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Risk Factors for Pregnancy-Associated Breast Cancer: A Report from the Nigerian Breast Cancer Study

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Abstract

Purpose—Little is known about risk factors for pregnancy-associated breast cancer (PABC), diagnosed during pregnancy or postpartum.

Methods—1,715 premenopausal women were enrolled from the Nigerian Breast Cancer Study, 1998-2011. Based on recency of last pregnancy from diagnosis, breast cancer cases were categorized as: 1) PABC diagnosed ≤2-year postpartum, 2) PABC diagnosed 3-5 year postpartum, and 3) non-PABC diagnosed >5-year postpartum. Controls were matched to cases on recency of last pregnancy. Multiple logistic regressions were performed comparing cases and controls within each group.

Results—Of the 718 cases, 152 (21.2%) had PABC ≤2-year postpartum, and 145 (20.2%) 3-5 years postpartum. Although not statistically significant, women with higher parity tend to have an elevated risk of PABC but reduced risk of non-PABC (*P*-for-heterogeneity=0.097). Family history of breast cancer might be a strong predictor particularly for PABC ≤2-year postpartum (OR=3.28, 95% CI: 1.05-10.3). Compared to non-PABC cases, PABC ≤2 year postpartum cases were more likely to carry *BRCA1/2* mutations (*P*=0.03).

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Conclusions—Parity may have different roles in the development of PABC versus other premenopausal breast cancer in Nigerian women. Prospective mothers with multiple births and a family history of breast cancer may have elevated risk of breast cancer during their immediate postpartum.

It is known that pregnancy may invoke two potentially opposing influences on the mother's risk of breast cancer (1), with a transient increased risk in the years immediately following pregnancy and a long-term protective effect (2). Time interval for this postpartum increase in breast cancer was estimated to range between 2-15 years. Although pregnancy-associated breast cancer (PABC) is usually defined as breast cancer diagnosed during pregnancy or within 1-2 years postpartum (3), there is no unified definition (4-7). Routine screening mammography is not recommended for women <50 years (9), and even with screening mammography, the physiologic changes associated with pregnancy and lactation make detection and evaluation of breast masses difficult (10), with diagnosis usually delayed for 5-7 months (11).

PABC tend to be large tumor in advanced-stage, high histological grade, and triple-negative (6, 12-15), and most studies found PABC patients had worse prognosis (3, 16) despite inconsistency (14, 17). A recent cohort study grouped breast cancer cases according to time between giving birth and diagnosis, and found cases diagnosed within 5-year postpartum have significantly higher risks for metastasis and mortality compared to nulliparous cases, suggesting the definition of PABC may include cases diagnosed up to 5-year postpartum to better delineate the increased risk imparted by a postpartum diagnosis (18).

PABC diagnosed within 1-year postpartum was estimated to be approximately 1 in 3000 pregnancies (19, 20) . Andersson et al observed that PABC cases (≤2-year postpartum) represented approximately 7% of all breast cancers in two national registers in Sweden (22). Given a global trend toward postponed childbearing, the PABC incidence is increasing (22-24). Furthermore, with the broader definition of PABC within 5-year postpartum, a higher proportion of breast cancer cases would be pregnancy-associated.

The concomitant occurrence of breast cancer and pregnancy remains a challenging clinical problem as treatments often conflict with protecting the fetus (25). Identifying high risk subgroups of premenopausal women are necessary for intervention and early detection. However, risk factors for PABC are not well understood (23, 26). As an understudied population, indigenous African women tend to have high parity and relatively young ages at diagnosis of breast cancer, making pregnancy and lactation more likely to co-exist with breast cancer than among the western populations (27) and therefore a great opportunity to study relevant risk factors.

MATERIALS AND METHODS

Study Sample

Nigerian Breast Cancer Study (NBCS) is a case-control study conducted in Ibadan, Nigeria, 1998-2011. The study setting and design were described in detail elsewhere (28, 29)_ENREF_1_ENREF_1_ENREF_1. Briefly, cases were identified through University College Hospital (UCH) in Ibadan. Serving a population of approximately 3 million, UCH is a referral center for other hospitals and thus treat the majority of breast cancer cases in the region. All consecutive female cases aged ≥18 with a histological or clinical diagnosis of invasive breast cancer between March 1998 and April 2011 were eligible. During the period of case enrollment, community-based controls were randomly selected to represent the diversity of UCH patients and invited to visit a clinic set up in the community for the study. We also enrolled controls through other clinics in the UCH matched for age and ethnicity.

