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# *Influence of Reproductive Factors on Breast Cancer Outcomes in Premenopausal Women*

***Theresa Relation[1]*; Marina Petsalis[1]; Caitlyn Balsay-Patel[1]; Nicholas Champion[1]; Brian Czerniecki[1]; David Detz[1]; Hyo Han[1]; Susan Hoover[2]; Nazanin Khakpour[1]; John Kiluk[1]; Laura Kruper[1]; Christine Laronga[1]; Melissa Mallory[1]; Weihong Sun[3]; Junmin Whiting[3]; Marie C Lee[1]***

*[1]Moffitt Cancer Center, Department of Breast Oncology, Tampa FL, USA.*

*[2]University of Texas Southwestern, Department of Surgery, Dallas TX, USA.*

*[3]Moffitt Cancer Center, Department of Biostatistics, Tampa FL, USA.*

**Abstract**

**Aims:** We aim to evaluate how reproductive factors influence tumor characteristics, treatment patterns, and clinical outcomes in women under 40 with breast cancer without genetic mutation.

**Methods:** IRB approved, single-institution retrospective review of breast cancer patients diagnosed before age 40 and treated between 2014 and 2024 was conducted. All patients underwent genetic testing and were confirmed to have no pathologic mutation. Pregnant (PABC) vs nonpregnant (control) patients were compared. For comparisons regarding gestation, nulliparous women were excluded from analysis. Clinical and demographic variables were examined with univariate and multivariate analyses, as well as Cox proportional analyses.

**Results:** Among 173 identified patients, 12.7% had Pregnancy-Associated Breast Cancer (PABC). Parity, age at first birth, and pregnancy interval were not associated with tumor subtype, stage, or survival outcomes, whereas breastfeeding was associated with a reduced risk of distant recurrence. Estrogen receptor negativity and nodal positivity were independently associated with worse overall survival. PABC patients did not differ from non-pregnant patients in race, tumor histology, receptor status, age at diagnosis, or rates of de novo metastatic disease, but had an older age at first birth and shorter intervals between pregnancies. PABC was associated with more advanced disease at presentation, including higher rates of clinically node-positive disease, larger tumors, higher pathologic stage, and increased lymph vascular invasion, leading to greater use of adjuvant chemotherapy.

**Conclusions:** Current literature rarely distinguishes young breast cancer patients by genetic status. This single-institution study is the first to focus specifically on women under 40 without genetic mutations, showing overall survival is strongly associated with tumor subtype and nodal positivity. Breastfeeding appeared protective against distant recurrence, while PABC was linked to more aggressive disease, advanced stage at presentation, and worse outcomes. This underscores the need for heightened clinical vigilance and larger, multi-institutional studies to clarify pregnancy-related biological mechanisms driving breast cancer development.

**Keywords:** Breast cancer; Pregnancy-associated breast cancer; Young women; Negative genetic testing; Premenopausal breast cancer.

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**Correspondance:** *Theresa Relation, Moffitt Cancer Center, Department of Breast Oncology, Tampa FL. 813-745-8000, USA.*

*Email: theresa.relation@moffitt.org*

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## Introduction

The incidence of breast cancer in young, premenopausal women has been steadily increasing since the 2000s. Surveillance, Epidemiology, and End Results (SEER) program data from 2019-2022 demonstrated an annual breast cancer incidence rate of 24-25 per 100,000 in women under 40. The rates vary across race, with higher frequency seen in Black women (26-28 per 100,000), followed by White women (25 per 100,000), Asian women (22-23 per 100,000), and lastly Hispanic women (19-23 per 100,000). Comparatively, the incidence rate for all women under 40 in 2000 was 17.2 per 100,000 [1].

While strong family history of breast cancer may lead patients to genetic risk discussion and early screening, women without this history do not typically start screening until age 40 [2]. Therefore, young women without genetic risk typically only undergo mammogram once they have clinical changes and thus are more likely to present with advanced disease. Young women are more likely to present with symptoms, such as a palpable breast mass or nipple discharge, and are more likely to have dense breast tissue [3].

