The Breast 66 (2022) 272–277

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Reproductive risk factors associated with breast cancer in young women by molecular subtype

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ARTICLE INFO

Keywords:
Breast neoplasms
Pregnancy
Lactation
Premenopausal

ABSTRACT

Background: Few studies have examined detailed features of pregnancy and the postpartum period as potential risk factors for early onset breast cancer (BC) by molecular subtype. These data may have value for improving risk assessment and prevention.

Methods: We surveyed parous enrollees in the prospective Mayo Clinic Breast Disease Registry (MCBDR) who had been diagnosed with BC at age <55 years between 2015 and 2020. Summary statistics were used to describe survey responses and reproductive risk factors by BC subtype (defined by estrogen/progesterone receptors and human epidermal growth factor receptor expression, nurse-abstracted from the medical record). Associations were assessed with Kruskal-Wallis and Chi-Square tests, followed by age-adjusted linear and logistic regression models. We compared results from this parous cohort to those from a separate cohort of nulliparous MCBDR participants with BC diagnosed at age <55 years.

Results: In 436 parous respondents with subtype data abstracted, we identified a higher frequency of *BRCA1* mutation, earlier age at diagnosis, and lower BI in patients with triple negative BC. Comparing parous to nulliparous young women with breast cancer, the proportion with TNBC was larger in the latter (12.2% vs. 15.1%, $p = 0.03$).

Conclusions: Early age at diagnosis and deleterious *BRCA1* mutation were more frequent among TNBC patients. In addition, parous young women with TNBC had a lower BI than those with other BC subtypes, a hypothesis-generating finding that supports the need for additional research on the cycle of pregnancy-lactation-postpartum involution and BC etiology.

1. Introduction

Pregnancy, lactation, and postpartum involution (which restores the breast to a near-baseline state) are inextricably linked, complex biological processes that profoundly affect breast cancer (BC) risk overall, and differentially impact risks of BCs stratified by age at diagnosis and molecular subtype. Parity, particularly if first birth occurs at an early age, is protective against estrogen receptor (ER)-positive BC, the numerically predominate subtype after menopause. In contrast, a recent meta-analysis found that parity was unrelated to risk of human epidermal growth factor receptor-2 (HER-2) over-expressing BC or triple negative BC (BC that does not express ER, progesterone receptor [PR], or HER-2) [1]. A 2010 pooled analysis of 15 studies found that nulliparity was substantially less frequent among triple-negative BCs as compared with ER-positive luminal BCs [2]. Triple-negative BCs (TNBCs) occur most frequently at younger ages, and risks are disproportionately high among Black women and among carriers of pathogenic variants of *BRCA1* [3]. Data suggest that breastfeeding may reduce risks of BC, especially TNBC, and low rates of sustained nursing have been proposed as contributing to higher rates of TNBC among Black women [4]. Further, the impact of the pregnancy-lactation-postpartum involution cycle may have important associations with age at BC development.

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https://doi.org/10.1016/j.breast.2022.11.004
Received 6 July 2022; Received in revised form 3 November 2022; Accepted 8 November 2022
Available online 9 November 2022

A nationwide pooled analysis including 18,826 patients with BC found that the incidence of BC is increased after childbirth compared to age-matched nulliparous women, irrespective of ER status, with peak relative risks at approximately 4.6 years for ER-positive BCs and 2.2 years for ER-negative BCs [5]. Risks for ER-positive BCs returned to baseline after several decades but never declined fully for ER-negative BCs. This postpartum increase in BC risk is more evident among women with an advanced maternal age [6,7], suggesting the hypothesis that delayed first birth and repeated menstrual cycling leads to a higher cumulative burden of mutations that may be stimulated to expand with the growth promoting effects of pregnancy [8]. Mutations would be more likely to persist among women with deficient DNA repair mechanisms, such as those with inherited *BRCA1* or *BRCA2* mutations.

Among white women aged 18–45 years, 45% of BCs occur within ten years of childbirth, and with more women delaying pregnancies [9], the incidence of postpartum BCs may rise. Data from the Surveillance, Epidemiology, and End Results program (SEER) show that incidence rates of ER-positive/HER2-negative BCs among women less than age 50 years have risen significantly in the U.S. from 2010 to 2019. Thus, clarifying the etiology of early onset BCs is an urgent public health issue, with important implications for risk assessment, screening, and prevention. Accordingly, we administered a detailed survey asking about reproductive events to women diagnosed with BC under age 55 years to discover pregnancy and postpartum features that might be linked to specific molecular subtypes of early onset BC.

