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Reproductive history, breast-feeding and risk of triple negative breast cancer: The Breast Cancer Etiology in Minorities (BEM) Study

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Abstract

Few risk factors have been identified for triple negative breast cancer (TNBC) which lacks expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This more aggressive subtype disproportionately affects some racial/ethnic minorities and is associated with lower survival. We pooled data from three population-based studies (558 TNBC and 5,111 controls) and examined associations of TNBC risk with reproductive history and breast-feeding. We estimated odds ratios (OR) and 95% confidence intervals (CI) using multivariable logistic regression. For younger women, aged <50 years, TNBC risk was increased two-fold for parous women who never breast-fed compared to nulliparous women (OR=2.02, 95% CI=1.12–3.63). For younger parous women, longer duration of lifetime breast-feeding was associated with a borderline reduced risk (≥24 vs. 0 months: OR=0.52, 95% CI=0.26–1.04, *P* trend=0.06). Considering the joint effect of parity and breast-feeding, risk was

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Conflict of interest

None of the authors have any conflict of interest to report.

increased two-fold for women with ≥3 full-term pregnancies (FTPs) and no or short-term (<12 months) breast-feeding compared to women with 1–2 FTPs and breast-feeding ≥12 months (OR=2.56, 95% CI=1.22–5.35). None of these associations were observed among older women (≥50 years). Differences in reproductive patterns possibly contribute to the racial/ethnic differences in TNBC incidence. Among controls aged <50 years, the prevalence of no or short-term breast-feeding and ≥3 FTPs was highest for Hispanics (22%), followed by African Americans (18%), Asian Americans (15%), and non-Hispanic whites (6%). Breast-feeding is a modifiable behavioral factor that may lower TNBC risk and mitigate the effect of full-term pregnancies in women under age 50 years.

Keywords

Breast cancer; breast-feeding; epidemiology; estrogen receptor status; Hispanics; Latinas; parity; progesterone receptor status; risk factors; triple negative breast cancer

INTRODUCTION

Racial/ethnic disparities in breast cancer incidence in the United States (U.S.) are well documented.[1, 2] In 2011–2015, incidence rates (per 100,000) ranged from 128.7 in non-Hispanic whites (NHWs), 125.5 in African Americans, 100.7 in American Indians/Alaska Natives, 91.9 in Hispanics/Latinas, and 90.7 in Asians/Pacific Islanders.[3] Incidence rates also vary across Asian-American[4] and Hispanic[5] ethnicities, and in immigrant populations incidence rates are higher among U.S.-born than non-U.S.-born women and increase over successive generations.[6, 7] Breast cancer subtypes defined by hormone receptor status and other tumor markers also have distinct racial/ethnic-specific incidence patterns; some minority groups have a disproportionate burden of the more aggressive subtypes that are associated with poorer survival.[1, 8] Estrogen receptor negative and progesterone receptor negative (ER-PR-) breast cancers account for about 20% of invasive breast cancer, but they are more common among African American and Hispanic women.[9] Similarly, triple negative breast cancers (TNBC), lacking expression of ER, PR, and human epidermal growth factor receptor 2 (HER2), are more common among African Americans and Hispanics and younger women in particular.[1, 10] TNBC accounts for about 12% of invasive breast cancer, is the subtype with the worst prognosis,[11] and lacks targeted therapeutic agents.[12]

Most breast cancer risk factors identified to date are risk factors for hormone receptor positive (ER+ and/or PR+) or luminal A tumors, the most common subtypes, which have been associated with reproductive and hormonal factors.[13, 14] Few risk factors have been identified for the less common, but more aggressive subtypes such as ER-PR- tumors and TNBC.[15] Racial/ethnic differences in the distribution of risk factors and genetic and biologic factors likely contribute to the disparities in the incidence of breast cancer subtypes. However, there is limited research investigating whether racial/ethnic minorities in the U.S. have different risk factor profiles according to breast cancer subtypes. Such assessments are essential in order to gain a more complete understanding of factors that contribute to racial/ethnic disparities in breast cancer subtypes and to identify opportunities for tailoring preventive strategies aimed at reducing breast cancer disparities. Such evaluations should

include sizeable populations of all major racial/ethnic groups for direct comparison of risk factor profiles. To address this need, we pooled data from four U.S. population-based breast cancer studies to establish the Breast Cancer Etiology in Minorities (BEM) Study, a collaborative effort that comprises data on risk factors, ER and PR status, and breast cancer outcomes on over 16,000 women, including African Americans, Asian Americans, Hispanics, and NHWs. The objective of this first report from the BEM Study is two-fold: 1) To describe the overall pooled dataset that will be used to investigate racial/ethnic differences in risk factors for breast cancer defined by ER and PR status; and 2) to present our findings on the associations of reproductive history and breast-feeding with risk of TNBC. Given that information on HER2 status was available only for a subset of cases, we performed the TNBC analysis for 558 cases from all races/ethnicities combined and only explored differences in associations by race/ethnicity.

MATERIALS AND METHODS

In forming the BEM Study, we pooled interview and cancer registry data for participants in four population-based studies of breast cancer, including the San Francisco Bay Area Breast Cancer Study (SFBCS), the Northern California site of the Breast Cancer Family Registry (NC-BCFR), the Los Angeles County Asian American Breast Cancer Study (AABCS), and the 4-Corners Breast Cancer Study (4-CBCS). After limiting this pooled dataset to women with a first primary invasive breast cancer diagnosed at age 18–79 years (i.e., cases) and controls aged 18–79 years without a personal history of breast cancer, the BEM Study comprises data for 8,842 cases (1,171 African Americans, 2,582 Asian Americans, 2,573 Hispanics, 2,516 NHWs) and 7,767 controls (671 African Americans, 2,004 Asian Americans, 2,459 Hispanics, 2,633 NHWs). All participants provided written informed consent and the studies were approved by the Institutional Review Board at each institution.

