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IMPACT OF EARLY PRIMIPARITY ON MAMMARY EPITHELIAL DIFFERENTIATION: A MECHANISTIC STUDY OF HORMONAL SIGNALLING AND BREAST CANCER SUSCEPTIBILITY IN RURAL INDIA.

Astha Topno [1*], Manshi Kumari [1], Purnima Kumari [1], Sakshee Kumari Goswami [1], Megha Chhattaraj [1], Sweta Verma [1], Nisha Kumari [1] , Deepika Kumari [1], Divyanshi [1], Anisha Kumari [1], Kajal Kumari [1], Annu Priya [1], Mona Singh [1], Rakhi Kumari [1], Amisha Kumari [1], Tamanna Parween [1], Priyanka Daniel [1], Shruti Kumari [1], Sneha Singh [1], Jasmine Kumari [1], Khusboo Kumari [1], Chhaya Kumari [1], Anushreya Soreng [1], Puja Kumari [1], Komal Singh [1], Misha Bharti [1], Sneha Sinha [1], Prajapati Riya Kumari Suresh [1], Rani Kumari [1], Archana Kumari [1], Pushpa Kumari [1], Priyanka Kumari [1], Khusboo Kumari [1], Raunaq Kumari [1], Meenu Kumari [1], Mukti Oraon [1], Manvi Kumari[1], Mira Kumari [1], Pushpa Kumari [1], Priyanka Kumari [1], Ayushi Raj Shree [2]

[1]**Student,** Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

[2] **Student,** School of Pharmacy, Sai Nath University, Ranchi, Jharkhand-835219, India.

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***Corresponding Author: Astha Topno**
Student, Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

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ABSTRACT

Background: Early age at first birth (primiparity) has long been epidemiologically associated with reduced lifetime risk of breast cancer in high-income countries. However, the biological and hormonal mechanisms underlying this protection remain incompletely understood, particularly in the context of rural Indian populations where early marriage and childbirth persist. This review critically examines the mechanistic pathways through which early primiparity influences mammary epithelial differentiation, hormonal signalling cascades, and the molecular determinants of breast cancer susceptibility. **Methods:** A systematic search of PubMed, Scopus, Web of Science, and Google Scholar databases was conducted using terms including 'early primiparity,' 'mammary gland differentiation,' 'breast cancer risk,' 'BRCA signaling,' 'prolactin,' 'estrogen receptor,' and 'rural India.' Studies published between 2000 and 2024 in peer-reviewed journals were included. Narrative synthesis was employed to integrate molecular, epidemiological, and clinical evidence. **Results:** Early full-term pregnancy triggers irreversible differentiation of mammary epithelial progenitor cells, reducing the pool of susceptible target cells for oncogenic transformation. Key hormonal mediators include pregnancy-induced prolactin, progesterone, oxytocin, and human placental lactogen, which collectively activate STAT5, PI3K/Akt, and Wnt/β-catenin pathways to promote terminal lobular differentiation. Epigenetic remodeling, including methylation of BRCA1 and p53 promoters, further modulates long-term cancer susceptibility. In rural Indian cohorts, unique sociodemographic and nutritional confounders complicate this protective paradigm. **Conclusion:** Early primiparity exerts a durable protective effect on breast cancer risk through hormonally mediated mammary epithelial differentiation. However, this protection is context-dependent and must be weighed against reproductive health risks in adolescent mothers. Future research should prioritize population-specific mechanistic studies in rural Indian settings.

KEYWORDS: primiparity, mammary epithelial differentiation, breast cancer, hormonal signaling, STAT5, epigenetics, rural India, reproductive biology

1. INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide, accounting for approximately 2.3 million new cases annually (World Health Organization, 2022). In India, it represents the leading cause of cancer-related mortality among women, with an estimated 178,361 new cases recorded in 2020 alone ***(Mathur et al., 2020)***. Despite advances in genomic profiling and targeted therapeutics, the etiology of breast cancer remains multifactorial, encompassing genetic susceptibility, reproductive history, hormonal milieu, and environmental exposures. Among reproductive factors, the age at first full-term pregnancy (FFTP) has been consistently identified as a significant modulator of breast cancer risk. Women who give birth before the age of 20 have a substantially lower lifetime risk of developing breast cancer compared to nulliparous women or those who first deliver after age 30 ***(MacMahon et al., 1970; Trichopoulos et al., 1983)***. This classical epidemiological observation has been validated across diverse populations, yet the mechanistic underpinnings remain subject to ongoing investigation. In rural India, early marriage remains prevalent, with approximately 23% of girls married before age 18 as of 2019, according to National Family Health Survey (NFHS-5) data ***(IIPS & ICF, 2021)***. Consequently, early primiparity—defined here as first childbirth at or before age 20—is disproportionately common in these communities. While this demographic reality carries significant public health implications for adolescent maternal health, its intersection with breast cancer biology warrants rigorous mechanistic examination. The mammary gland is a uniquely dynamic organ that undergoes profound structural and functional remodeling during pregnancy and lactation. Pregnancy-induced hormonal signals drive terminal differentiation of mammary epithelial progenitor cells (MEPCs), which are widely regarded as the primary cellular targets for malignant transformation ***(Bhatt et al., 2021; Visvader, 2009)***. Early primiparity may permanently reduce the abundance and proliferative capacity of these susceptible progenitors, thereby limiting the target cell pool for subsequent oncogenic events.

This review synthesizes current molecular and epidemiological evidence to elucidate the mechanistic pathways through which early primiparity influences mammary gland biology, hormonal signaling, and breast cancer susceptibility, with particular attention to the sociocultural and biological context of rural Indian women.

2. Mammary Gland Development and Epithelial Hierarchy

2.1 Developmental Architecture of the Mammary Epithelium

The mammary gland is organized into a bilayered epithelial architecture comprising an inner luminal layer and an outer basal/myoepithelial layer, embedded within a collagen-rich stromal matrix. Luminal progenitor cells, characterized by expression of EpCAM, CD24, and the transcription factor GATA3, are responsible for secretory alveolar development during pregnancy ***(Shehata et al., 2012; Lim et al., 2010)***. Basal cells, marked by CD49f and p63 expression, provide structural and contractile support and harbor the mammary stem cell (MaSC) population. Lineage-tracing studies in murine models have established that luminal progenitors serve as the primary cell-of-origin for hormone receptor-positive breast cancers, while basal cells are implicated in the development of triple-negative and claudin-low subtypes ***(Marjanovic et al., 2013; Proia et al., 2011)***. The functional state of these progenitor populations at the time of carcinogenic insult therefore critically determines the molecular subtype of any resulting malignancy.

2.2 Pregnancy-Induced Terminal Differentiation

Full-term pregnancy induces terminal lobular differentiation of the mammary epithelium through a coordinated hormonal program. During the first and second trimesters, rising estrogen and progesterone levels drive ductal elongation and alveolar budding. The third trimester is characterized by a surge in prolactin and human placental lactogen (hPL), which collectively activate lactogenic differentiation programs ***(Brisken & O'Malley, 2010; Gass et al., 2003)***. Post-partum involution, regulated by STAT3 and transforming growth factor-β (TGF-β), remodels the gland back toward a resting state, albeit one that retains an epigenetic memory of prior differentiation. Crucially, this differentiation program is irreversible: post-parous mammary glands harbor a reduced proportion of undifferentiated luminal progenitors relative to nulliparous counterparts. Russo and Russo (1987, 2006) demonstrated through pioneering rodent experiments that early parity permanently alters mammary gland morphology, increasing the proportion of Lobule Type 3 and 4 alveoli—highly differentiated structures with minimal proliferative activity and correspondingly low susceptibility to carcinogen-induced transformation ***(Russo & Russo, 2006)***.

