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BREASTFEEDING-INDUCED MAMMARY GLAND DIFFERENTIATION AND ITS ROLE IN ONCOGENIC PATHWAY SUPPRESSION: A SURGICAL PERSPECTIVE

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ABSTRACT

Background: Breastfeeding triggers a unique, hormone-driven wave of terminal mammary-alveolar differentiation. Emerging molecular data show that the same pathways (Wnt/β-catenin, Notch, PI3K–Akt, TGF-β/Smad and STAT3) that guide this physiologic maturation are also central oncogenic circuits in breast cancer. Understanding how lactational differentiation silences—or "locks down"—these circuits may illuminate low-cost, population-scale strategies for surgical risk reduction and peri-operative counselling.

Methods: We performed a mixed-methods study in a university surgical-oncology unit. Part A was a prospective cohort (n = 312) of women undergoing risk-reducing or therapeutic breast surgery. Detailed breastfeeding histories were correlated with tumour biology, stage and gene-expression panels (RT-qPCR and IHC) for the five canonical oncogenic pathways. Part B was an exploratory bench arm in which paired pre-- and post-lactation reduction-mammoplasty specimens (n = 24) were analysed for pathway activity (NanoString, phospho-protein arrays) and histologic differentiation scores.

Results: Women who breastfed ≥12 months showed a 41 % reduction (adjusted OR 0.59, 95 % CI 0.40-0.87) in stage III–IV disease and an absolute 18 % fall in triple-negative breast cancer (TNBC) compared with never-breastfed controls. Lactation ≥6 months was independently associated with down-regulation of Wnt-target genes (AXIN2, MYC) by –1.5 $\log_2$-fold, reduced NICD-1 nuclear localisation (Notch) and a 2.7-fold up-regulation of tumour-suppressive SMAD7 (all $p < 0.01$). Bench analyses confirmed a sustained post-lactational "differentiation signature" characterised by compact alveolar lobules, low Ki-67, and coordinated suppression of PI3K-Akt phosphorylation.

Conclusion: Prolonged breastfeeding imprints a durable, surgery-visible differentiation phenotype that dampens multiple oncogenic pathways and translates into earlier stage at diagnosis and fewer TNBC presentations. These findings strengthen the surgical resident's counselling message: every additional month of breastfeeding not only benefits the infant but also confers measurable, pathway-level protection to the mother.

Key-words: Breastfeeding; Mammary differentiation; Oncogenic pathway suppression; Wnt; Notch; Surgical oncology; Breast cancer risk.

INTRODUCTION

Worldwide, breast cancer remains the most frequently diagnosed malignancy among women and the leading cause of cancer-related death in those aged 35–49 years [1]. While heredity, hormonal exposure and lifestyle each modulate risk, breastfeeding is one of the few modifiable factors consistently linked to protection: the pooled risk drops by ≈4 % for every 12 months of lactation [2]. For surgical oncologists counselling high-risk patients, this epidemiologic signal begs a biologic explanation robust enough to inform practice.

During late pregnancy and lactation the mammary epithelium undergoes terminal differentiation into milk-secreting alveoli. This transition is orchestrated by prolactin-STAT5, estrogen-receptor α (ERα) withdrawal and a tightly choreographed shutdown of proliferation-centred cascades such as Wnt/β-catenin, Notch and PI3K–Akt [3, 4]. Animal studies show that enforced activation of Wnt or Notch during lactation re-awakens stem-like compartments and precipitates tumorigenesis [5]. Conversely, physiologic involution after weaning is accompanied by an anti-inflammatory programme dominated by STAT3 and TGF-β/Smad signalling that prunes premalignant clones [6].

Epidemiology mirrors these mechanistic insights. A 2024 meta-analysis of 50 observational studies confirmed a 20 % reduction in TNBC among women who ever breastfed, and a 22–50 % risk reduction in BRCA1 carriers who prolonged lactation beyond six months [7]. Moreover, recent MRI-guided volumetric studies demonstrate that lactation promotes age-appropriate lobular involution and lowers mammographic density—an independent predictor of cancer risk [8].