2. Methods

The Mayo Clinic Breast Disease Registry (MCBDR) prospectively consents patients with newly diagnosed BC who are seen at least once at Mayo Clinic in Rochester, Minnesota. Our study (approved by the Mayo Clinic institutional review board) surveyed a subset of MCBDR enrollees diagnosed between 2015 and 2020 who were younger than age 55 years at the time of their BC diagnosis (and who were not already known to be nulliparous based on previous MCBDR survey responses). Current survey items asked about timing of pregnancies and patterns of lactation and weaning. Those who reported themselves nulliparous on this survey were excluded from analyses related to pregnancy timing and lactation, but their data were combined with patients known to be nulliparous from previous surveys to serve as a comparison group for an assessment of BC subtype distribution. Tumor characteristics were collected via nurse abstraction.

Descriptive statistics were used to summarize survey responses. We compared characteristics of parous respondents to parous non-respondents using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. We compared BC subtype in parous respondents to BC subtype in nulliparous women using chi-square tests. Amongst the parous responders, we compared the univariate relationships between various lactational and pregnancy timing variables and BC subtype using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables, with $p < 0.05$ considered statistically significant. To capture the effect of timing and spacing of births on risk of BC, we have calculated a birth index (BI) variable (mirroring the one used previously in the Nurses' Health Study) [10]. Briefly, BI is a summation of times from each birth to BC diagnosis; a higher BI reflects a greater period of elapsed time between birth(s) and diagnosis and/or more total births, whereas a lower value reflects shorter times between births and BC diagnosis (and/or fewer total births). For example, a woman diagnosed with BC at age 40 years with births at ages 20 years and 25 years would have a BI of 35, as would a woman diagnosed with BC at age 45 with births at ages 30, 34, and 36. Univariate comparisons were followed by age-adjusted comparisons, with analyses using linear regression for continuous variables and logistic regression for categorical variables, modeling the reproductive variable as the outcome, BC subtype as the independent variable, and age as a covariate.

3. Results

Surveys were returned by 512 (60% response rate) of 854 patients, 22 of whom declared on this survey that they were nulliparous, leaving 490 eligible parous respondents (see Fig. 1). The 490 parous responders were older at the time of their cancer diagnosis compared to the 342 non-responders to the survey (median age 46.2 vs. 44.6 years, $p = 0.003$, Supplemental Table 1). Cancer diagnosis was slightly more recent (2.6 years vs. 2.9 years prior to the survey, univariate $p < 0.001$), and ethnicity was more likely to be non-Hispanic (94.3 vs. 89.8%, univariate $p = 0.040$) among parous responders than among non-responders.

For our assessment of BC subtype distribution, there were 123 nulliparous-at-diagnosis women eligible. This included 101 women who self-identified as nulliparous on a previous MCBDR survey (and therefore were not sent this survey) as well as the 22 women who received this survey because their parity was uncertain and then responded stating that they were nulliparous. Subtype data were missing for 17 of these 123 nulliparous-at-diagnosis women and for 54 of the 490 eligible parous respondents. Among the 106 remaining participants who were nulliparous at diagnosis and the 436 remaining parous responders, BC subtype distribution was as follows: ER-/PR- and Her2+ in 1 (0.9%) and 37 (8.5%), respectively; ER+ and/or PR+ and Her2+ in 13 (12.3%) and 69 (15.8%), respectively; ER+ and/or PR+ and Her2-in 76 (71.7%) and 277 (63.5%), respectively; and triple negative in 16 (15.1%) and 53 (12.2%), respectively (chi-square $p = 0.03$).