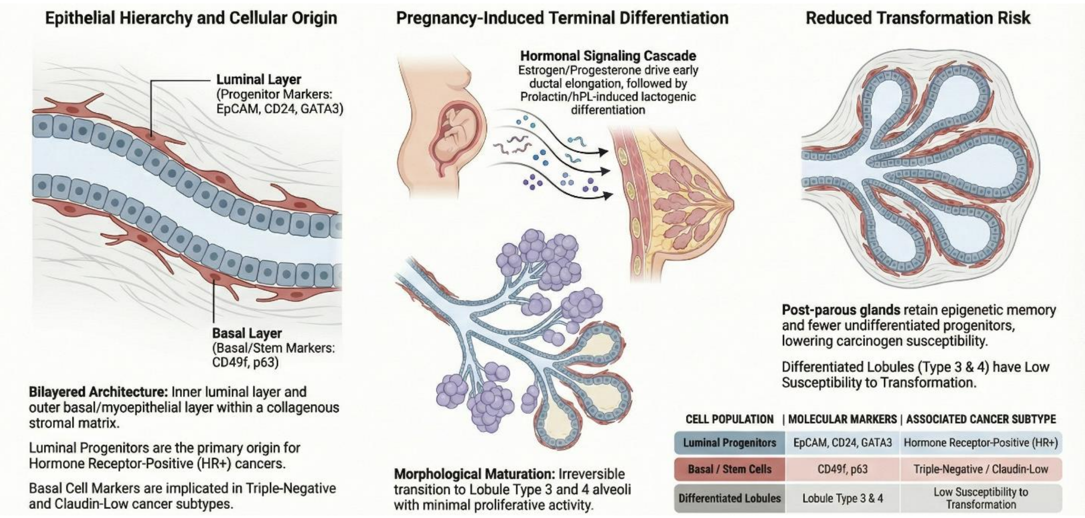

Fig.1. Pathophysiology of Mammary Epithelial Differentiation and Cancer Susceptibility

3. Hormonal Signalling Mechanisms in Early Primiparity

3.1 Prolactin and STAT5 Pathway Activation

Prolactin (PRL) is a pleiotropic hormone secreted by the anterior pituitary that plays a central role in mammary gland development and lactation. During pregnancy, PRL levels increase up to tenfold above basal concentrations, binding to the prolactin receptor (PRLR) on mammary epithelial cells to activate the JAK2/STAT5 signaling axis ***(Hennighausen & Robinson,***

2005; Clevenger et al., 2003). Phosphorylated STAT5a and STAT5b translocate to the nucleus, where they transcriptionally activate genes encoding milk proteins (casein, whey acidic protein) and cell cycle inhibitors including p21 Cip1 and p27 Kip1. STAT5 activation also promotes the expression of Bcl-2 family pro-survival proteins, paradoxically enhancing epithelial survival during peak lactation while simultaneously suppressing the proliferative signaling required for malignant progression ***(Iavnilovitch et al., 2002; Furth et al., 2011)***. Importantly, early-onset prolactin signaling—as occurs in teenage primiparous women—may durably alter the epigenetic landscape of the PRLR gene, reducing sensitivity to subsequent mitogenic PRL stimulation in adult life.

3.2 Estrogen Receptor Dynamics and ERα/ERβ Ratio

Estrogen exerts its mitogenic effects on mammary epithelium primarily through estrogen receptor alpha (ERα), encoded by the ESR1 gene. ERα-positive luminal progenitor cells proliferate in response to estradiol (E2) via induction of cyclin D1, c-Myc, and activation of the PI3K/Akt/mTOR pathway ***(Liang & Shang, 2013; Yue et al., 2017)***. In contrast, ERβ generally exerts anti-proliferative, pro-differentiative effects and may counterbalance ERα-mediated mitogenesis. Pregnancy transiently downregulates ERα expression in mammary epithelial cells while upregulating ERβ, shifting the ERα/ERβ ratio in favor of differentiation over proliferation ***(Speirs et al., 1999; Palmieri et al., 2002)***. In young primiparous women, this shift occurs during a developmentally critical window when the mammary gland is maximally responsive to hormonal cues, potentially establishing a durable anti-proliferative epigenetic set point.