The American College of Radiology offers guidelines for diagnosis and staging of young symptomatic women with palpable masses or nipple discharge as there are important differences from standard screening [4,5]. Tumors in younger women are more aggressive. They are typically diagnosed at later stages, are larger, and more likely to be Estrogen Receptor (ER) negative than their postmenopausal counterparts [6-9]. Additionally, all patients diagnosed under the age of 40 should be offered genetic screening as there is a 10-15% chance of a BRCA1 or BRCA2 mutation. Including other genetic mutations, the overall rate is approximately 17% [3,10,11]. Existing studies on young women with breast cancer include both genetic carriers and non-genetic carriers within their study populations. This does not allow one to elucidate risks independent of genetic mutations.

Breastfeeding and parity are independent risk factors for breast cancer in young women. Most studies have found protective effects of breastfeeding on breast cancer risks in premenopausal women, particularly against ER- cancers [6,8,12-14]. However, there is a paucity of literature examining the relationship between breastfeeding and breast cancer-specific outcomes. Parity's impact on risk is dependent on time and ER status. Overall breast cancer risk is increased (compared to nulliparous women) starting immediately after birth, peaking around 5 years, and remaining elevated for approximately 15-20 years [15-17]. The risk for ER- cancer declines over time but remains higher than nulliparous women up to 30 years post-birth [17]. For ER+ cancers, the risk steadily declines after 5 years, intersects with nulliparous women around 24 years, and has a nadir around 35 years post-birth [17]. This long-term protection has been attributed to breast remodeling and involution during lactation as well as decreased lifetime exposure to estrogen [18]. A shorter interval between pregnancy and breast cancer diagnosis has been associated with worse outcomes, such as higher risk for metastases and death [19]. The many modifying factors including breastfeeding, family history, and age at first birth make it challenging to fully elucidate the impact of parity on breast cancer risk [17,20,21].

Pregnancy-Associated Breast Cancer (PABC) is defined as diagnosis during pregnancy, lactation, or within 1 year of delivery. PABC can be difficult to identify as women may attribute cancer-related symptoms to the natural breast changes that occur during pregnancy [22]. Estimates of incidence vary by study. A recently published meta-analysis of over 51 million individuals in 22 studies reported an incidence rate of 14.4 cases of PABC per 100,000 pregnancies in the USA, with the rate increasing from 13.3 cases in 1969. PABC accounts for 10-20% of all breast cancers in women under 30 and up to 7% in women under 45 [23,24]. First pregnancy in older ages is associated with increased risk of PABC [23]. While PABC remains rare, the incidence of cancer in this cohort is expected to rise as women increasingly defer childbearing [23].

Understanding the unique challenges that young women with breast cancer face is crucial in tailoring obstetric and oncologic care. Research on this population has been limited by its relative rarity requiring large national datasets and difficulty in comparing across institutions. Here, we aim to evaluate how reproductive factors influence tumor characteristics, treatment patterns, and clinical outcomes in women under 40 with breast cancer without genetic mutation.

## Materials and methods

An IRB approved, single-institution retrospective review of breast cancer patients diagnosed before age 40 and treated between 2014 and 2024 was conducted. All patients underwent genetic testing and were confirmed to have no pathologic mutation. Reproductive variables evaluated included parity, pregnancy interval (defined as the mean number of years from age at first birth to age at diagnosis), age at first birth, and breastfeeding status (yes vs. no). Associations between these variables, receptor status, and clinical outcomes were assessed.

Patients with Pregnancy-Associated Breast Cancer (PABC) were compared with non-pregnant controls. For analyses involving gestational history, nulliparous women were excluded. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, and continuous variables were compared using the Wilcoxon rank-sum test. Survival outcomes, including Overall Survival (OS), Locoregional Recurrence (LRR), and distant recurrence (DRR), were analyzed using univariable and multivariable Cox proportional hazard regression models. Kaplan-Meier curves were generated to visualize survival outcomes stratified by parity. All statistical tests were two-sided, and a p-value $<0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## Results

**Patient demographics:** We identified 173 patients under the age of 40 with a diagnosis of breast cancer and negative genetic testing; 113 (65%) were White, 28 (16%) were Black, 11 (6%) were Asian, and 21 (12.1%) were other races. The majority of women were between 35-39 years old. Nulliparous women made up 24% (42) of the population. Of the parous women, 87 had 1-2 births and 31 had ≥3. The median age at first birth was 27 years (range 13-40) and median time to diagnosis from age at first birth (AFB) was 8 years (range -1 to 25). 22 patients (12.7%) had PABC (Table

1). The mean interval between pregnancies for all patients was 4.89 years. Median overall follow-up was 53.2 months (range 25.5-92.9), with a median of 38.8 months among PABC group only.