For women who were parous at diagnosis, the clinical, sociodemographic, pregnancy-related, and lactational data are presented in Table 1, segmented by BC subtype. Compared to other subtypes, women with TNBC were more likely to have a pathogenic *BRCA1* mutation ($p < 0.001$) and less likely to have been given antibiotics to treat mastitis ($p = 0.04$). Women with TNBC also tended to be younger at diagnosis ($p = 0.014$), to have an older age at first birth ($p = 0.035$) and to have a lower BI value ($p = 0.002$) than those with other subtypes. In analyses adjusting for age at first birth and BI, only the latter remained significantly associated with TNBC. Associations of BC subtype with combinations of age at diagnosis and BI were even more apparent: 46% of patients with TNBC were less than 45 years of age at diagnosis and had a BI value of less than 25, compared to 8% of subjects with ER and PR-/HER + BC, ER or PR+/HER2+ BC, and ER or PR+/HER2- BC ($p < 0.001$). Exploratory visual analyses of age at diagnosis, BI, and BRCA mutation status by BC subtype can be found in Fig. 2. Although sample size is limited, two possible clusters of TNBCs were observed: those with low values for age at BC and BI, who were more likely to have a pathogenic *BRCA1* or *BRCA2* mutation, and those with moderate values of age and BI, for whom BRCA mutations were less common. Associations of BI with BC subtype attenuated after adjustment for age, likely because BI is partly dependent upon age.

Additional data regarding types of breastfeeding issues and regularity of menses in parous responders are displayed in Supplemental Table 2. The only variable that differed significantly by subtype was patient-reported history of having sought care due to breast or nipple pain that interfered with breastfeeding, which was most common in patients with TNBC.

4. Discussion

Our case-case comparison of reproductive risk factors among women diagnosed with BC by age 55 years suggests that there are differences by age and molecular subtype. Consistent with the literature, we found that *BRCA1* mutations were more frequent among women with TNBCs than those with other subtypes. Also, this age-restricted analysis found that, compared to other subtypes, TNBCs are disproportionately diagnosed in younger women and women with lower BI (i.e., fewer births and/or shorter cumulative intervals since births). In this dataset, the vast majority of *BRCA* mutation carriers with TNBC were diagnosed with cancer under age 40 and with a BI below 30, suggesting that combinations of

