenvironment—encompassing gene expression, protein regulation, and the components of the ECM—may also be influenced by breastfeeding. All this evidence indicates that the varied epidemiological findings on the association between breastfeeding and mammographic density could be a reflection of the complex mechanisms that regulate mammary gland development, as well as the multifaceted determinants of mammographic density. The biological impact of lactation on mammographic density is summarized in Fig. 3.

Breastfeeding and involution

The post-lactational involution of breast tissues involve unique changes in the microenvironment, distinctly different from those that have not undergone lactation [115]. During mammary gland involution, a significant portion of mammary epithelial cells undergo programmed cell death, while others return to their pre-pregnancy state [120]. This remodeling process is influenced by the duration of breastfeeding, suggesting that longer periods of lactation may lead to more pronounced changes in the breast tissue's structure and composition. These alterations could potentially impact the overall breast microenvironment. When breastfeeding is not initiated after birth or is abruptly discontinued shortly after, the breast tissue undergoes a forced and abrupt involution. Conversely, when breastfeeding is sustained over an extended period and concludes gradually, the breast tissue undergoes a slow remodeling process known as gradual involution. Considering the clinical significance of understanding breast tissue dynamics, particularly in the context of breast cancer risk, it becomes imperative to delve into the implications of these distinct involution patterns. By elucidating the differences between abrupt and gradual involution and their consequences for breast tissue composition and microenvironment, we can potentially uncover novel avenues for risk assessment and

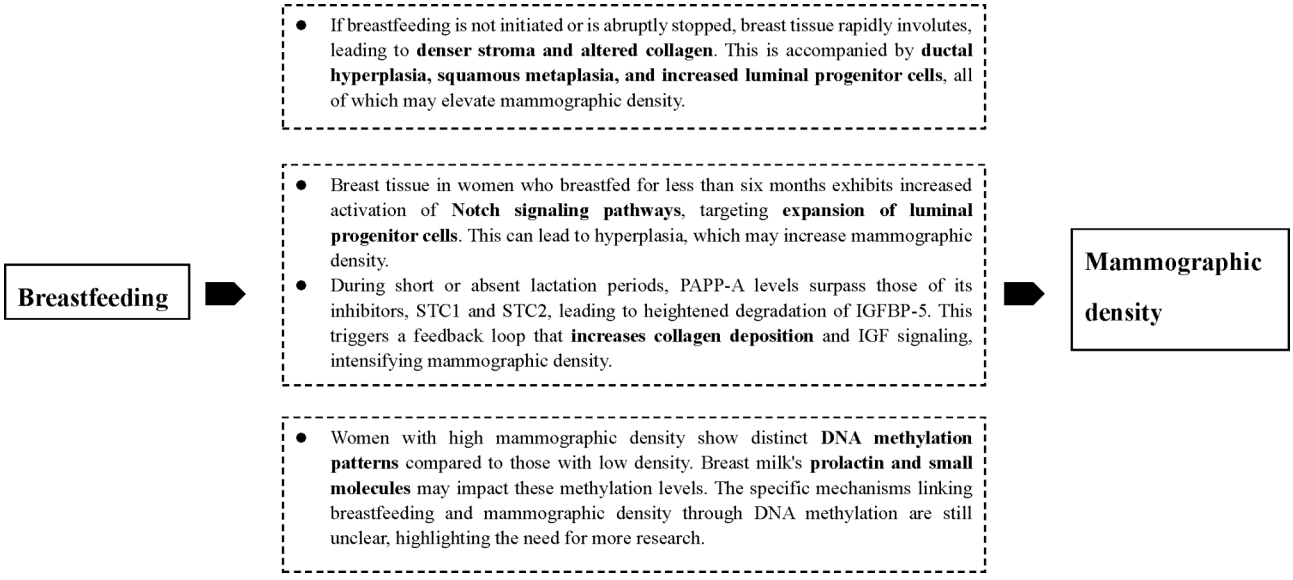

Fig. 3 The biological impact of lactation on mammographic density

prevention strategies. It is shown that under abrupt involution mammary glands from mice exhibited characteristics distinct from those undergoing gradual involution [129]. Specifically, they displayed denser stroma, altered collagen composition, heightened inflammation and proliferation, along with increased expression of estrogen receptor α (ERα) and progesterone receptor, compared to gradual involution. Furthermore, abrupt involution led to significant ductal hyperplasia, squamous metaplasia, and a sustained increase in luminal progenitor cells. These findings highlight the profound impact of the involution process on breast microenvironment, suggesting potential implications for understanding breast tissue changes and cancer risk associated with different breastfeeding patterns.