**Tumor subtype and stage at diagnosis:** 118 patients (68.2%) were Hormone Receptor (HR) positive, 52 (30.1%) were HER2+, and 37 (21.4%) had triple-Negative Breast Cancer (TNBC). The vast majority were ductal histology (150, 86.7%). 14 patients (8.1%) were diagnosed stage 0, 27 patients (15.6%) were stage I, 56 patients (32.4%) were stage II, 26 patients (15%) were stage III, and 49 patients (28.3%) were stage IV at diagnosis. The stage at diagnosis varied by subtype (Figure 1). Notably, over 50% of patients with HER2+ disease presented at stage III or IV (Table 1).

**Overall outcomes:** In non-metastatic patients, Locoregional Recurrence (LRR) was observed in 6.9% and distant recurrence (DR) in 13.3%. On multivariate Cox regression analysis, ER negative receptor subtype and an increasing number of non-sentinel lymph node–positive axillary nodes were independently associated with worse overall survival (OS) (hazard ratio 2.94 p=0.016; hazard ratio 1.17 p<0.001). On univariate analysis, TNBC was associated with worse OS (hazard ratio 3.44, p<0.001). At the last known follow up, 136 patients (78.6%) were alive and 37 (21.5%) were deceased.

**Parity, age at first birth, and breastfeeding:** Non-parous women were diagnosed at a younger age (median 34.5 vs. 36, p=0.021). Age at first birth and pregnancy interval had no associations with receptor status or stage at diagnosis. There was a nonsignificant increase in the proportion of HR- cancers with increasing parity (p 0.691). Parous women had more HER2+ cancers (33.9% vs 24.4%), but this difference did not persist when stratified by number of births. The rate of TNBC was similar across non-parous and parous women. There were no significant differences in OS, DR, or LRR when stratified by pregnancy interval (Table 2). When stratified by parity, no significant differences were seen in Kaplan Meier curves, although the curves started to separate around 3 years post-diagnosis (Figure 2). Breastfeeding of any duration was seen in 68 patients. Breastfeeding was associated with lower incidence of DR (hazard ratio 0.23, p=0.01) but did not reach significance for OS (hazard ratio 0.57, p=0.144) (Table 3).

**Pregnancy-associated breast cancer:** There was no significant difference between PABC and non-pregnant patients (control) regarding race, tumor histology, and hormone receptor expression. Despite no significant difference in age at diagnosis (mean 35 years, range 23-40), PABC was associated with older mean age at first birth (30.2 vs 25.9 years, p=0.003) and lower average years between pregnancies (1.4 vs 5.6 years, p<0.001) when excluding nulliparous women from control group. Patient's parity was not associated with increased risk of PABC. PABC demonstrated similar rates of de novo metastatic disease when compared to control (10% vs 9.2%) (Table 4).

While there was no difference in type of surgery given to patients, surgical pathology findings varied significantly between groups. PABC more frequently presented with clinically node-positive disease (63.6% vs 53.5% control, p=0.010) and had larger tumor size at surgery (33.3% with T3 disease vs 15.7% with T1-T2, p=0.002). This was reflected in higher pathologic staging (Stage III/IV 45% vs 21.7% control; p=0.026) (Figure 3). PABC was associated with higher rates of lymph vascular invasion (63.2% vs 25% in control, p<0.001), with no difference in extra nodal extension or dermal lymphatic invasion (Table 4).

PABC pts were more likely to receive chemotherapy in the adjuvant setting (45.5% vs 15.9%, p=0.001). 13.2% of the control group had no chemotherapy compared to 4.5% in PABC; this difference was not significant. Treatment with radiation to breast/chest and axilla was not significantly different between groups. There was no difference in LRR, yet PABC was associated with a higher rate of DR (31.8% vs 10.6%, p=0.006) (Table 4).