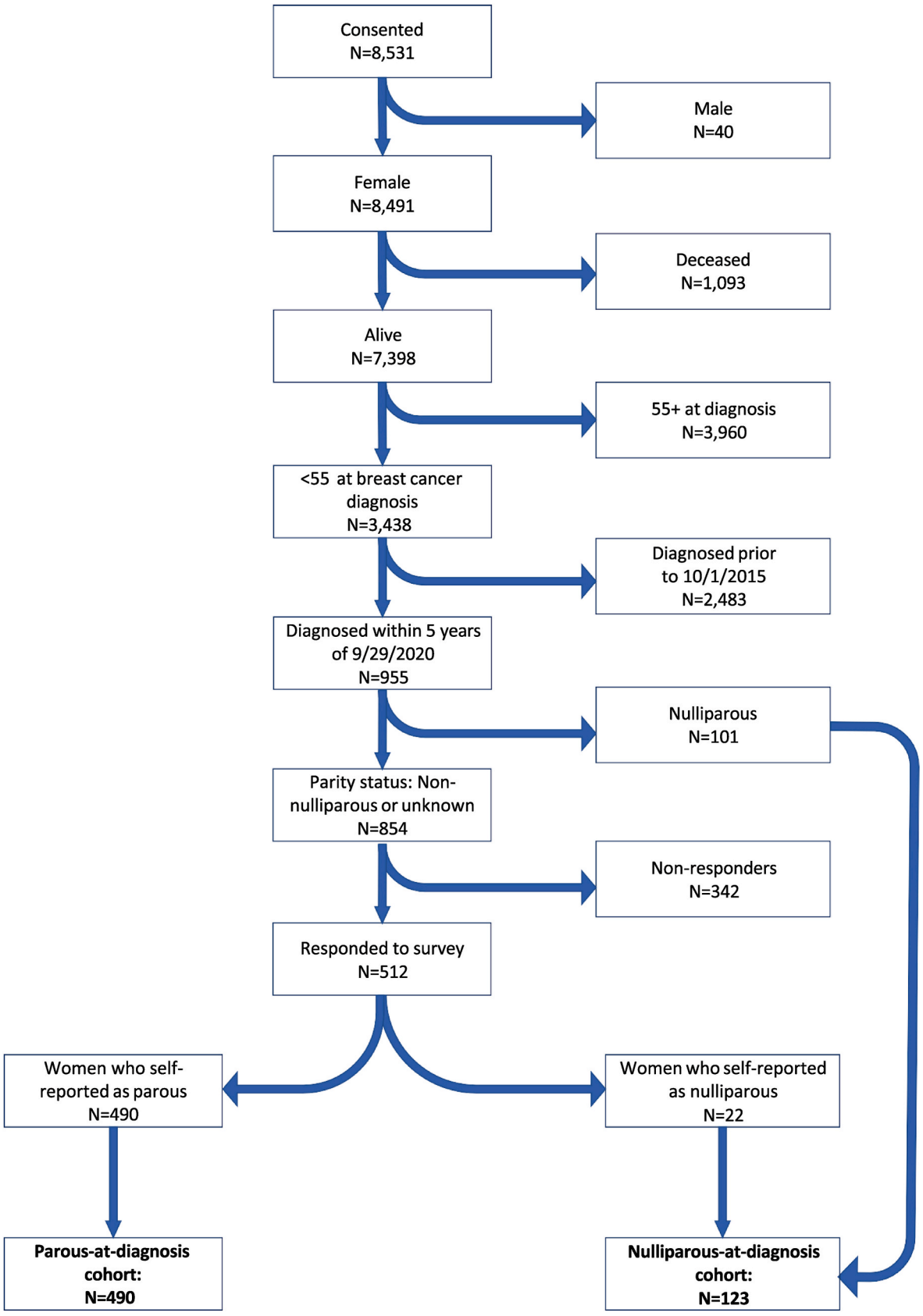

Fig. 1. Flow diagram of eligible participants.

Table 1
Associations between BC subtype and patient characteristics.