After obtaining informed consent, trained nurse interviewers administered a structured questionnaire, measured height and weight, and obtained blood samples. In this analysis, we included premenopausal women between 21 and 50 years old.

Measurements

While PABC is often restricted to breast cancer diagnosed within 1 or 2 years postpartum, most studies focused on prognosis and treatment (3-7). We believe a broader definition is desirable when studying risk factors for PABC, because the "transient" increase in breast cancer risk after pregnancy has been shown to persist for up to 15 years (2, 30), with the highest risk within 5 years postpartum (31, 32). Therefore, we defined PABC as breast cancer diagnosed during pregnancy or ≤5 year postpartum. In order to investigate whether the risk factor profiles vary according to the timing of diagnosis relative to pregnancy, we further divided PABC into two subgroups: PABC during pregnancy or ≤2 years postpartum (N=152) and PABC occurring 3-5 years postpartum (N=145). Breast cancer diagnosed 5+ years postpartum or in nulliparous women was labeled as non-PABC (N=421, 22.3% nulliparous). Despite of potential biological differences and prognoses (33, 34), we did not separate PABC cases diagnosed during pregnancy from those diagnosed during postpartum, due to extremely small number of PABC cases diagnosed during a current pregnancy (N=1). Accordingly, controls were categorized by recency of the last pregnancy (≤2-year postpartum, 3-5 year postpartum, and 5+ years postpartum or nulliparous), to match each of the three case groups.

We examined five reproductive factors in relation to breast cancer risk: age at menarche, parity, age at first live birth, duration of breastfeeding, and abortion. In order not to force a linear relationship, we categorized these variables as shown in Table 2. Since lifetime duration of breastfeeding accumulates with parity, we calculated the mean duration per live birth as lifetime duration divided by number of live births. Other potential risk factors include family history of breast cancer, benign breast disease, hormonal contraceptive use, alcohol drinking, height, and body mass index (BMI). Age at diagnosis or interview, ethnicity, and level of education were included as potential confounders. We categorized age into 3-years windows to remove residual confounding due to the age difference by case status.

In a subset of breast cancer patients unselected for age and family history of breast cancer, we performed complete sequence analysis of all *BRCA1*/*2* exons and intron-exon boundaries to identify deleterious mutations (35).

Statistical analysis

Demographic characteristics and risk factor variables were compared across case and control groups, using analysis of variance (ANOVA) or Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. For the subgroup with BRCA tests, the mutation statuses of *BRCA1*/*2* were compared among the three case groups using Fisher's exact test. Stratifying by recency of the last pregnancy (≤2 years postpartum, 3-5 years postpartum, and 5+ years postpartum), we performed multiple logistic regressions to examine the associations between breast cancer risk and potential risk factors. We fit two sets of multiple logistic models after adjusting for potential confounding variables listed above. The first set of models examined pregnancy-related factors, including parity, age at first live birth, breastfeeding and abortion, in parous women only. The second set of models examined other risk factors such as age at menarche and family history of breast cancer, in all eligible women. Heterogeneity was tested for each risk factor of interest by comparing the three strata after fitting an overall logistic regression that includes interaction terms between each risk factor and the stratum indicator (recency of last pregnancy). Because the

study results were similar for hospital-based and community controls, the two types of controls were pooled. All statistical analyses were conducted with Stata 12.0 (StataCorp, College Station, TX, USA).

RESULTS

In total, 1,715 premenopausal women were included in this study: 297 PABC cases (152 within 2 years postpartum, 145 between 3-5 years postpartum), 421 non-PABC cases, and 997 healthy controls (282 were ≤2 years postpartum, 188 were during 3-5 years postpartum, and 525 were 5+ years postpartum). Cases were significantly older than their matched controls (*P-values*≤0.01), and non-PABC cases were older than PABC cases (*P-values*<0.0001) (Table 1). The age difference between PABC and non-PABC is expected since pregnancy usually occurs at younger age. The majority of the subjects were Yoruba (81.0%), with a higher proportion in the controls (89.8%). There was a significantly higher proportion of non-PABC cases with a family history of breast cancer (10.5%), compared to the other groups (ranging from 2.5-6.7%, *P*=0.002). Contrasting to non-PABC cases, PABC ≤2 years postpartum cases were more likely to carry *BRCA1/2* deleterious mutations (25.0% vs. 11.5%; *P*=0.034). After adjusting for age and family history, this association remained significant (OR 3.52, 95% CI: 1.26-9.82; *P*=0.016).