Breastfeeding and breast microenvironment

Breastfeeding significantly impacts the breast microenvironment, influencing the behavior and characteristics of epithelial cells and the ECM. In scenarios where breastfeeding is not initiated or is of short duration, a terminal bud structure persists in the breast tissue following involution [130]. This structural remnant leaves epithelial cells more susceptible to carcinogenic stimulation, potentially facilitating the transformation of these cells into cancerous ones [130]. Abrupt involution in mouse mammary glands has been shown to correlate with increased collagen deposition and a higher ratio of type I to type III collagen [129]. This finding suggests that the duration of breastfeeding following each pregnancy could influence mammographic density. Moreover, abrupt involution is associated with heightened expression of ERα, increased proliferation index, and the presence of hyperplasia and squamous metaplasia [129]. The findings further revealed that breast tissue from healthy women who breastfed for less than 6 months exhibited a positive enrichment of genes within the Notch signaling pathways which indicated an active regulatory mechanism in these women's breast tissue, which may influence breast development. It was demonstrated that constitutive Notch signaling specifically targets luminal progenitor cells for expansion [131]. This continuous activation can lead to hyperplasia, an abnormal increase in the number of cells, and potentially to tumorigenesis, the formation of tumors. This suggests that while Notch signaling is crucial for normal breast development, its dysregulation may contribute to breast cancer pathogenesis. This observation provides additional evidence suggesting that never breastfeeding or brief periods of breastfeeding might promote the expansion of luminal progenitor cells, which are associated with breast cancer. These changes indicate that never breastfeeding or short-term breastfeeding may contribute to the development of a pro-tumorigenic environment.

Extended lactation has been demonstrated to offer protection against carcinogenesis mediated by pregnancy-associated plasma protein-A (*PAPP-A*), a pregnancy-dependent oncogene [132]. Research involving transgenic mice with *PAPP-A* expression in the mammary gland during pregnancy and involution demonstrated that *PAPP-A* promotes collagen deposition [132]. This increase in collagen facilitates the proteolytic activity of *PAPP-A* on insulin-like growth factor-binding proteins 4 and 5 (IGFBP-4 and IGFBP-5), enhancing insulin-like growth factor (IGF) signaling and further collagen deposition. Notably, *PAPP-A* transgenic mice that lactated for extended periods did not develop mammary tumors, whereas those that lactated for shorter durations

exhibited mammary tumors characterized by a specific collagen signature associated with tumors (TACS-3). The lactation-induced protective effect was linked to the upregulation of *PAPP-A* inhibitors, stanniocalcin-1 (STC1), and stanniocalcin-2 (STC2), with prolonged lactation correlating with higher levels of these inhibitors [132]. These elevated levels of STC1 and STC2 during extended lactation inactivate *PAPP-A*, even when overexpressed, preventing IGFBP-5 cleavage and allowing normal involution to proceed. Conversely, in the absence of lactation or during short lactation periods, *PAPP-A* levels surpass those of its inhibitors, STC1 and STC2, leading to excessive IGFBP-5 degradation. This imbalance establishes a positive feedback loop between increased collagen deposition and enhanced IGF signaling. This augmented collagen deposition intensifies mammographic density, which is a recognized risk factor for tumorigenesis. Thus, the altered microenvironment not only contributes to higher mammographic density but also directly influences the progression towards breast cancer.

Breastfeeding and DNA methylation

DNA methylation, a common epigenetic modification in mammals, is facilitated by DNA methyltransferase enzymes, such as DNMT1, DNMT3a, and DNMT3b [133]. DNA methylation plays an important role in modulating gene expression without changing the underlying DNA sequence. This modification is pivotal in regulating gene expression, enabling the silencing or activation of genes without altering the DNA sequence itself. Importantly, DNA methylation has been identified as a key factor in the tumorigenesis of breast cancer, suggesting that alterations in methylation patterns can contribute to the initiation and progression of cancers [134]. Recent research has revealed distinct DNA methylation patterns between women with high mammographic density and those with low mammographic density who later develop breast cancer [135]. Specifically, differences were noted in genes responsible for regulating DNA transcription and cell apoptosis. This finding suggests that variations in DNA methylation related to mammographic density may influence key biological pathways, potentially affecting the risk of developing breast cancer. The protective effect of breastfeeding against breast cancer is partly attributed to the stimulation of prolactin, which enhances the expression of DNA methyltransferase enzymes in mammary epithelial cells during lactation [136, 137]. This hormonal influence facilitates epigenetic modifications that could play a role in reducing cancer risk. Additionally, the presence of small molecules in breast milk, such as miR-29s, has been investigated for their role in regulating DNA methylation levels. MiR-29s specifically targets and inversely regulates DNMT3a and DNMT3b in mammary epithelial cells [138], suggesting a mechanism by which breastfeeding may influence the epigenetic landscape of the breast tissue. These findings highlight the complex interplay between hormonal changes during lactation and molecular mechanisms in breast milk that contribute to the protective effects of breastfeeding on breast cancer risk. Despite the recognition of the potential mechanisms by which breastfeeding influences breast cancer risk through DNA methylation, there have been limited studies directly evaluating the relationship between DNA methylation, breastfeeding, and mammographic density. This gap in research highlights the need for further investigation into how breastfeeding may impact mammographic density through epigenetic modifications such as DNA methylation. Understanding this relationship could provide valuable insights into the complex interplay between genetic and environmental factors in breast cancer risk and the protective role of breastfeeding.