	BC subtype						
	Missing (N = 54)	ER and PR-/HER2+ (N = 37)	ER or PR+/HER2+ (N = 69)	ER or PR+/HER2- (N = 277)	triple negative (N = 53)	Total (N = 436)	p-value
AgeDx, median years (IQR)	47.9 (44.3, 52.1)	49.9 (44.7, 52.8)	45.5 (40.8, 51.4)	47.3 (43.0, 50.7)	44.5 (37.3, 49.9)	47.1 (41.5, 50.9)	0.014[a]
Mean (SD)	47.6 (4.84)	47.8 (5.97)	45.5 (6.08)	46.3 (5.47)	43.8 (7.06)	46.0 (5.89)	
First degree relative with breast or ovarian cancer, n (%)							0.116[b]
No	44	36 (97.3%)	55 (79.7%)	234 (84.5%)	45 (84.9%)	370 (84.9%)	
Yes	10	1 (2.7%)	14 (20.3%)	43 (15.5%)	8 (15.1%)	66 (15.1%)	
Race n (%)							0.095[b]
American Indian/Alaskan Native	0	1 (2.7%)	0 (0.0%)	4 (1.4%)	0 (0.0%)	5 (1.1%)	
Asian	0	1 (2.7%)	1 (1.4%)	5 (1.8%)	2 (3.8%)	9 (2.1%)	
Black or African American	1	0 (0.0%)	0 (0.0%)	2 (0.7%)	1 (1.9%)	3 (0.7%)	
Other/Unknown	2	0 (0.0%)	0 (0.0%)	6 (2.2%)	5 (9.4%)	11 (2.5%)	
White	51	35 (94.6%)	68 (98.6%)	260 (93.9%)	45 (84.9%)	408 (93.6%)	
Ethnicity n (%)							0.540[b]
Not Hispanic/Latino	50	36 (97.3%)	66 (95.7%)	263 (94.9%)	47 (88.7%)	412 (94.5%)	
Other	4	1 (2.7%)	2 (2.9%)	7 (2.5%)	3 (5.7%)	13 (3.0%)	
Unknown	0	0 (0.0%)	1 (1.4%)	7 (2.5%)	3 (5.7%)	11 (2.5%)	
Age at menarche, median years (IQR)	13.0 (12.5, 14.0)	13.0 (12.0, 13.0)	13.0 (12.0, 14.0)	13.0 (12.0, 14.0)	13.0 (12.0, 14.0)	13.0 (12.0, 14.0)	0.872[a]
Mean (SD)	13.3 (1.32)	12.8 (1.68)	12.9 (1.31)	12.8 (1.58)	12.8 (1.41)	12.8 (1.53)	
Number of children prior to BC, median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)	0.042[a]
Mean (SD)	2.4 (0.96)	2.5 (1.07)	2.4 (0.82)	2.3 (0.81)	2.1 (1.09)	2.3 (0.87)	
BRCA1 mutation status, n (%)							<.001[b]
Non-pathogenic	32	27 (100.0%)	47 (100.0%)	186 (98.4%)	33 (75.0%)	293 (95.4%)	
Pathogenic	2	0 (0.0%)	0 (0.0%)	3 (1.6%)	11 (25.0%)	14 (4.6%)	
Not tested	20	10	22	88	9	129	
BRCA2 mutation status, n (%)							0.524[b]
Non-pathogenic	34	27 (100.0%)	46 (97.9%)	179 (94.7%)	42 (95.5%)	294 (95.8%)	
Pathogenic	0	0 (0.0%)	1 (2.1%)	10 (5.3%)	2 (4.5%)	13 (4.2%)	
Not tested	20	10	22	88	9	129	
Age at first birth, median years (IQR)	27.5 (25.0, 31.0)	26.0 (23.0, 29.0)	26.0 (23.0, 30.0)	28.0 (25.0, 31.0)	28.5 (25.0, 31.0)	27.0 (24.0, 30.0)	0.035[a]
Mean (SD)	27.7 (5.29)	26.3 (4.72)	26.3 (4.67)	27.7 (4.85)	28.1 (4.88)	27.4 (4.84)	
Birth index, median (IQR)	40.5 (24.0, 53.0)	36.0 (27.0, 57.0)	34.5 (20.0, 54.0)	38.0 (23.0, 49.0)	19.5 (11.0, 41.0)	35.0 (20.0, 50.0)	0.002[a]
Mean (SD)	41.9 (24.35)	44.8 (24.37)	39.3 (24.62)	37.6 (21.25)	29.4 (27.08)	37.5 (23.03)	