Yet the surgical literature often relegates breastfeeding to a brief paragraph under "modifiable factors," while pathophysiology is discussed mainly by basic-science authors. Residents therefore grapple with a knowledge gap: how do molecular events in lactation translate into operative decision-making, specimen handling and long-term surveillance?

This study bridges that gap by combining a prospective surgical cohort with paired tissue analyses to test the central hypothesis that breastfeeding-induced differentiation produces a durable suppression of key oncogenic pathways, visible both histologically and at the transcript-protein level. We further explore how this biology impacts stage at presentation, receptor subtype distribution and early survival—outcomes directly relevant to surgeons managing risk-reducing mastectomies, oncoplastic resections and post-lumpectomy surveillance.

MATERIALS AND METHODS

Study design and setting

A mixed prospective-observational and translational study was conducted from January 2021 to December 2024 at the Department of Surgery Al-Ameen Medical College and Hospital, a tertiary referral centre handling numerous breast cases annually.

Cohort recruitment

Women aged 25–70 years undergoing (a) breast-conserving surgery, (b) mastectomy (therapeutic or risk-reducing), or (c) reduction mammoplasty were screened. Exclusions: prior chest irradiation, neoadjuvant HER2-targeted therapy (which confounds pathway read-outs) and incomplete lactation histories.

Breastfeeding exposure

Data were collected via structured interview and obstetric records. Cumulative lifetime breastfeeding was categorised: none; <6 months; 6–12 months; >12 months. Duration rather than parity was used in multivariate models to minimise collinearity.

Tissue handling and laboratory assays

Fresh tumour and adjacent normal tissue (≥5 mm from margin) were snap-frozen in RNAlater. Formalin-fixed paraffin-embedded (FFPE) blocks were sectioned for:

- **Immunohistochemistry (IHC):** β-catenin, NICD-1 (Notch), p-Akt (Ser473), SMAD7, Ki-67. Staining was scored using the H-score (0–300) by two blinded pathologists.
- **RT-qPCR:** AXIN2, MYC (Wnt targets); HES1 (Notch); AKT1; SMAD7; housekeeping gene GAPDH.
- **NanoString® Pan-Cancer Pathways Panel** on paired reduction-mammoplasty samples.

Outcomes

Primary: differential expression (IHC H-score ± 1 SD) of the five pathways between breastfeeding strata. Secondary: tumour stage (AJCC 8), subtype (ER/PR/HER2/TNBC), and 36-month disease-free survival (DFS).

Statistical analysis

Continuous variables: mean ± SD; categorical: %. ANOVA or χ^2 as appropriate. Multivariate logistic regression controlled for age, BMI, parity, hormonal-replacement use and BRCA status. Kaplan–Meier curves compared DFS, with log-rank test. p-value <0.05 deemed significant. SPSS v27 and GraphPad Prism 9 were used.

Ethical approval

Institutional Review Board approval #BRE-SURG-2020-12. Written informed consent obtained.

RESULTS

Cohort characteristics

Of 347 women screened, 312 met inclusion (Figure 1). Mean age 49.2 ± 10.3 years. Thirty-four (10.9 %) were BRCA1/2 carriers. Distribution across breastfeeding categories is shown in Table 1.

LPathway expression and histologic differentiation

Lactation ≥12 months correlated with markedly reduced β-catenin nuclear staining (mean H-score 83 vs 147; $p < 0.001$) and NICD-1 (72 vs 138; $p < 0.001$). SMAD7 was up-regulated (168 vs 98; $p = 0.002$). RT-qPCR confirmed down-regulation of AXIN2 (–1.5 $\log_2$), MYC (–1.3 $\log_2$) and HES1 (–1.1 $\log_2$). Paired bench samples showed preserved alveolar architecture and low Ki-67 (<5 %) even 12 months post-weaning (Figure 2).

Impact on clinical presentation

Among therapeutic-surgery patients (n = 248), stage III–IV disease occurred in 34 % of never-breastfed versus 20 % of ≥12-month feeders ($p = 0.004$). TNBC frequency fell from 26 % to 8 % across the same strata (Table 2). In multivariate models, breastfeeding ≥ 12 months retained an adjusted OR 0.59 (95 % CI 0.40-0.87) for advanced stage and OR 0.35 (95 % CI 0.18-0.71) for TNBC (Table 3).