Future directions

Mammographic density is a key indicator of the breast tissue microenvironment, subject to modulation by several established breast cancer risk factors. As a protective factor against breast cancer, prolonged lactation has been shown to reduce the risk of developing the disease. Drawing insights from contemporary epidemiological and molecular biology studies, our review sheds light on how lactation impacts on the mammographic density and explores their role in influencing the development of breast cancer (Fig. 4).

To address the complex relationship between breastfeeding, mammographic density, and breast cancer, a multi-faceted research strategy is paramount. Firstly, future research should focus on combining advanced imaging techniques and genetic analysis to better understand how breastfeeding affects mammographic density and breast cancer risk. This entails not only the refinement of imaging methodologies to accurately quantify changes in mammographic density but also the exploration of genetic markers that may influence these changes and their correlation with cancer development. Secondly, long-term studies are essential, especially those that consider different ethnic groups and extend over long periods. These studies should carefully record details about reproduction, such as the number of pregnancies, time between pregnancies, how long breastfeeding lasted after each pregnancy, and the duration of exclusive breastfeeding. This approach aims to clearly understand the connection between breastfeeding, changes in mammographic density, and breast cancer development over time among various populations. Thirdly, it is essential to probe into the interconnections between breastfeeding, mammographic density, lifestyle and environmental determinants. A holistic integration of these factors could

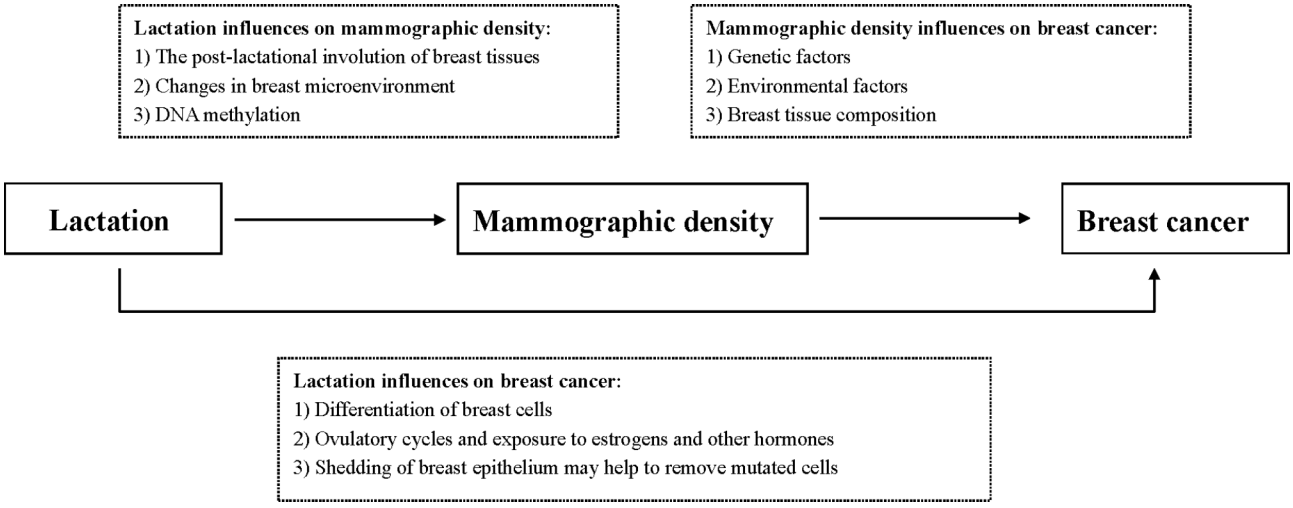

Fig. 4 The association between lactation, breast density and breast cancer

unveil their cumulative influence on breast cancer risk, paving the way for identifying synergistic avenues for risk mitigation. Lastly, deepening our understanding of the association between breastfeeding, mammographic density, and breast cancer, developing innovative preventive and screening methodologies are helpful for breast cancer screening. Such strategies, particularly advantageous for individuals at elevated risk, would integrate insights into mammographic density and breastfeeding history into predictive models and screening protocols. Customizing screening timetables and methodologies to reflect individual risk profiles holds the potential to markedly amplify the efficacy of early detection.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This review involves the use of patient images for Fig. 2, which was approved by the Medical Ethical Committee of Liaoning Cancer Hospital and Institute (20220327G).

Consent for publication
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Competing interests
The authors declare no competing interests.

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