3.3 Progesterone and Wnt/β-Catenin Signalling

Progesterone, acting through the progesterone receptor (PR), orchestrates alveologenesis during pregnancy in concert with PRL. PR signaling activates the Wnt/β-catenin pathway, driving symmetric divisions of luminal progenitor cells to populate the expanding alveolar tree ***(Joshi et al., 2010; Brisken et al., 1998)***. RANKL (receptor activator of NF-κB ligand), a downstream effector of PR signaling, acts as a paracrine amplifier of cell proliferation among PR-negative neighbors. In the context of early primiparity, progesterone-mediated Wnt signaling during adolescent pregnancy may prematurely deplete the luminal progenitor pool through terminal differentiation, leaving fewer undifferentiated cells susceptible to subsequent transforming events ***(Asselin-Labat et al., 2010; Sleeman et al., 2007)***. This depletion represents one of the most compelling mechanistic explanations for the epidemiological observation of reduced breast cancer risk following early parity.

3.4 Oxytocin and Human Placental Lactogen

Oxytocin, synthesized in the hypothalamus and released from the posterior pituitary, promotes myoepithelial contraction during lactation and has direct effects on mammary epithelial cell differentiation. Oxytocin receptor (OTR) activation in mammary cells has been reported to suppress cell proliferation and induce apoptosis via nitric oxide synthase (NOS) pathways ***(Cassoni et al., 2001; Copland et al., 1999)***. Human placental lactogen (hPL), structurally homologous to both prolactin and growth hormone, contributes to alveolar development by activating the GH receptor (GHR) and PRLR, complementing prolactin-driven STAT5 signalling.

4. Epigenetic Remodelling Following Early Primiparity

Epigenetic modifications—including DNA methylation, histone acetylation/methylation, and non-coding RNA regulation—translate transient hormonal signals into durable changes in gene expression that persist long after pregnancy ends ***(Jones & Baylin, 2002; Bhatt et al., 2021)***. This epigenetic memory of early parity is increasingly recognized as a key mechanism underlying the sustained protective effect against breast cancer. Pregnancy-induced methylation changes at CpG islands within the promoters of oncogenes such as c-Myc, and tumor suppressors including BRCA1 and p53, have been documented in post-parous mammary tissue from murine models ***(Huh et al., 2015; Bodelon et al., 2019)***. Specifically, post-parous glands exhibit increased methylation at the c-Myc promoter—consistent with reduced proliferative drive—and altered hydroxymethylation patterns at loci regulated by the ten-eleven translocation (TET) enzymes. MicroRNA-mediated regulation also plays a significant role. miR-29 family members, induced by progesterone signaling during pregnancy, target DNA methyltransferases DNMT3A and DNMT3B, preventing aberrant methylation of tumor suppressor loci ***(Shimizu et al., 2010; Garzon et al., 2009)***. MiR-200 family members, which suppress the epithelial-to-mesenchymal transition (EMT) regulator ZEB1/ZEB2, are upregulated in parous mammary glands, maintaining an epithelial differentiation program that is resistant to EMT-driven invasion. Histone modifications are equally critical: pregnancy is associated with increased H3K27 trimethylation (a repressive mark) at the promoters of proliferation-associated genes, mediated by the Polycomb repressive complex 2 (PRC2) component EZH2 ***(Bhan et al., 2014; Bhatt et al., 2021)***.

These modifications establish a chromatin state that suppresses mitogenic responsiveness even decades after the initial pregnancy.

5. BRCA1 and p53 in the Context of Parity-Mediated Protection

BRCA1 functions as a master regulator of DNA damage response and cell fate decisions in mammary progenitor cells. Notably, BRCA1 expression is significantly higher in luminal progenitor cells than in mature luminal cells, and BRCA1-mutant mammary glands are characterized by an expanded progenitor compartment ***(Lim et al., 2009; Molyneux et al., 2010)***. Pregnancy-induced hormonal signals may partially rescue the differentiation defect associated with BRCA1 haploinsufficiency, explaining the reported—though controversial—protective effect of early parity even in BRCA1 mutation carriers. p53, encoded by TP53, is the most frequently mutated gene in breast cancer and functions as a critical guardian of genomic integrity during periods of rapid cell division. In mammary progenitors of young primiparous women, p53 activation in response to pregnancy-associated replication stress may enforce a differentiation checkpoint that permanently reduces the progenitor pool ***(Bhatt et al., 2021; Jerry et al., 2018)***. Evidence from p53-null murine models demonstrates that loss of this checkpoint permits the persistence of undifferentiated progenitors post-partum, negating the protective effect of early parity.