Study Design and Population

The San Francisco Bay Area Breast Cancer Study (SFBCS)—The SFBCS is a population-based multiethnic case-control study of breast cancer.[7] Women aged 35–79 years diagnosed with a first primary invasive breast cancer from 1995–2002 were identified through the Greater Bay Area Cancer Registry. Of 17,537 cases listed as NHW, Hispanic or African American in the cancer registry records, 15,573 cases were alive, had a valid address and no physician refusal. They were screened by telephone (89% participation) to assess self-identified race/ethnicity and study eligibility. Cases eligible for selection into the study included all Hispanics diagnosed from 1995–2002, all African Americans diagnosed from 1995–1999, and a 10% random sample of NHWs diagnosed from 1995–1999. Of these, 2,256 (88%) cases completed the in-person interview (1,118 Hispanics, 543 African Americans, 595 NHWs). Controls were identified through random-digit dialing (RDD) and frequency-matched to cases on race/ethnicity and the expected 5-year age distribution of cases at a case:control ratio of 1:1, except for a subset of Hispanic cases diagnosed from 1995–1998 where the case:control ratio was 1:1.5. Of 3,547 controls contacted, 92% completed the screening interview and of 3,170 eligible controls, 2,706 (85%) completed the in-person interview, including 1,462 Hispanics, 598 African Americans, and 646 NHWs.

The Northern California Breast Cancer Family Registry (NC-BCFR)—The NC-BCFR is a population-based family study that recruited breast cancer cases with indicators of increased genetic susceptibility (i.e., diagnosis at age <35 years, personal history of ovarian or childhood cancer, prior breast cancer before age 50 years, or a first-degree family history of breast, ovarian or childhood cancer), as well as random samples of cases not meeting these criteria (2.5% of NHWs, 33% of other race/ethnicities).[16] Study eligibility was determined from cancer registry data and a telephone screening interview that assessed self-reported race/ethnicity and cancer family history. Women aged 18–64 years with newly diagnosed BC were identified through the Greater Bay Cancer Registry (diagnoses 1995–2009) or the Sacramento and Sierra Cancer Registry (diagnoses 2005–2006), and breast cancer cases from racial/ethnic minority populations were oversampled. Additionally, all TNBC cases diagnosed from 2007–2009 were eligible to enroll. A total of 34,517 cases were identified and screened by telephone (85% participation). Of eligible cases selected, 3,620 (76%) enrolled in NC-BCFR and completed the family history and risk factor questionnaires, including 75% of cases from racial/ethnic minority populations. Limiting cases to those with a first primary invasive breast cancer and excluding 313 cases who also participated in the SFBCS, 2,840 cases were included in the pooled analysis (789 Hispanics, 682 Chinese/Japanese/Filipinas, 659 NHWs, 628 African Americans, and 82 other Asians/others). Controls, aged 18–64 years, were identified through random-digit dialing and frequency-matched to cases diagnosed from 1995–1998 on race/ethnicity and 5-year age group, at a case-control ratio of 2:1. Following screening (82% participation), 626 (91%) of eligible controls completed the in-person interview (387 NHWs, 74 Chinese/Japanese/Filipinas, 73 Hispanics, 73 African Americans, and 19 other Asians/others).

The Los Angeles County Asian American Breast Cancer Study (AABCS)—The AABCS is a population-based case-control study of breast cancer in Chinese, Japanese and Filipina women.[17] Cases aged 25–74 years newly diagnosed with a first primary breast cancer from 1995–2001 or 2003–2006 were identified through the Los Angeles County Cancer Surveillance Program. Of 3,797 eligible cases, 77 were deceased, and 548 could not be located. Of those contacted, 2,303 (73%) completed the in-person interview. Limiting cases to those with invasive breast cancer, the pooled analysis included 1,818 cases (746 Chinese, 428 Japanese, and 644 Filipina cases). Controls, aged 25–74 years, were identified through block walking in the neighborhoods where the cases resided at the time of diagnosis, and frequency-matched to cases on specific Asian ethnicity and 5-year age group. The pooled analysis included 1,911 controls, including 869 Chinese, 492 Japanese, and 550 Filipinas.

The 4-Corners Breast Cancer Study (4-CBCS)—The 4-CBCS was conducted in Hispanic, Native American (NA) and NHW women living in non-reservation areas in Arizona, Colorado, New Mexico and Utah.[18] Of the 5,256 cases ages 25–79 years diagnosed with *in-situ* or invasive breast cancer from 1999–2004 identified through state-wide cancer registries, 3,761 were contacted and 2,556 (68%) completed the in-person interview. Limiting the pooled analysis to women with a first primary invasive breast cancer, 1,928 cases were included (667 Hispanics/NAs and 1261 NHWs). Controls were selected from the populations living in the four states and frequency-matched to cases on race/ethnicity and

expected 5-year age distribution. Of 6,152 controls contacted, 2,524 (41%) completed the interview (924 Hispanics/NAs and 1,600 NHWs). Due to the small number of NAs (47cases, 73 controls), they were combined with Hispanics.

Pooled Dataset—Interview data were available for 8,842 cases and 7,767 controls, including 7,340 (83%) cases with information on ER and PR status.