Table 2 shows distribution of reproductive factors across case groups and the matched control groups. Age at menarche was not significantly different across groups in the unadjusted analysis. The parous non-PABC cases had an average of 4.1 live births, which was higher than the average of 3.4 live births in PABC ≤2-year postpartum cases and controls (all pair-wise *P-valuess*≤0.002). Non-PABC cases had a first live birth at 21.9 years of age on average, earlier than those in the other groups (about 23-26 years, all pair-wise *P-values*<0.001). Moreover, non-PABC cases and PABC ≤2 years postpartum cases had about 10 month longer life-time duration of breastfeeding than controls (*P*<0.001).

Table 3 shows the multivariable-adjusted odds ratios and 95% CIs for reproductive factors among parous women. After adjusting for potential confounders, none of the associations were statistically significant. However, we observed a tendency toward positive association between parity and PABC ≤2 years postpartum (OR 1.20 per birth; 95% CI: 0.92-1.57), and a tendency toward inverse association between parity and non-PABC (OR 0.92 per birth; 95% CI: 0.76-1.11) (*P*-for-heterogeneity = 0.097).

Table 4 presents multivariable analysis results of other factors in all women. Although not statistically significant, late age at menarche tend to be inversely associated with the three types of breast cancer. Family history of breast cancer was significantly associated with PABC ≤2-year postpartum (OR 3.28, 95% CI: 1.05-10.3), while the associations for other PABC cases and non-PABC cases were not significant. The associations for both benign breast disease and BMI were consistent across subgroup of cases. After combining the subgroups of cases (N=718) and adjusting for recency of last pregnancy, a history of benign breast disease (pooled OR=1.67, 95% CI 1.04-2.66) was significantly associated with premenopausal breast cancer, while BMI had an inverse association (pooled OR=0.80, 95% CI: 0.71-0.89) with premenopausal breast cancer. Alcohol drinking was marginally associated with non-PABC (OR=1.76, 95% CI: 0.99-3.13, *P*=0.054). We did not find hormonal contraceptive use was associated with any type of premenopausal breast cancer in this study.

DISCUSSION

Using data from an understudied African population, we examined risk factors for premenopausal breast cancer according to childbearing recency. To our knowledge, this is the first study that explicitly examines risk factors associated with PABC, and we collected comprehensive pregnancy data in a unique Nigerian cohort expanding over a decade. We hypothesized that PABC is more likely to be observed in our study due to the strong culture of high parity in Nigeria. Different tumor characteristics between PABC and non-PABC (6, 12-14), suggest that PABC may have distinct etiology and risk factors. However, even though we were able to obtain a decent sample size among women with reported pregnancy history, the relatively small PABC subgroup limited our analytical power. Although we did not identify strong reproductive risk factor for PABC, we did observe a pattern that parity may have heterogeneous effect on breast cancer risk by recency of pregnancy. On the other hand, family history of breast cancer may be a stronger risk factor for PABC than non-PABC, and PABC cases were more likely to carry *BRCA* mutations than non-PABC cases.

Although not always consistent (36, 37), the transient increase in breast carcinoma risk after a pregnancy has been observed in many studies (2, 31, 38) and this knowledge has been transmitted to physicians (39). It was reported that incidence rates of breast cancer jump to a higher level after each childbirth, and then increase with age more slowly thereafter (40). Considering accumulated effect of multiple pregnancies, our finding of heterogeneous association between parity and breast cancer by recency of pregnancy could be well explained. Moreover, recent studies reported parity to be differentially associated with breast cancer subtypes: nulliparity significantly decreased the risk of triple-negative or basal-like breast cancer but increased the risk of estrogen receptor (ER) positive breast cancer (41-43). Several studies have shown that PABC patients were more likely to be estrogen receptor negative compared to non-PABC patients (6, 14, 15), though a recent study found no difference (18). It is plausible that the heterogeneous association of parity and PABC status involves with hormonal mechanisms. However, the current study did not have sufficient data on tumor molecular subtype to investigate this hypothesis.