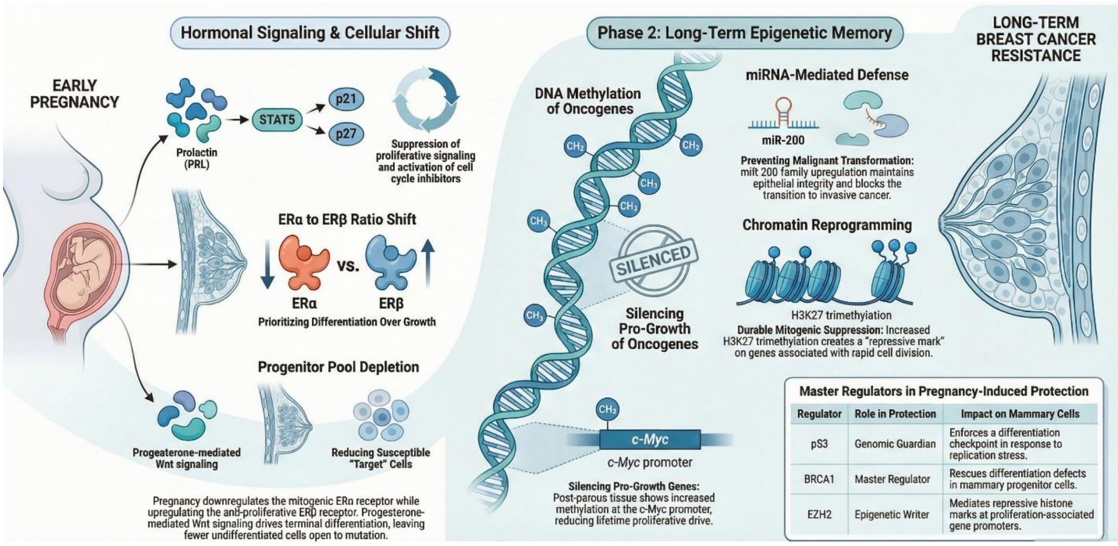

Fig.2. **The Biology of Protection: How Early Pregnancy Shields Against Breast Cancer.**

6. Breast Cancer Epidemiology and Early Primiparity in Rural India

6.1 Epidemiological Landscape

India presents a paradoxical epidemiological picture: despite high rates of early primiparity—traditionally considered protective—breast cancer incidence is rising rapidly, with the age-standardized incidence rate increasing from 13.6 to 25.8 per 100,000 women between 1990 and 2016 ***(Malvia et al., 2017; Dhillon et al., 2020)***. This trend is particularly pronounced in urban populations but increasingly affects rural communities as well, driven by lifestyle transitions including earlier menarche, dietary westernization, and reduced breastfeeding duration. Population-based studies from rural Rajasthan, Maharashtra, and West Bengal have identified early age at first birth as an independent protective factor in multivariable logistic regression analyses, consistent with global data ***(Gajalakshmi et al., 2009; Dinshaw et al., 2001)***. However, the protective effect is attenuated among women with very short breastfeeding duration (<6 months), poor nutritional status, or concurrent vitamin D deficiency—all prevalent conditions in rural Indian communities.