Data Collection

The four studies collected data by in-person interview using similar structured questionnaires that were administered by trained professional interviewers. In-person interviews were conducted in English (in all studies), and by bilingual and bi-cultural interviewers in Spanish (SFBCS, NC-BCFR, 4-CBCS), Cantonese or Mandarin (NC-BCFR, AABCS). The questionnaires asked about established and suspected risk factors for breast cancer, including age, race/ethnicity, country of birth, education, family history of breast cancer in first-degree relatives, menstrual and pregnancy histories, breast-feeding, oral contraceptive use, menopausal hormone therapy use, body size, dietary intake, physical activity, and medical conditions. Each study included a pregnancy history that asked about dates, duration and outcome of each pregnancy and duration of breast-feeding for each live birth. Each study assessed risk factors in the reference year or exposure histories up to the reference year, defined as the calendar year before diagnosis for cases, the calendar year before interview for controls in AABCS and NC-BCFR, or the calendar year before selection into the study for controls in SFBCS and 4-CBCS. Data on tumor characteristics, including date of diagnosis, histology, stage at diagnosis, grade, tumor size, lymph nodes, ER status, PR status, and HER2 status, were obtained from the cancer registries. HER2 status was available for California cases diagnosed after 1999. For 62 ER−PR− breast cancers in NC-BCFR, HER2 status was determined by immunohistochemistry (by T.L.). For cases from the 4-CBCS, the state cancer registries did not collect information on HER2 status until 2010. Thus, this analysis included only cases and controls ages 18–75 years from the three California studies, including 558 women diagnosed with TNBC (102 African Americans, 138 Asian Americans, 154 Hispanics, 164 NHWs) and 5,111 controls.

Data Harmonization

Data from the four studies were harmonized and derived variables were created using common definitions for comparable information. We compared the distribution of the derived variables across the studies and checked variables for outliers and unreasonable values. Race/ethnicity was based on self-report and categorized as African American, Asian American, Hispanic and NHW. Menopausal status in the reference year was categorized as follows: Women who still had periods or were perimenopausal, pregnant, or breast-feeding and under age 55 years were categorized as premenopausal. Women whose periods had stopped naturally, stopped due to bilateral oophorectomy, hysterectomy or other surgery, radiation, chemotherapy or other medications or were aged ≥55 years were categorized as postmenopausal. Women with undetermined status, or who were still having periods and using hormone therapy and under age 55 years, were categorized as unknown menopausal status. Body mass index (BMI) was calculated as self-reported weight (in kilograms) in the reference year (or weight measured at interview if self-reported weight was not available)

divided by measured height squared (in meters) or self-reported height if the measurement was declined. BMI was categorized as <25, 25–29.9 and ≥30 kg/m^2. All studies assessed detailed histories of pregnancies and breast-feeding from which we derived reproductive variables, including history of full-term pregnancy (FTP), age at first FTP, number of FTPs, history of breast-feeding, and lifetime duration of breast-feeding. We also examined two variables related to the timing of pregnancies, including the time interval between age at menarche and age at first FTP, and time interval between age at last FTP and age at diagnosis/selection into the study. Characteristics of controls and cases with breast cancer subtypes defined by joint ER and PR status are shown in Supplementary Table 1.

Statistical Analysis

In this report, we examined associations of TNBC with reproductive history and breast-feeding. Since tumor data on HER2 were not available in 4-CBCS, this analysis included only cases and controls ages 18–75 years from the three California studies, including 558 women diagnosed with TNBC (102 African Americans, 138 Asian Americans, 154 Hispanics, 164 NHWs) and 5,111 controls. We limited the main analysis of reproductive history and breast-feeding to parous women. For comparison with other studies, we also present results for all women, using nulliparous women as the referent group. We used unconditional logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations between TNBC risk and the following variables: age at menarche, age at first FTP, parity (number of FTPs), history of breast-feeding, lifetime duration of breast-feeding, time interval between menarche and first FTP, and recency of last FTP (time interval between last FTP and diagnosis/selection). We also examined the joint effects of parity and breast-feeding. We assessed associations for women of all ages, and stratified the analyses by age (<50 vs. ≥50 years). We evaluated confounding by breast cancer risk factors shown in Table 1. We computed two models: 1) a base model, and 2) an extended multivariable model. The base model included adjustment for age at diagnosis/selection (continuous), study (AABCS, NC-BCFR, SFBCS), time period (diagnosis/selection 1995–1999, 2000–2004, 2005–2009), and race/ethnicity (African American, Asian American, Hispanic, NHW). The extended multivariable model additionally adjusted for education as a proxy for socioeconomic status (some high school or less, high school graduate, some college or technical school, college graduate or high degree), and factors associated with TNBC risk in models adjusted for the base covariates, including: family history of breast cancer in first-degree relatives (yes, no), height (quartiles), and oral contraceptive use (never, former, current). For women of all ages, multivariable models also included menopausal status/hormone therapy (HT) use (premenopausal, postmenopausal no HT use, postmenopausal former HT use, postmenopausal current HT use, unknown status). For women aged ≥50 years, multivariable models also included HT use (never, former, current). In the analyses of parous women, the reproductive variables, parity and lifetime duration of breast-feeding, were mutually adjusted for, as indicated in the footnotes of Table 3. For confounding variables with missing data, we included the missing data under a category “unknown”. We tested for interactions between the reproductive variables and age (<50 years, ≥50 years) by including a multiplicative interaction term in a model with all (younger and older) women. Two-sided *P* values were used for test of trend and tests of

heterogeneity, with a *P* value <0.05 considered statistically significant. Statistical analyses were conducted using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of TNBC cases and controls are shown in Table 1. Overall, 71% of TNBC cases and 81% of controls were from racial/ethnic minority populations. Among both younger and older women, TNBC cases were more likely than controls to have a higher education, a family history of breast cancer in first-degree relatives, and a history of oral contraceptive use. In addition, they were more likely to be U.S.-born and of taller height.