Birth index less than 25, n (%)							<.001[b]
No	40	31 (83.8%)	49 (72.1%)	192 (71.1%)	22 (44.0%)	294 (69.2%)	
Yes	14	6 (16.2%)	19 (27.9%)	78 (28.9%)	28 (56.0%)	131 (30.8%)	
Missing	0	0	1	7	3	11	
Combinations of age and birth index, n (%)							<.001[b]
age ≥45 and birth index ≥25	30	22 (59.5%)	32 (47.1%)	155 (57.4%)	19 (38.0%)	228 (53.6%)	
age ≥45 and birth index <25	8	3 (8.1%)	2 (2.9%)	16 (5.9%)	5 (10.0%)	26 (6.1%)	
age <45 and birth index ≥25	10	9 (24.3%)	17 (25.0%)	37 (13.7%)	3 (6.0%)	66 (15.5%)	
age <45 and birth index <25	6	3 (8.1%)	17 (25.0%)	62 (23.0%)	23 (46.0%)	105 (24.7%)	
Missing	0	0	1	7	3	11	
Years between last birth and BC diagnosis, median (IQR)	15.5 (11.0, 21.0)	17.0 (10.0, 22.0)	14.0 (6.0, 19.0)	14.0 (8.0, 19.0)	11.0 (5.0, 19.0)	14.0 (8.0, 19.0)	0.102[a]
Mean (SD)	14.9 (6.66)	15.9 (8.28)	13.3 (7.67)	13.7 (7.01)	11.7 (7.99)	13.6 (7.39)	
Time between last birth and BC diagnosis, n (%)							0.097[b]
5 years	3	5 (13.5%)	10 (14.7%)	28 (10.4%)	12 (24.0%)	55 (12.9%)	
5–9 years	9	3 (8.1%)	15 (22.1%)	54 (20.0%)	9 (18.0%)	81 (19.1%)	
10+ years	42	29 (78.4%)	43 (63.2%)	188 (69.6%)	29 (58.0%)	289 (68.0%)	
Missing	0	0	1	7	3	11	
Total months feeding breast milk, median (IQR)	18.7 (5.1, 33.0)	12.0 (3.0, 29.0)	22.0 (2.3, 39.0)	16.8 (3.2, 34.0)	16.0 (0.9, 34.0)	17.0 (2.8, 35.2)	0.759[a]
Mean (SD)	22.7 (22.88)	19.3 (20.83)	25.3 (26.13)	22.2 (23.81)	23.4 (29.20)	22.6 (24.62)	
Sought care due to difficulty breastfeeding, n (%)							0.272[b]
No	34	30 (81.1%)	53 (76.8%)	221 (79.8%)	36 (67.9%)	340 (78.0%)	
Yes	20	7 (18.9%)	16 (23.2%)	56 (20.2%)	17 (32.1%)	96 (22.0%)	
Given antibiotics within a year after last pregnancy, n (%)							0.040[b]
No	45	29 (80.6%)	56 (84.8%)	236 (90.1%)	48 (98.0%)	369 (89.3%)	
Yes	5	7 (19.4%)	10 (15.2%)	26 (9.9%)	1 (2.0%)	44 (10.7%)	
Missing	4	1	3	15	4	23	
Oral contraceptive use within the first year after child(ren) were born, n (%)							0.729[b]
No OC use	18	16 (43.2%)	30 (43.5%)	114 (41.2%)	23 (43.4%)	183 (42.0%)	
Mini-pill only	4	5 (13.5%)	6 (8.7%)	39 (14.1%)	7 (13.2%)	57 (13.1%)	
E2/prog pill only	16	6 (16.2%)	14 (20.3%)	71 (25.6%)	10 (18.9%)	101 (23.2%)	
Other or combination of OC	16	10 (27.0%)	19 (27.5%)	53 (19.1%)	13 (24.5%)	95 (21.8%)	
Weight increase since prior to last pregnancy, median pounds (IQR)	13.0 (4.0, 20.0)	20.0 (5.0, 40.0)	10.0 (0.0, 25.0)	15.0 (1.0, 30.0)	10.0 (5.0, 30.0)	15.0 (3.0, 30.0)	0.240[a]
Mean (SD)	13.1 (37.92)	24.8 (22.91)	15.3 (21.14)	17.8 (25.92)	17.3 (24.55)	17.9 (24.84)	