6.2 Sociodemographic Confounders Specific to Rural India

Nutritional deficiencies, endemic in rural India, may modify hormonal responses during adolescent pregnancy. Iron-deficiency anemia, affecting approximately 54% of pregnant adolescent girls in rural India per NFHS-5 data, has been associated with impaired prolactin secretion and suboptimal mammary gland development ***(IIPS & ICF, 2021; Katoch et al., 2019)***. Vitamin D deficiency, prevalent in over 70% of rural Indian women due to dietary limitations and cultural practices limiting sun exposure, further compromises hormone-receptor signaling since VDR (vitamin D receptor) directly modulates ERα activity and mammary differentiation. Psychosocial stress—a chronic feature of early forced marriages and adolescent pregnancies in rural communities—elevates cortisol and adrenaline, which may counteract the differentiation-promoting hormonal program of pregnancy through glucocorticoid receptor (GR)-mediated suppression of STAT5 signaling ***(Bhatt et al., 2021; Sinha et al., 2016)***. This neuroendocrine interference may partially explain why the theoretically protective effect of early primiparity does not always translate to the degree predicted by models derived from Western populations. Genetic heterogeneity is another important consideration. The distribution of ESR1 polymorphisms (notably rs2234693 and rs9340799), BRCA1/2 founder mutations, and TP53 codon 72 polymorphisms differs substantially between Indian ethnic groups ***(Saxena et al., 2006; Rajkumar et al., 2003)***. These genetic variations may differentially modulate the hormonal signaling responses to early pregnancy across ethnic subgroups within rural India.

7. Breastfeeding as a Co-modulator of Protective Differentiation

Lactation extends and reinforces the differentiation-promoting hormonal environment established during pregnancy. Sustained prolactin and oxytocin secretion during breastfeeding maintain terminal differentiation of secretory alveolar cells and suppress ovarian estrogen production through hypothalamic-pituitary suppression—a phenomenon known as lactational amenorrhea ***(Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Victora et al., 2016)***. A landmark meta-analysis of 47 epidemiological studies encompassing 50,302 women with breast cancer found that each 12 months of breastfeeding conferred an additional 4.3% reduction in breast cancer risk, over and above the 7% reduction attributable to each birth ***(Collaborative Group on Hormonal Factors in Breast Cancer, 2002)***. In rural India, where breastfeeding rates are high but exclusive breastfeeding for six months is declining, the interplay between early primiparity and lactation duration constitutes a critical area for public health intervention.

8. The Paradox of Early Primiparity: Transient Risk Elevation

A critical nuance of the primiparity-breast cancer relationship is the well-documented transient increase in breast cancer risk in the first 5–10 years following first birth, regardless of the age at which it occurs. This phenomenon, first described comprehensively by Lambe and colleagues in 1994, is attributed to pregnancy-induced proliferation of partially transformed mammary progenitor cells that harbor pre-existing somatic mutations ***(Lambe et al., 1994; Nichols et al., 2019)***. During the rapid proliferative phase of early pregnancy, the probability of replication errors in cells harboring oncogenic mutations is elevated, potentially initiating or promoting early-stage carcinogenesis. The tumor-promoting microenvironment of pregnancy—characterized by angiogenesis, immune tolerance, and tissue remodeling—further supports nascent tumor cell survival ***(Schedin, 2006; Lyons et al., 2011)***. In adolescent primiparous women, whose mammary glands are undergoing accelerated developmental remodeling, this risk window may be quantitatively different from that observed in adult primiparous women.

9. Implications for Public Health Policy in Rural India

The complex relationship between early primiparity and breast cancer risk should not be misinterpreted to justify or encourage early childbearing as a cancer-preventive strategy. Adolescent pregnancy carries substantial maternal and neonatal morbidity, including anemia, obstetric complications, preterm delivery, and low birth weight ***(Ganchimeg et al., 2014;***

WHO, 2020). Public health policy must unequivocally prioritize the prevention of child marriage and adolescent pregnancy through education, legal enforcement, and economic empowerment of girls. From a cancer prevention standpoint, the mechanisms elucidated in this review suggest that pharmacological mimicry of pregnancy-induced mammary differentiation could represent a viable preventive strategy. Short-term progesterone and prolactin receptor agonist regimens have been explored in preclinical models as 'differentiation therapy' for breast cancer prevention ***(Swaminathan et al., 2019; Bhatt et al., 2021)***. Such approaches warrant clinical translation, particularly for high-risk Indian women who are nulliparous or late primiparous. Nutritional interventions targeting vitamin D sufficiency, iron repletion, and omega-3 fatty acid supplementation may optimize hormonal signalling during pregnancy among adolescent mothers in rural India, potentially enhancing the protective differentiation program and reducing breast cancer risk in adulthood ***(Hatse et al., 2012; Sinha et al., 2016)***.