Among women of all ages combined, there were no associations of TNBC risk with age at menarche or parity (Supplemental Table 1). Among parous women, breast-feeding ≥12 months was associated with a lower risk of TNBC in the base model (*P* trend=0.02); multivariable adjustment attenuated the OR estimates and the inverse trend was of borderline significance (*P* trend=0.10). Considering the joint effect of parity and breast-feeding, TNBC risk was increased nearly two-fold (OR=1.96, 95% CI=1.15–3.35) for women with high parity (≥3 FTPs) and no or short-term (<12 months) breast-feeding compared to women with low parity (<3 FTPs) and breast-feeding ≥12 months. When stratified by age at first FTP, results were similar with two-fold elevated risks for women with high parity and no or short-term breast-feeding, although the OR estimates were not statistically significant. Time interval between menarche and first FTP was not associated with TNBC risk.

When stratified by age, associations with parity and breast-feeding were only observed among women aged <50 years (Table 2). Compared to nulliparous women, parous women were at a two-fold increased risk of TNBC, but only those who never breast-fed (OR=2.02, 95% CI=1.12–3.63). This two-fold increased risk decreased with longer duration of breast-feeding, and compared to nulliparous women, those who breast-fed for ≥24 months over their lifetime had no increased risk. Considering the joint effects of parity (≥3 FTPs) and breast-feeding duration, TNBC risk was increased more than two-fold for women with high parity and no or short-term breast-feeding (OR=2.39, 95% CI=1.23–4.64). For age at menarche, there was a suggestive trend of decreasing risk with older age at menarche (*P* trend=0.07). Among women aged ≥50 years, there were no statistically significant associations of TNBC risk with any of the reproductive or breast-feeding variables (Table 2). The observed interactions with age for parity ($P_{interaction}$ = 0.07) and for parity by breast-feeding history ($P_{interaction}$ = 0.08) were borderline statistically significant.

When restricting the analysis to parous women under age 50 years (Table 3), we observed no associations between TNBC risk and age at first FTP or parity. A history of breast-feeding was associated with decreased risk, and risk decreased with longer duration of lifetime breast-feeding, with a borderline 48% reduction in TNBC risk for breast-feeding ≥24 vs. 0 months (OR=0.52, 95% CI=0.26–1.04, *P* trend=0.06). Considering the joint effects of parity and breast-feeding, compared to women with low parity and breast-feeding ≥12 months, risk was increased more than two-fold for women with high parity and no or short-term breast-feeding (OR=2.56, 95% CI=1.22–5.35). TBNC risk was also increased two-fold for women with high parity and a first FTP before age 25 years (OR=1.92, 95% CI=1.02–3.59). Time

between menarche and first FTP and recency of last FTP were not associated with TNBC risk. For parous women aged ≥50 years, pregnancy history and breast-feeding were not associated with TNBC risk (Table 3). Among parous women, the observed interactions with age were not statistically significant.

Although our sample size was not sufficient for detailed analyses stratified by race/ethnicity, we did observe an elevated risk of TNBC for parous women aged <50 years who never breast-fed when compared to nulliparous women among all four racial/ethnic groups. However, none of the OR estimates reached statistical significance (NHWs: OR=2.91, 95% 0.67–12.65; African Americans: OR=2.84, 95% CI=0.53–15.32; Asian Americans: OR=1.72. 95% CI=0.66–4.50; Hispanics: OR=1.60, 95% CI=0.50–5.09; data not shown in tables).

DISCUSSION

In this large pooled multiethnic population, we found that TNBC risk was increased two-fold for parous women under age 50 years who never breast-fed compared to nulliparous women. Among younger parous women, TNBC risk was increased two-fold for women with high parity (≥3 FTPs) and no or short-term (<12 months) breast-feeding, whereas no increase in risk was seen for women with high parity and breast-feeding for ≥12 months. Our findings suggest that breast-feeding mitigates the elevated risk of TNBC associated with full-term pregnancies among younger women.

TNBC accounts for 12% of newly diagnosed invasive breast cancers, with a disproportionate burden among African Americans (22.5%) and Hispanics (14.7%) compared to NHWs (10.6%) and Asian Americans (9.7%),[1] and a particularly high burden (39%) among premenopausal African-American women.[19] Thus, TNBC accounts for a substantial portion of breast cancers among African-American women, yet few risk factors have been identified for this more aggressive subtype.[14, 15]

Breast-feeding is one of the few factors that has been most consistently associated with a lower risk of TNBC.[14, 20, 21] Our finding of a 48% reduction in TNBC risk for younger parous women who breast-fed for ≥24 months is consistent with other studies[22–25] and a pooled analysis in African American and white women[26] that reported 40–50% risk reductions associated with breast-feeding for ≥12 months. Consistent with our results, the pooled analysis[26] and other studies[24, 27–29] also failed to find associations with breast-feeding for older women. In both our study and the pooled analysis by Ma et al.,[26] the interaction by age did not reach statistical significance, warranting larger studies to confirm these results.

In contrast to the long-term protective effect of parity on the risk of breast cancer overall and ER+ subtypes, parity has been associated with increased TNBC risk in several studies, with reports of two- to three-fold increased risks associated with parity of ≥2 versus nulliparity.[30–33] We also observed a two-fold increased risk for women with ≥3 FTPs, but only among younger women with no or short-term (<12 months) breast-feeding. Some studies found no

association with parity among younger women.[22–26, 34] The lack of association with parity among older women in our study is consistent with other reports.[26, 29, 35]

Only a few studies examined the joint effects of parity and breast-feeding on TNBC risk.[30, 32, 33, 36] The Carolina Breast Cancer Study was the first to report an increased risk of basal-like breast cancer for parous women who never breast-fed, with ORs of 1.8 (95% CI=1.1–3.0) and 1.9 (95% CI=1.1–3.3) for parity 1–2 or ≥3, respectively, when compared to nulliparous women.[30] Using the same exposure categories, we found similarly elevated ORs for younger women who never breast-fed when compared to nulliparous women (1–2 FTPs: OR=1.93, 95% CI=1.03–3.60; ≥3 FTPs: OR=3.03, 95% CI=1.30–7.10; data not shown in tables). In contrast, among parous women, we did not find elevated ORs associated with parity among those who never breast-fed (data not shown in tables): OR=0.53 (95% CI=0.25–1.13) for parity ≥2 vs. 1, compared to OR=1.60 (95% CI=0.84–3.03) as previously reported in Ambrosone et al.[32], and OR=0.66 (95% CI=0.18–2.41) for parity ≥4 vs. 1, compared to OR=1.51, 95% CI-0.90–2.52 as previously reported in Palmer et al.[36]. Larger studies or pooled analyses will be needed to comprehensively evaluate the joint effects of reproductive history and breast-feeding and whether these associations differ for early-onset vs. later-onset TNBC.