**Table 1:** Patient demographics and clinicopathological features.

| Variable | | N= 173 | % |
|---|---|---|---|
| Race | White | 113 | 65.3 |
| | Black/AA | 28 | 16.2 |
| | Asian | 11 | 6.4 |
| | Other | 21 | 12.1 |
| Number of pregnancies | 0 | 31 | 17.9 |
| | 1-2 | 79 | 45.7 |
| | 3+ | 47 | 27.2 |
| | Unknown | 16 | 9.2 |
| Breastfeeding history | Yes | 68 | 39.3 |
| | Never/Not applicable | 68 | 39.3 |
| | Unknown | 37 | 21.4 |
| Pregnancy-associated breast cancer | Yes | 22 | 12.7 |
| | No | 151 | 87.3 |
| Age at diagnosis | 20-24 | 4 | 2.3 |
| | 25-29 | 13 | 7.5 |
| | 30-34 | 61 | 35.3 |
| | 35-39 | 95 | 54.9 |
| | Mean | 35.03 | |
| | St Dev | 3.61 | |
| Age at first birth | Mean | 26.66 | |
| | St Dev | 5.65 | |
| Years between pregnancies | Mean | 4.89 | |
| | St Dev | 4.11 | |
| Hormone receptor status | HR+/HER2- | 79 | 45.7 |
| | HR+/HER2+ | 35 | 20.2 |
| | HR-/HER2+ | 17 | 9.8 |
| | TNBC | 37 | 21.4 |
| | Unknown | 5 | 2.9 |
| Histology | Ductal | 150 | 86.7 |
| | Lobular | 5 | 2.9 |
| | Mixed | 3 | 1.7 |
| | Other | 15 | 8.7 |
| Clinical TNM stage | 0 | 14 | 8.1 |
| | I | 27 | 15.6 |
| | II | 56 | 32.4 |
| | III | 26 | 15.0 |
| | IV | 49 | 28.3 |
| | Unknown | 1 | 0.6 |

**Table 2:** Parity-related variables.

| Variable | | Nulliparous N (%) | Parous N (%) | P-value |
|---|---|---|---|---|
| ER/PR status | Positive | 31 (73.8) | 80 (67.8) | >0.05 |
| | Negative | 11 (26.2) | 38 (32.2) | |
| HER2 status | Positive | 10 (24.4) | 39 (33.9) | >0.05 |
| | Negative | 31 (75.6) | 76 (66.1) | |
| TNBC | Yes | 8 (19) | 25 (21.2) | >0.05 |
| | No | 34 (81) | 93 (78.8) | |
| Clinical stage | 0 | 3 (7.1) | 10 (8.5) | >0.05 |
| | I | 4 (9.5) | 21 (17.9) | |
| | II | 12 (28.6) | 38 (32.5) | |
| | III | 9 (21.4) | 15 (12.8) | |
| | IV | 14 (33.3) | 33 (28.2) | |
| OS | Alive | 34 (81) | 93 (78.8) | >0.05 |
| | Deceased | 8 (19) | 25 (21.2) | |
| LRR | Yes | 3 (7.1) | 9 (7.6) | >0.05 |
| | No | 39 (92.9) | 109 (92.4) | |
| DR | Yes | 9 (21.4) | 13 (11) | >0.05 |
| | No | 33 (78.6) | 105 (89) | |

**Table 3:** Breastfeeding-related variables. Column percentage in parentheses.

| Variable | | Yes | Parous N (%) | P-value |
|---|---|---|---|---|
| N (%) | No | 31 (73.8) | 80 (67.8) | >0.05 |
| N (%) | P-value | 11 (26.2) | 38 (32.2) | |
| ER/PR status | Positive | 43 (63.2) | 51 (75) | >0.05 |
| | Negative | 25 (36.8) | 17 (25) | |
| HER2 status | Positive | 22 (33.8) | 17 (25.4) | >0.05 |
| | Negative | 43 (66.2) | 50 (74.6) | |
| TNBC | Yes | 17 (25) | 13 (19.1) | >0.05 |
| | No | 51 (75) | 55 (80.9) | |
| Clinical stage | 0 | 8 (11.8) | 5 (7.5) | >0.05 |
| | I | 13 (19.1) | 7 (10.4) | |
| | II | 23 (33.8) | 20 (29.9) | |
| | III | 7 (10.3) | 13 (19.4) | |
| | IV | 17 (25) | 22 (32.8) | |
| OS | Alive | 57 (83.8) | 50 (73.5) | >0.05 |
| | Deceased | 11 (16.2) | 18 (26.5) | |
| LRR | Yes | 4 (5.9) | 5 (7.4) | >0.05 |
| | No | 64 (94.1) | 63 (92.6) | |
| DR | Yes | 4 (5.9) | 14 (20.6) | **0.021** |
| | No | 64 (94.1) | 54 (79.4) | |