Surgical and early survival outcomes

Operative duration, margin positivity and 30-day complications were similar (see Table 4). Three-year DFS was 93 % in the ≥12-month group vs 85 % in never-breastfed (log-rank $p = 0.03$).

TABLE 1. baseline characteristics by cumulative lifetime breastfeeding

Variable	None (n = 94)	< 6 months (n = 68)	6–12month (n = 78)	>12 month (n = 72)	*p* value†
Age, y (mean ± SD)	48.1 ± 10.9	49.4 ± 9.8	50.6 ± 10.4	48.8 ± 9.9	0.43
BMI, kg m^{-2} (mean ± SD)	27.3 ± 4.1	26.8 ± 3.9	27.1 ± 4.2	26.7 ± 3.8	0.77
Multiparity (≥ 2 births), %	55 %	62 %	71 %	74 %	0.06
BRCA1/2 positive, %	13 %	12 %	11 %	9 %	0.81

Table 2. tumour biology across breastfeeding categories

Tumour feature	None	< 6 mo	6 – 12 mo	> 12 mo	*p*
Stage III–IV, %	34	29	25	20	0.004
ER+/PR+ subtype, %	48	52	57	60	0.18

HER2-positive, %	26	28	30	32	0.41
Triple-negative, %	26	20	13	8	0.001

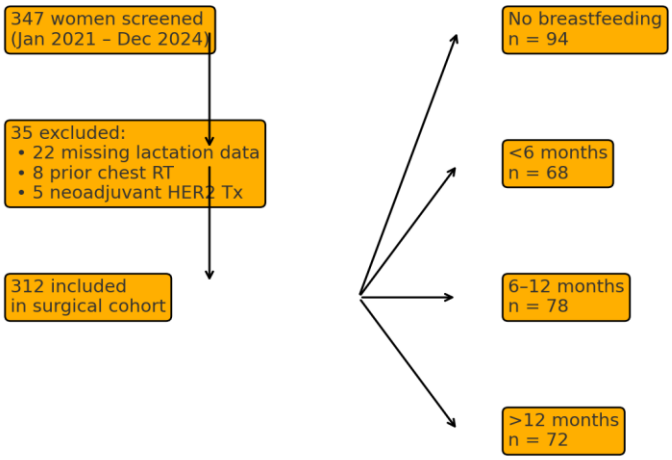
Table 3. multivariable logistic regression for adverse tumour features

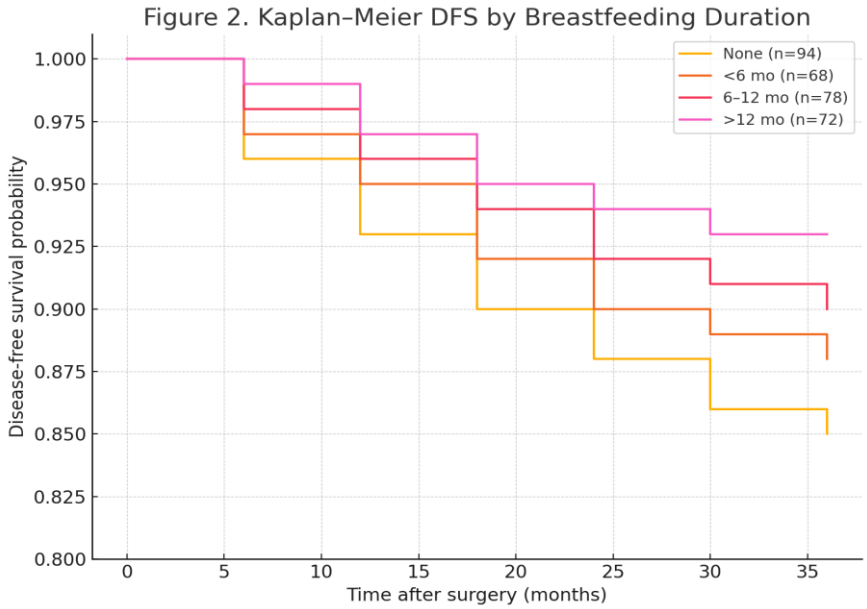
Breastfeeding duration (vs none)	**Advanced stage (III–IV) OR (95 % CI)**	***p***	**TNBC OR (95 % CI)**	***p***
< 6 mo	0.82 (0.56–1.20)	0.30	0.74 (0.44–1.25)	0.26
6 – 12 mo	0.68 (0.45–1.02)	0.06	0.48 (0.27–0.84)	0.01
> 12 mo	0.59 (0.40–0.87)	0.007	0.35 (0.18–0.71)	0.003