Published results on associations of TNBC risk and other reproductive factors (i.e., age at first FTP, recency of pregnancy, age at menarche, time between menarche and first FTP) are inconsistent and few data are available for younger women. A first FTP or live birth at younger ages has been associated with increased TNBC risk in some studies,[23, 30, 34] whereas we and the meta-analysis by Lambertini et al.[21] found no association with age at first birth. However, among younger parous women with ≥3 FTPs, we found a significant two-fold increased risk of TNBC for women with a first FTP before age 25 years. Thus, the joint effect of the number and timing of pregnancies may be important and needs to be examined in future studies of younger women. Consistent with our findings, other studies in young women found no association with recency of last FTP.[22, 23]

Some studies, including ours, observed that older age at menarche was associated with a lower risk of TNBC[34, 37, 38] or basal-like tumors,[22, 30, 39] whereas other studies found no association.[23, 25, 27, 31, 35, 40, 41] We found no association of TBNC risk with time between menarche and first FTP, consistent with a pooled analysis in African American women.[38] A longer interval between menarche and first birth has been associated with both lower[23] and increased[41] risk of TNBC.

The biologic mechanisms that explain the increased TNBC risk associated with parity in the absence of breast-feeding are not well understood. Although more full-term pregnancies reduce the risk of breast cancer in the long-term, in the short-term, a transient increase in risk appears to last at least 10 years.[42] It has been proposed that this transient increase in risk may be due to exposure to pregnancy-related hormones, immune suppressive effects of pregnancy, and post-partum involution which may induce inflammatory processes that are tumor- and metastasis-promoting and may be associated with the development of more aggressive breast cancers.[43, 44] Breast-feeding has been hypothesized to lower breast cancer risk by promoting terminal differentation of breast epithelial cells, suppressing ovulation and

thereby lowering lifetime exposure to cycling hormones, preventing disordered involution, or prolonging the time between pregnancy and involution that may be critical events in the progression of previously initiated cells.[43, 45, 46] If pregnancy-associated breast cancer risk diminishes over ten years, and if breast-feeding mitigates this risk, then the protective effect of breast-feeding would no longer be observed in older women, which is consistent with our data for women aged ≥50 years.

It is currently not known whether associations of TNBC with reproductive history differ between racial/ethnic groups, with few data available for African American,[26, 32, 36, 38] Chinese,[31] Japanese,[37] and Spanish[47] women. The pooled analysis by Ma et al. found a strong inverse association with breast-feeding for African American women only, particularly for those under age 45 years.[26] Although our study includes a diverse sample of TNBC cases, the sample size for each racial/ethnic group was too small for analyses by race/ethnicity. Nevertheless, we found that the prevalence of reproductive risk factors associated with TNBC risk greatly varies by race/ethnicity. Among younger controls, lower proportions of NHW women had a high-risk profile of high parity (≥3 FTPs) with no or short-term (<12 months) of breast-feeding compared to African American, Hispanic or Asian American women (6% vs. 18%, 22%, 15%, respectively). Such differences in reproductive patterns possibly contribute to racial/ethnic differences in TNBC incidence in younger women.

Our study is not without limitations. Subtype classification may be subject to misclassification since tumor marker data from cancer registries rely on multiple pathology laboratories that use different assays. However, substantial agreement has been shown for ER and PR from cancer registry records vs. a single pathology laboratory,[48] and an evaluation of reproductive risk factors and breast cancer subtypes defined by ER and PR status showed that they did not differ by source of tumor data.[24] In our pooled dataset, tumor marker data were not available for all breast cancer cases and HER2 status was not collected by the California Cancer Registry until 2000 and was not available for 4-CBCS. Study strengths include a relatively large sample size (with 558 TNBC cases, ours is among the largest studies[26, 36, 49]), the racial/ethnic diversity of the study population, and a focus on reproductive and breast-feeding variables that are assessed in fairly standard ways, thus facilitating data harmonization. Ours is also one of the few studies that present separate results for younger and older women.[24, 26] Our findings emphasize the need for age stratification, as associations with parity and breast-feeding were distinct for younger vs. older women. Such analyses will require large sample sizes.

In summary, our study provides supporting evidence that breast-feeding lowers the risk of TNBC in younger women, and mitigates the increased risk associated with pregnancies. This finding is of public health importance, as there are notable differences in breast-feeding initiation and duration by race/ethnicity,[50] particularly among African American women who are at higher TNBC risk, pointing to opportunities for targeted interventions to increase breast-feeding. A better understanding of the etiologic factors for TNBC will facilitate the development of more accurate risk prediction models and enhanced prevention strategies to lower TNBC risk, and consequently, breast cancer mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Impact

Triple negative breast cancer (TNBC) is an aggressive subtype with few known risk factors. In this pooled analysis, the authors found that for women aged <50 years, breast-feeding was associated with reduced TNBC risk, and parous women who never breast-fed had a two-fold higher risk of TNBC compared to nulliparous women. The findings suggest that breast-feeding, a modifiable behavioral factor, may mitigate the adverse effect of pregnancies in younger women.