**Table 4:** Pregnancy-associated breast cancer clinicopathological variables. Column percentage in parentheses.

| Variable | | Control N=151(%) | PABC N=22 (%) | P-value |
|---|---|---|---|---|
| Race | White | 98 (64.9) | 15 (68.2) | >0.05 |
| | Black/AA | 24 (15.9) | 4 (18.2) | |
| | Asian | 10 (6.6) | 1 (4.5) | |
| | Other | 19 (12.6) | 2 (9.1) | |
| Age at diagnosis | Mean | 35.2 | 33.6 | >0.05 |
| | Std Dev | 3.4 | 4.5 | |
| Age at first birth | Mean | 25.9 | 30.2 | 0.003 |
| | Std Dev | 5.4 | 5.4 | |
| Number of pregnancies | 0 | 31 (22.8) | 0 (0) | 0.021 |
| | 1-2 | 67 (49.3) | 12 (57.1) | |
| | 3+ | 38 (27.9) | 9 (42.9) | |
| Years between pregnancies | Mean | 5.6 | 1.4 | <0.001 |
| | Std dev | 4.1 | 1.5 | |
| Hormone receptor status | HR+/HER2+ | 30 (20) | 5 (22.7) | >0.05 |
| | HR+/HER2- | 69 (46) | 10 (45.5) | |
| | HR-/HER2+ | 15 (10) | 2 (9.1) | |
| | TNBC | 32 (21.3) | 5 (22.7) | |
| Histology | Ductal | 130 (86.1) | 20 (90.9) | >0.05 |
| | Lobular | 4 (2.6) | 1 (4.5) | |
| | Mixed | 3 (2.0) | 0 (0) | |
| | Other | 14 (9.3) | 1 (4.5) | |
| Clinical TNM stage | 0 | 12 (8.0) | 2 (9.1) | >0.05 |
| | I | 22 (14.7) | 5 (22.7) | |
| | II | 49 (32.7) | 7 (31.8) | |
| | III | 22 (14.7) | 4 (18.2) | |
| | IV | 45 (30.0) | 4 (18.2) | |
| Clinical node status | 0 | 66 (46.5) | 8 (36.4) | 0.010 |
| | 1 | 49 (34.5) | 7 (31.8) | |
| | 2 | 11 (7.7) | 7 (31.8) | |
| | 3 | 16 (11.3) | 0 (0) | |
| Chemotherapy | Neoadjuvant | 103 (68.2) | 11 (50) | 0.003 |
| | Adjuvant | 24 (15.9) | 10 (45.5) | |
| | None | 24 (15.9) | 1 (4.5) | |
| Breast surgery | Partial mastectomy | 17 (11.3) | 3 (113.6) | >0.05 |
| | Mastectomy | 103 (68.2) | 17 (77.3) | |
| | None | 31 (20.5) | 2 (9.1) | |
| Nodal surgery | Axillary dissection | 24 (16.1) | 8 (36.4) | >0.05 |
| | Sentinel node biopsy | 68 (45.6) | 8 (36.4) | |
| | Targeted node excision | 21 (14.1) | 4 (18.2) | |
| | None | 36 (24.2) | 2 (9.1) | |
| Pathological stage | 0/I/II | 94 (78.3) | 11 (55) | 0.026 |
| | III/IV | 26 (21.7) | 9 (45) | |

| | | | | |
|---|---|---|---|---|
| Pathology Findings | DLI | 8 (8.2) | 1 (6.3) | >0.05 |
| | LVI | 28 (25) | 12 (63.2) | <0.001 |
| | ENE | 14 (15.7) | 4 (21.1) | >0.05 |
| | Positive Margins | 4 (3.3) | 2 (10) | >0.05 |
| Radiation | No | 73 (49) | 9 (45) | >0.05 |
| | Yes | 76 (51) | 11 (55) | |
| Locoregional Recurrence | No | 142 (94.0) | 19 (86.4) | >0.05 |
| | Yes | 9 (6.0) | 3 (13.6) | |
| Distant Recurrence | No | 135 (89.4) | 15 (68.2) | 0.006 |
| | Yes | 16 (10.6) | 7 (31.8) | |