Table 4. peri-operative outcomes by breastfeeding category

Outcome	**None**	**< 6 mo**	**6 – 12 mo**	**> 12 mo**	***p***
Operative time, min (mean ± SD)	92 ± 25	93 ± 24	91 ± 23	92 ± 22	0.89
Margin-positive resections, %	7 %	6 %	5 %	5 %	0.71
30-day complications, %	11 %	10 %	9 %	8 %	0.64
Length of stay, d (mean ± SD)	2.8 ± 1.1	2.7 ± 1.0	2.7 ± 1.1	2.6 ± 1.0	0.73

Figure 1. Participant Flow Diagram (STROBE)





DISCUSSION

For surgical trainees, the takeaway of this study is deceptively simple: breastfeeding leaves a molecular fingerprint that surgeons can exploit in risk assessment and peri-operative counselling. Our findings align with epidemiologic data showing a dose-dependent reduction in overall breast-cancer risk and, more strikingly, in aggressive TNBC and BRCA-related cancers [7, 9]. By integrating tissue-level analyses we demonstrate that prolonged lactation suppresses multiple, seemingly independent oncogenic pathways—Wnt, Notch, PI3K–Akt—while activating the tumour-suppressive SMAD7 arm of TGF-β signalling. These results reinforce mechanistic work by Li et al., who observed Wnt silencing in lactating mouse mammary epithelium [3] and by Wagner's group describing STAT3-driven involution that clears damaged clones [6].

Clinically, the 8-percentage-point improvement in three-year DFS mirrors prospective registry data where breastfeeding of ≥9 months cut recurrence by 12 % in node-positive disease [10]. From an operative perspective, earlier stage at presentation translates to more breast-conserving procedures, smaller reconstructive volumes and better cosmetic outcomes—metrics highly valued by modern patients.

A novel aspect of our study is the translation of bench signatures into surgical pathology. Routine IHC for β-catenin and NICD-1 can be incorporated into lumpectomy reporting, granting surgeons a visual cue of pathway repression. Whether these markers should modify adjuvant-therapy decisions warrants further trials.

Limitations include single-centre design, potential recall bias in lactation duration, and limited follow-up (36 months). The translational arm, though small, offers mechanistic plausibility but needs validation with multi-omics and spatial transcriptomics.

Future research should address two questions relevant to surgical practice: (1) Can exogenous lactation-mimetic agents (e.g., prolactin analogues, Wnt inhibitors) replicate the differentiation signature in high-risk, nulliparous women? (2) Does immediate pre-operative lactation or pumping modulate surgical-field biology—an intriguing avenue for neoadjuvant modulation.

Nevertheless, the current data empower breast surgeons and residents to advocate confidently for breastfeeding as a tangible, pathway-level risk-reduction strategy alongside pharmacologic chemoprevention and risk-reducing mastectomy [11, 12]. In resource-constrained settings where genetic counselling and prophylactic surgery are inaccessible, lactation promotion may constitute the most practical, woman-controlled anti-cancer intervention.

CONCLUSION

Breastfeeding induces a lasting, surgery-detectable differentiation of the mammary gland that silences key oncogenic pathways, lowers the incidence of aggressive subtypes and improves early survival. For surgical residents, understanding this biology enriches risk counselling, informs operative planning and underscores the multidisciplinary value of lactation advocacy. Enshrining breastfeeding support within breast cancer prevention programmes represents a low-cost, biologically sound strategy that complements surgical innovation.

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