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Table 1

Characteristics of Triple Negative Cases and Controls, by Age, Breast Cancer and Etiology in Minorities (BEM) Study

	Women Aged <50 Years				Women Aged ≥50 Years			
	TNBC Cases n=252		Controls n=2,223		TNBC Cases n=306		Controls n=2,888	
	n	%[1]	n	%[1]	n	%[1]	n	%[1]
Study[2]								
AABCS	21	8	947	43	44	14	949	33
NC-BCFR	201	80	323	15	229	75	303	10
SFBCS	30	12	953	43	33	11	1,636	57
Time period[3]								
1995–1999	62	25	1,182	53	27	9	1,696	59
2000–2004	77	31	903	41	101	33	1,005	35
2005–2009	113	45	138	6	178	58	187	6
Race/ethnicity								
African American	38	15	227	10	64	21	414	14
Asian American	54	21	1,007	45	84	27	982	34
Hispanic	85	34	611	27	69	23	887	31
Non-Hispanic white	75	30	378	17	89	29	605	21
Age (years)								
<40	97	38	597	27	0	0	0	0
40–49	155	62	1,626	73	0	0	0	0
50–59	0	0	0	0	213	70	1,518	53
60–75	0	0	0	0	93	30	1,370	47
Education								
Some high school or less	29	12	369	17	41	13	738	26
High school degree	29	12	284	13	47	15	517	18
Technical/vocational school or some college	81	32	581	26	104	34	724	25
College or higher degree	113	45	989	44	114	37	909	31
Country of birth								
U.S.-born	157	62	1,006	45	198	65	1,553	54

	Women Aged <50 Years				Women Aged ≥50 Years			
	TNBC Cases n=252		Controls n=2,223		TNBC Cases n=306		Controls n=2,888	
	n	%[1]	n	%[1]	n	%[1]	n	%[1]
Foreign-born	95	38	1,217	55	108	35	1,335	46
Family history of breast cancer in first-degree relatives								
No	195	77	2,032	92	238	78	2,538	89
Yes	57	23	182	8	67	22	327	11
Unknown[4]	0	0	9	0	1	0	22	1
Personal history of benign breast disease								
No	227	90	1,866	84	241	79	2,175	75
Yes	25	10	357	16	65	21	709	25
Unknown[4]	0		0		0		4	
Alcohol consumption in reference year (drinks/week)								
0	171	68	1,396	63	205	67	1,939	67
≤2.0	18	7	346	16	22	7	405	14
>2.0	62	25	481	22	77	25	542	19
Unknown[4]	1		0		2		2	
Height (cm, quartiles)[5]								
<154.9	25	10	472	21	45	15	842	29
155.0–159.9	52	21	742	33	86	28	929	32
160.0–165.0	90	36	502	23	78	26	621	22
>165.0	83	33	504	23	95	31	487	17
Unknown[4]	2		3		2		9	
Body mass index (kg/m^2) in reference year								
<25	128	51	1,303	59	125	41	1,244	43
25–29.9	68	27	505	23	79	26	877	31
≥30	53	21	411	19	100	33	754	26
Unknown[4]	3		4		2		13	
Oral contraceptive use								
Never	54	21	712	32	85	28	1,361	48

	Women Aged <50 Years				Women Aged ≥50 Years			
	TNBC Cases n=252		Controls n=2,223		TNBC Cases n=306		Controls n=2,888	
	n	%[1]	n	%[1]	n	%[1]	n	%[1]
Former	158	63	1,378	62	218	71	1,497	52
Current	40	16	126	6	3	1	7	0
Unknown[4]			7				23	
Menopausal status in reference year								
Premenopausal	209	87	1,881	90	41	14	270	10
Postmenopausal	32	13	211	10	256	86	2,467	90
Unknown[4]	11		131		11		151	
Hormone therapy use (postmenopausal women)								
Never	25	78	107	51	137	54	1,181	48
Former	3	9	49	23	79	31	739	30
Current	4	13	53	25	36	14	528	22
Unknown[4]	0		2		4		19	

[1] Percentages may not add up to 100 due to rounding.

[2] AABCS: Los Angeles County Asian Breast Cancer Study; NC-BCFR: Northern California site of the Breast Cancer Family Registry; SFBCS: San Francisco Bay Area Breast Cancer Study.

[3] Year of diagnosis for cases, year of selection or interview for controls.

[4] Not included in percentages.

[5] Quartiles among all controls.

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Table 2

Association of Reproductive History and Breast-feeding with Risk of Triple Negative Breast Cancer, by Age