10. Research Gaps and Future Directions

Significant research gaps remain in understanding the intersection of early primiparity and breast cancer risk specifically within rural Indian populations. First, prospective cohort studies incorporating both molecular biomarkers and detailed reproductive histories are lacking in this demographic. Cross-sectional data dominate the existing literature, limiting causal inference. Second, the epigenomic profiling of mammary tissue from young Indian primiparous women has not been performed. Given known ethnic differences in DNA methylation patterns, it cannot be assumed that observations from European or North American cohorts are directly transferable ***(Sandoval et al., 2011; Ziv et al., 2019)***. Tissue biobanks linked to population-based cancer registries in rural India would provide an invaluable resource for addressing this gap. Third, single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics of mammary tissue from primiparous versus nulliparous rural Indian women could reveal cell-type-specific transcriptional programs associated with parity-induced differentiation in this population ***(Nguyen et al., 2018; Pal et al., 2021)***. Such studies would generate mechanistic hypotheses testable in organoid and in vivo models. Finally, the role of the microbiome—increasingly recognized as a modulator of estrogen metabolism and immune function—in mediating the protective effects of early primiparity remains entirely unexplored in Indian women and represents a frontier of investigation with potential therapeutic implications.

Table 1: Epidemiology and Modulators of Breast Cancer Risk in Rural India.

Category	Parameter / Factor	Statistical Value / Finding	Clinical/Biological Significance
Epidemiological Trends	Age-Standardized Incidence Rate (1990 vs 2016)	13.6 → 25.8 per 100,000	Indicates a rapid doubling of incidence despite traditional protective factors.
Nutritional Status	Iron-Deficiency Anemia (Rural Adolescents)	54% (NFHS-5)	Impairs prolactin secretion and suboptimal mammary gland development.
	Vitamin D Deficiency (Rural Women)	>70%	Compromises VDR-mediated modulation of ER-alpha and mammary differentiation.
Protective Factors	Parity-Related Risk Reduction	7% reduction per birth	Attributed to terminal differentiation of mammary epithelial cells.
	Lactation-Related Risk Reduction	4.3% reduction per 12 months	Mediated by lactational amenorrhea and suppressed estrogen production.
Risk Modifiers	Post-Partum Transient Risk Window	5–10 years post-birth	Proliferation of progenitor cells harboring pre-existing somatic mutations.
	Breastfeeding Duration (Short)	<6 months	Attenuates the protective effect of early primiparity.
Biological Interferences	Psychosocial Stress (Early/Forced Marriage)	Elevated Cortisol/Adrenaline	Glucocorticoid receptor (GR) suppression of STAT5 signaling.
	Genetic Heterogeneity	ESR1, BRCA1/2, TP53 polymorphisms	Varies by ethnic group; modulates hormonal signaling responses.

11. CONCLUSION

Early primiparity exerts a mechanistically complex and durable influence on mammary gland biology, operating through coordinated hormonal signaling cascades—prominently including prolactin/STAT5, estrogen receptor dynamics, and progesterone/Wnt pathways—to drive terminal epithelial differentiation and reduce the pool of oncogenically susceptible progenitor cells. This protective biological program is reinforced by epigenetic remodeling that preserves a differentiated chromatin state for decades following first birth. In the context of rural India, this protective mechanism operates within a complex matrix of nutritional deficiencies, psychosocial stressors, genetic heterogeneity, and sociodemographic factors that may attenuate or modify the theoretically derived protection. Comprehensive, population-specific mechanistic research is urgently needed to translate these biological insights into evidence-based cancer prevention strategies appropriate to this high-risk and underserved demographic. From a policy perspective, while the biological data underscore the protective potential of early first births, this must never be conflated with advocacy for early marriage or adolescent pregnancy—practices that carry unacceptable maternal and infant health risks. Rather, the mechanistic insights derived from studying early primiparity should inspire novel pharmacological and nutritional preventive strategies that can deliver analogous mammary epithelial differentiation without the harms of adolescent childbearing.

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