[a] Kruskal-Wallis p-value.

[b] Chi-Square p-value.

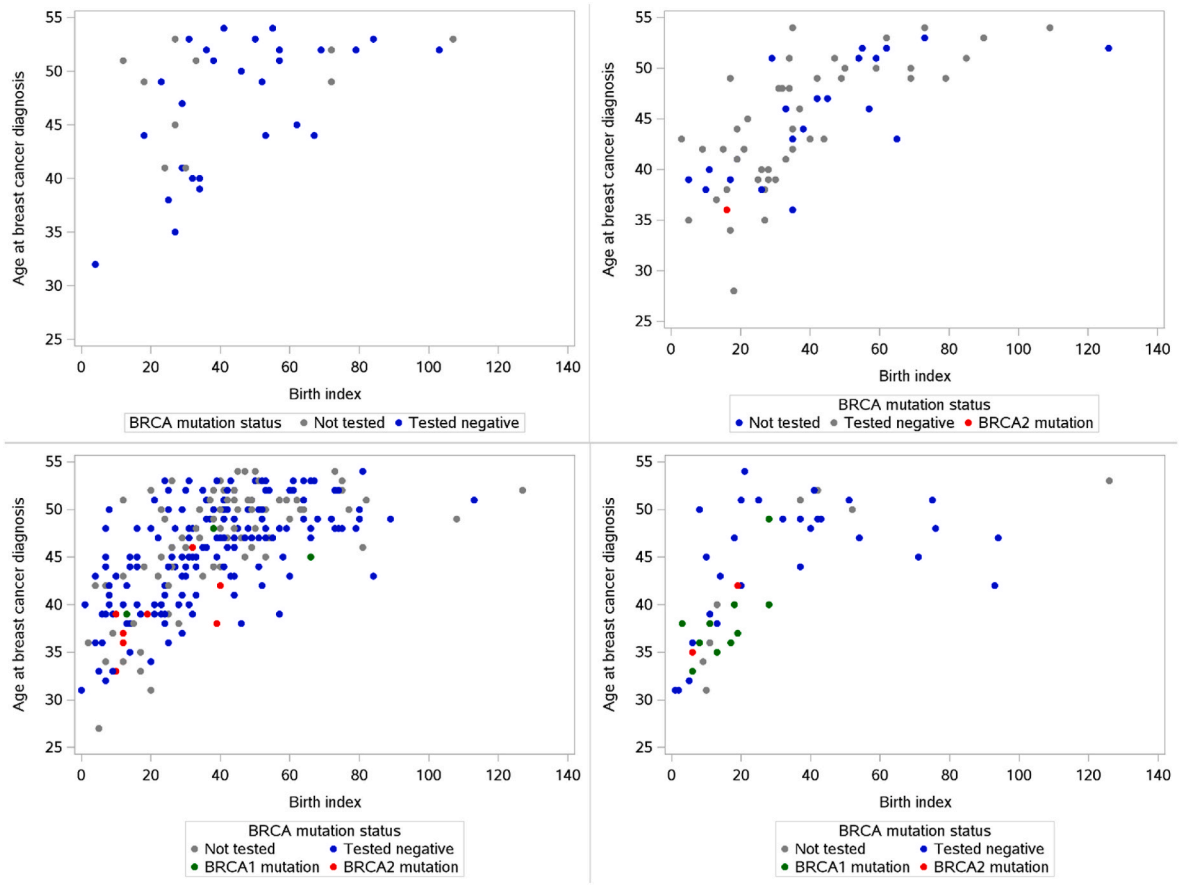

Fig. 2. Scatterplots of age at breast cancer diagnosis and birth index by breast cancer subtype and BRCA mutation status, among 490 parous breast cancer survivors. Top left panel: ER and PR-/HER2+ breast cancer. Top right panel: ER or PR+/HER2+ breast cancer. Bottom left panel: ER or PR+/HER2-breast cancer. Bottom right panel: triple negative breast cancer.

age and patterns of births might be predictive of the likelihood that a patient with TNBC has a *BRCA* mutation. TNBCs were also marginally less likely in those who had used antibiotics to treat mastitis; however, it is unknown whether this reflects a lower incidence of mastitis or missed detection without treatment. These data suggest that larger detailed studies of events during the postpartum period may help identify etiological factors that uniquely increase the risk of specific subtypes of BC. In prior studies of etiological heterogeneity in BC, the sharpest contrasts have been found between postmenopausal ER-positive BC and TNBC [2,3].

Early age at BC diagnosis would tend to result in a shorter period between births and diagnosis and would not allow as much time for pregnancies to occur before diagnosis (both of which would lead to a lower BI), such that we cannot exclude confounding as the reason for the observed association of low BI with TNBC risk compared to other subtypes. However, BI was substantially lower for TNBC than for hormone receptor-positive/HER2-positive BC, even though the median age at diagnosis was nearly identical. In contrast, the time between last birth and BC diagnosis was suggestively shorter for TNBCs than other subtypes. Preclinical studies have implicated the wound healing process associated with postpartum involution in the development of aggressive BC, through mechanisms that are inhibitable with anti-inflammatory agents, consistent with human data linking showing increased risk of BC in the postpartum period [8,11]. These data suggest that understanding how dysregulated postpartum involution might contribute to early onset BC is important and could lead to improved risk assessment and prevention.

Our study was limited by a small sample size and by the fact that we surveyed a highly educated and financially secure cohort of women who had been seen at an academic medical center in the Midwest. Our 60% survey response rate could also affect the generalizability of our conclusions. Furthermore, our data do not allow us to definitively understand the biologic rationale for our findings (e.g., why parous women with TNBC have a lower birth index than parous women with other breast cancer subtypes). Future research on the association of reproductive and postpartum events with BC subtype should include a larger and more diverse population of young women.

Funding

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number R01CA262393 (PIs: Sherman/Radisky/Ruddy) and P30CA 15083-48 (PI: Willman). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest statement

All authors state no conflicts of interest to declare.

Ethical approval

Protocol was approved by the Mayo IRB and informed consent was obtained as part of Mayo Clinic Breast Disease Registry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.11.004.

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