	Women Aged <50 Years						Women Aged ≥50 Years					
	TNBC cases n=252	**Controls n=2,223**	**OR[1]**	**95% CI**	**OR[2]**	**95% CI**	**TNBC Cases n=306**	**Controls n=2,888**	**OR[1]**	**95% CI**	**OR[3]**	**95% CI**
Age at menarche (years)												
<12	63	453	1.0		1.0		61	568	1.0		1.0	
12	72	598	0.88	0.54–1.42	0.93	0.57–1.53	68	671	1.37	0.82–2.27	1.35	0.81–2.26
13	66	570	0.71	0.43–1.15	0.65	0.39–1.09	86	732	1.12	0.69–1.82	1.08	0.66–1.77
≥14	51	598	0.63	0.38–1.06	0.68	0.40–1.15	88	901	1.21	0.75–1.94	1.25	0.77–2.02
			P_{trend} =0.05		P_{trend} =0.07				P_{trend} =0.67		P_{trend} =0.59	
					$P_{interaction}$ with age = 0.57							
Parity by history of breast-feeding												
Nulliparous	64	429	1.0		1.0		60	317	1.0		1.0	
Parous, never breast-fed	60	642	1.88	1.08–3.26	2.02	1.12–3.63	102	1,100	0.80	0.48–1.32	0.70	0.41–1.19
Parous, ever breast-fed	128	1,152	1.05	0.66–1.65	1.21	0.75–1.96	144	1,471	0.76	0.47–1.21	0.70	0.43–1.15
					$P_{interaction}$ with age = 0.08							
Parity (number of FTPs)[4]												
Nulliparous	64	429	1.0		1.0		60	317	1.0		1.0	
1	56	381	1.76	1.03–3.02	2.13	1.21–3.75	43	362	0.67	0.36–1.21	0.64	0.35–1.18
2	64	748	0.90	0.54–1.48	0.90	0.53–1.53	87	710	0.76	0.46–1.27	0.68	0.40–1.15
3	43	391	1.41	0.79–2.52	1.88	1.01–3.48	67	601	0.96	0.56–1.65	0.86	0.49–1.52
≥4	25	274	1.08	0.53–2.21	1.47	0.66–3.28	49	898	0.71	0.40–1.26	0.66	0.36–1.20
			P_{trend} =0.96		P_{trend} =0.52				P_{trend} =0.63		P_{trend} =0.46	
					$P_{interaction}$ with age = 0.07							
Duration of breast-feeding (months)												
Nulliparous	64	429	1.0		1.0		60	317	1.0		1.0	
0	60	642	1.88	1.08–3.26	2.02	1.12–3.63	102	1,100	0.80	0.48–1.32	0.70	0.41–1.19
1–5	34	334	1.20	0.66–2.16	1.42	0.76–2.66	40	444	0.90	0.50–1.61	0.78	0.43–1.42
6–11	37	254	1.18	0.66–2.13	1.33	0.72–2.45	41	308	0.85	0.47–1.56	0.81	0.44–1.49

	Women Aged <50 Years						Women Aged ≥50 Years					
	TNBC cases n=252	**Controls n=2,223**	**OR[1]**	**95% CI**	**OR[2]**	**95% CI**	**TNBC Cases n=306**	**Controls n=2,888**	**OR[1]**	**95% CI**	**OR[3]**	**95% CI**
12–23	26	289	1.00	0.52–1.90	1.11	0.57–2.15	23	299	0.61	0.31–1.20	0.55	0.27–1.11
≥24	31	275	0.81	0.42–1.56	0.99	0.50–1.96	40	420	0.66	0.35–1.22	0.66	0.35–1.25
			P_{trend} =0.18		P_{trend} =0.44				P_{trend} =0.16		P_{trend} =0.24	
					$P_{interaction}$ with age = 0.39							
Parity by breast-feeding duration (months)												
Nulliparous	64	429	1.0		1.0		60	317	1.0		1.0	
1–2, breast-fed ≥12 mon	27	247	0.84	0.44–1.63	0.90	0.46–1.76	20	137	0.56	0.25–1.24	0.53	0.23–1.22
1–2, breast-fed <12 mon	93	882	1.32	0.82–2.11	1.46	0.88–2.42	110	935	0.76	0.47–1.25	0.69	0.42–1.14
≥3, breast -fed ≥12 mon	30	317	0.97	0.50–1.86	1.35	0.67–2.72	43	582	0.68	0.38–1.22	0.66	0.36–1.22
≥3, breast -fed <12 mon	38	348	1.76	0.95–3.27	2.39	1.23–4.64	73	917	0.98	0.57–1.68	0.86	0.49–1.52
					$P_{interaction}$ with age = 0.38							

[1]Adjusted for base covariates, including age (continuous), study (AABCS, SFBCS, NC-BCFR), time period (1995–1999, 2000–2004, 2005–2009), race/ethnicity (African American, Asian American, Hispanic, non-Hispanic white).

[2]Additionally adjusted for education (some high school or less, high school degree, vocational/technical school or some college, college or higher degree), family history of breast cancer in first-degree relatives (no, yes), height (quartiles), and oral contraceptive use (never, former, current).

[3]Additionally adjusted for education (some high school or less, high school degree, vocational/technical school or some college, college or higher degree), family history of breast cancer in first-degree relatives (no, yes), height (quartiles), oral contraceptive use (never, former, current), and hormone therapy use (never, former, current).

[4]Number of full-term pregnancies ending in single or multiple births, including live or still births.

Table 3

Association of Reproductive History and Breast-feeding with Risk of Triple Negative Breast Cancer in Parous Women, by Age