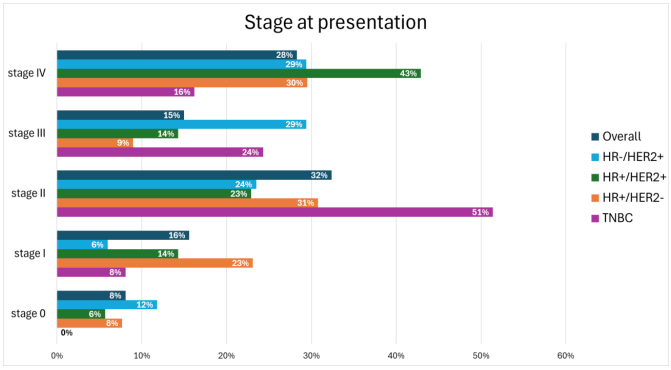


**Figure 1:** Stage at presentation by subtype. Clinical stage at presentation of breast cancer patients under 40 without genetic mutation. Overall (navy), HR-/HER2+ (light blue), HR+/HER2+ (green), HR+/HER2- (orange), and TNBC (purple) cohorts are presented.

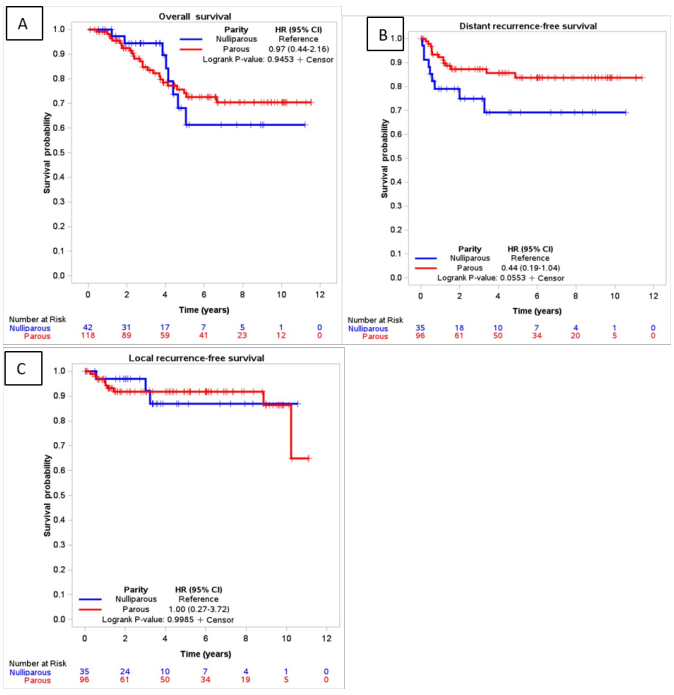


**Figure 2:** Kaplan-Meier curves in years representing overall survival **(A)** Distant recurrencefree survival **(B)** and local recurrence-free survival **(C)** Nulliparous (blue) and parous (red).

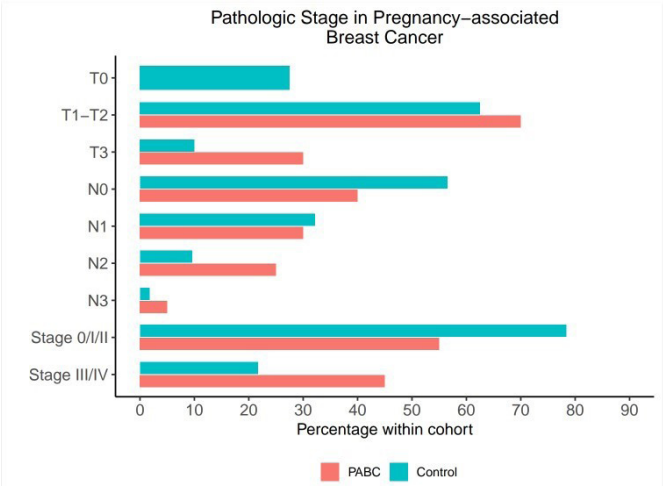


**Figure 3:** Pathologic Stage in Pregnancy-associated Breast Cancer (PABC). Percentage of cohort is depicted by pathologic stage. PABC (red) and control (green).