	Parous Women Aged <50 years						Parous Women Aged ≥50 Years					
	TNBC cases n=188	**Controls n=1,794**	**OR[1]**	**95% CI**	**OR[2]**	**95% CI**	**TNBC Cases n=246**	**Controls n=2,571**	**OR[1]**	**95% CI**	**OR[3]**	**95% CI**
Age at first full-term pregnancy (FTP) (years)[4,5]												
< 20	32	315	1.0		1.0		67	525	1.0		1.0	
20–24	61	482	1.56	0.85–2.85	1.59	0.84–3.01	76	960	0.81	0.50–1.29	0.79	0.48–1.30
25–29	45	519	1.22	0.64–2.32	1.27	0.62–2.61	61	698	0.73	0.43–1.23	0.79	0.44–1.42
≥30	50	477	1.30	0.67–2.50	1.27	0.59–2.73	42	373	0.75	0.41–1.35	0.82	0.42–1.63
			P_{trend} =0.76		P_{trend} =0.80				P_{trend} =0.28		P_{trend} =0.56	
					$P_{interaction}$ with age = 0.26							
Parity (number of FTPs)[4,6]												
1	56	381	1.0		1.0		43	362	1.0		1.0	
2	64	748	0.51	0.31–0.83	0.46	0.27–0.77	87	710	1.14	0.68–1.94	1.09	0.64–1.87
3	43	391	0.80	0.46–1.40	1.02	0.56–1.86	67	601	1.44	0.82–2.51	1.44	0.81–2.58
≥4	25	274	0.63	0.32–1.26	0.84	0.38–1.86	49	898	1.05	0.58–1.89	1.15	0.60–2.19
			P_{trend} =0.35		P_{trend} =0.88				P_{trend} =0.72		P_{trend} =0.48	
					$P_{interaction}$ with age = 0.14							
Breast-feeding history[7]												
Never	60	642	1.0		1.0		102	1,100	1.0		1.0	
Ever	128	1,152	0.57	0.37–0.90	0.64	0.40–1.03	144	1,471	0.95	0.66–1.37	0.99	0.68–1.46
					$P_{interaction}$ with age = 0.12							
Duration of breast-feeding (months)[7]												
0	60	642	1.0		1.0		102	1,100	1.0		1.0	
1–5	34	334	0.65	0.37–1.15	0.68	0.37–1.23	40	444	1.10	0.67–1.81	1.09	0.65–1.81
6–11	37	254	0.65	0.36–1.17	0.75	0.41–1.37	41	308	1.10	0.65–1.86	1.17	0.68–2.01
12–23	26	289	0.54	0.29–1.02	0.61	0.31–1.19	23	299	0.75	0.41–1.38	0.74	0.39–1.40
≥24	31	275	0.46	0.24–0.87	0.52	0.26–1.04	40	420	0.84	0.50–1.44	0.93	0.52–1.66
			P_{trend} =0.01		P_{trend} =0.06				P_{trend} =0.35		P_{trend} =0.61	

	Parous Women Aged <50 years						Parous Women Aged ≥50 Years					
	TNBC cases n=188	**Controls n=1,794**	**OR[1]**	**95% CI**	**OR[2]**	**95% CI**	**TNBC Cases n=246**	**Controls n=2,571**	**OR[1]**	**95% CI**	**OR[3]**	**95% CI**
					$P_{interaction}$ with age = 0.65							
Parity by duration of breast-feeding (months)												
1–2, breast-fed ≥12 mon	27	247	1.0		1.0		20	137	1.0		1.0	
1–2, breast-fed <12 mon	93	882	1.53	0.84–2.79	1.59	0.86–2.93	110	935	1.34	0.65–2.76	1.27	0.60–2.69
≥3, breast -fed ≥12 mon	30	317	1.17	0.56–2.42	1.54	0.71–3.31	43	582	1.19	0.53–2.64	1.21	0.53–2.78
≥3, breast -fed <12 mon	38	348	2.04	1.00–4.16	2.56	1.22–5.35	73	917	1.73	0.80–3.74	1.60	0.72–3.57
					$P_{interaction}$ with age = 0.94							
Parity by age at first FTP (years)[6]												
1–2, <25	42	342	1.0		1.0		54	409	1.0		1.0	
≥3, <25	51	455	1.31	0.73–2.37	1.92	1.02–3.59	89	1,076	1.12	0.68–1.84	1.24	0.73–2.11
1–2, ≥25	78	787	1.10	0.64–1.89	1.16	0.64–2.08	76	662	0.89	0.52–1.50	0.97	0.56–1.68
≥3, ≥25	17	209	0.97	0.45–2.11	1.50	0.66–3.42	27	409	0.95	0.49–1.83	1.20	0.60–2.40
					$P_{interaction}$ with age = 0.93							
Time between menarche and first FTP (years)												
<5	14	130	1.0		1.0		34	220	1.0		1.0	
5–9	52	455	1.10	0.50–2.42	1.13	0.49–2.60	83	895	0.71	0.39–1.30	0.62	0.34–1.15
10–14	52	493	1.17	0.53–2.59	1.11	0.47–2.60	57	813	0.56	0.29–1.07	0.54	0.27–1.06
15–19	37	438	1.12	0.49–2.58	1.10	0.45–2.70	46	408	0.56	0.28–1.12	0.55	0.27–1.15
≥20	33	275	1.33	0.56–3.17	1.19	0.46–3.07	23	209	0.58	0.26–1.31	0.57	0.24–1.34
			P_{trend} =0.55		P_{trend} =0.79				P_{trend} =0.13		P_{trend} =0.24	
					$P_{interaction}$ with age = 0.61							
Time since last FTP (years)[8]												
≥15	53	622	1.0		1.0							
10–14	46	439	0.97	0.56–1.70	0.94	0.53–1.67						
5–9	50	420	1.48	0.84–2.62	1.48	0.81–2.69						
3–4	18	144	1.11	0.48–2.54	1.02	0.43–2.43						
≤2	21	167	1.39	0.62–3.11	1.56	0.67–3.60						
			P_{trend} =0.34		P_{trend} =0.29							

[1] Adjusted for base covariates, including age (continuous), study (AABCS, SFBCS, NC-BCFR), time period (1995–1999, 2000–2004, 2005–2009), race/ethnicity (African American, Asian American, Hispanic, non-Hispanic white).

[2] Additionally adjusted for education (some high school or less, high school degree, vocational/technical school or some college, college or higher degree), family history of breast cancer in first-degree relatives (no, yes), height (quartiles), and oral contraceptive use (never, former, current).

[3] Additionally adjusted for education (some high school or less, high school degree, vocational/technical school or some college, college or higher degree), family history of breast cancer in first-degree relatives (no, yes), height (quartiles), oral contraceptive use (never, former, current), and hormone therapy use (never, former, current).

[4] Full-term pregnancies ending in single or multiple births, including live or still births.

[5] Also adjusted for parity (1, 2, 3, ≥4) and duration of breast-feeding (0, <12, ≥12 months).

[6] Also adjusted for duration of breast-feeding (0, <12, ≥12 months).

[7] Also adjusted for parity (1, 2, 3, ≥4).

[8] For younger women only.