## Discussion

Current literature investigating patterns of breast cancer in young women is limited, and most studies fail to differentiate between genetic carriers compared to those without genetic mutation. Here, our single institution retrospective review of young women with breast cancer and negative genetic testing represents the first study to specifically identify young patients without genetic mutations. This study demonstrates that OS is strongly associated with tumor subtype (ER-, TNBC) and positive nodal status.

Breastfeeding for any length of time appears to be protective against distant recurrence; it is possible there are also significant effects on survival that would be better elucidated with a larger sample size. Although the results did not reach statistical significance, the survival curves and distant recurrence-free survival curves for non-parous vs parous women begin to diverge around the 3 years from diagnosis. There is likely some crossover effect between parity and breastfeeding, since the significance of breastfeeding on distant recurrence-free survival did not persist in a multivariable analysis. Future studies should investigate physiological changes related to breastfeeding and how these might mitigate risk. Our study did not find any correlation between breastfeeding, parity, or pregnancy interval and locoregional recurrence. Due to the rarity of young breast cancer in non-genetic carriers, nationwide multi-institution databases will be needed.

There were striking differences in stage at presentation compared to national data for women aged 50-75. Over 28% of our population presented with de novo metastatic disease. This is likely related to a combination of delayed diagnosis, lack of screening, and more aggressive tumor biology. Other studies have shown de novo metastatic rates in young patients of 3.8%-6% [7,8]. Similar to existing literature, we saw an increase in the amount of HR- cancers as parity increased [8,17,20].

In this study, PABC accounted for 12.7% of all breast cancers in women under 40 without genetic mutations. This is higher than nationally reported rates of PABC in young women, which do not

differentiate between genetic and non-genetic carriers [23,24]. Current theories for the development of PABC include hormone-driven cell proliferation, immunosuppression and immune tolerance associated with pregnancy, and the inflammatory microenvironment in the breast after delivery [25]. Together, this highlights the importance of pregnancy-related breast changes as a driver of cancer.

Here, we show that PABC is associated with advanced stage at presentation and poor outcomes. PABC presented with higher nodal burden and surgical pathology showed larger tumor size, higher stage, and higher rates of lymph vascular invasion. Most concerningly, the PABC cohort had a higher risk of distant recurrence despite intensive systemic therapy. Clinicians providing care for pregnant women must maintain a high index of suspicion and initiate workup promptly if there is concern for breast cancer so as not to delay diagnosis and treatment.

### Limitations

This study has several limitations. Firstly, a single-center study may not adequately represent the national population, and thus large epidemiological studies are needed. Molecular studies will be needed to identify unique cancer-promoting physiologic changes associated with pregnancy and to develop therapies to mitigate their influence. Secondly, this study is underpowered to elucidate the effect of diagnosis during pregnancy compared to diagnosis during the postpartum period. Thirdly, while excluding known genetic mutations from our cohort significantly reduces the impact of familial inheritance on breast cancer, it does not remove its influence entirely and does not account for yet-to-be-identified genetic mutations.

## Conclusions

This study demonstrates that the biological and clinical progression of breast cancer in non-genetic carriers diagnosed before the age of 40, notably those with PABC, is distinctly more aggressive. The physiologic impact of pregnancy and breastfeeding should be further investigated to determine the ultimate impact on outcome.

**Abbreviations:** AFB: Age at First Birth; DLI: Dermal Lymphatic Invasion; DR: Distant Recurrence; ENE: Extra Nodal Extension; ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormone Receptor; LRR: Locoregional Recurrence; LVI: Lymph Vascular Invasion; OS: Overall Survival; PR: Progesterone Receptor; PABC: Pregnancy-Associated Breast Cancer; SEER: Surveillance, Epidemiology, and End Results Program; TNBC: Triple-Negative Breast Cancer.

## Declarations

**Conflicts of interest:** The authors declare that they have no conflicts of interest. All research was conducted under the approval of the Institutional Review Board. Informed consent and consent to publish was not applicable to this research. There are no relevant funding sources to disclose. The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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