Growing epidemiologic evidence supports risk reduction with prolonged breastfeeding. A pooled analysis from 30 countries reported a significant decline in breast cancer risk associated with breastfeeding (44). In Africa, there are strong traditions of breastfeeding and African women often breast-feed an infant for two years. We previously reported protective effect of long-term breastfeeding on breast cancer risk in Nigerian women (28), though others observed no association in South Africa (45). In the present study, we observed no association between breastfeeding and the risk of PABC.

Age at menarche appears protective against premenopausal breast cancer, with marginal significance that may due to small sample size. The relationship between spontaneous or induced abortion and breast cancer risk is controversial but most studies show either a slight increase or no effect of abortion on breast cancer risk (46) ENREF 33. In the present study, we did not find abortion increased the risk of premenopausal breast cancer (neither PABC nor non-PABC).

Family history is an important risk factor for breast cancer. A large collaborative reanalysis on familial breast cancer suggested that women with one affected first-degree relative were 1.8 fold more likely to develop breast cancer, with the greatest risk increase of 2.9 fold for age<35 years (47). This may partially explain the positive association observed between family history and PABC, but not for non-PABC, who are usually older than PABC cases.

Previous studies suggested that *BRCA1/2* mutation carriers may be at elevated risk for PABC (48, 49). Interestingly, we found that 25% of PABC cases were *BRCA1*/*2* mutation

carriers, significantly higher than non-PABC cases. All genetic sequencings were conducted after diagnosis, so the results (BRCA status) had no influence on women's childbearing choices. Although this finding is based on a subset of our study sample, it suggests a potential gene-environmental interaction. We hypothesize that pregnancy may serve as a trigger for breast cancer occurrence for women with *BRCA1/2* mutations.

Our study has several strengths. First, it helps fill the research gap, since PABC is understudied particularly its risk factors (26). The present study collected samples in Nigerian women, who traditionally have multiple children throughout childbearing age. It turned out that 41.4% of all premenopausal breast cancers in this sample were PABC (21.2% diagnosed ≤2 years postpartum, and 20.2% diagnosed 3-5 years postpartum). Second, our study sample is unique and comprehensive. Nigeria is Africa's most populous country and has the third largest number of persons living with HIV/AIDS in the world (50). In Nigeria, life expectancy was 48 years for males and 50 years for females (51). The major ethnic group in our study is Yoruba, one of the largest ethnic groups in Africa, with the highest twinning rate in the world (52) as well as high maternal and neonatal mortality rates (53). In our sample, Nigerian women averagely have four pregnancies with 3.6% newborns being multiple births, similar to report from other Nigerian cohorts (54). We were able to obtain high quality data on pregnancy history, with information on pregnancy status/outcome, gestational length, date of delivery, and duration of breastfeeding for each pregnancy. We considered both lifetime lactation duration and mean duration per live birth. Third, as the transient increase of breast cancer risk after pregnancy may fade gradually over the 5-year window during postpartum, we further categorized PABC based on timing (0-2 years and 3-5 years postpartum) to capture the transition of risk from PABC to non-PABC. We have conducted sensitivity analysis using different cut-off points for PABC and found the pattern of associations remains robust.

The uniqueness of our sample is a strength but also a limitation for the results to be generalized to other populations. In addition to the unique reproductive patterns, the disease pattern of low incidence, high mortality, and dominant triple-negative subtype of breast cancer (55, 56) differentiates indigenous African women from other race/ethnicities. Another potential issue is the delayed diagnosis of PABC, potentially causing an underestimate of cases since the categorization of PABC is time-sensitive. Diagnosis of breast cancer in general population is often delayed in African countries for months (57) due to limited access to health care, high cost and so on. Since PABC detection is naturally difficult with delayed diagnosis even in Western countries (5), we anticipate that the gap between disease onset and diagnosis to be larger in Nigeria. With latent/preclinical time period being considered, it is likely that more breast cancer cases are pregnancy-associated (58). Recent publications suggest that PABC occurred during 5-year postpartum has worse prognosis comparing to those occurred during pregnancy (33), possibly due to mammary gland involution upon weaning (59); while another study using the one-year postpartum definition found the two groups (pregnancy vs. lactation) very similar (60). In our study, there was only one PABC case diagnosed during pregnancy and we could not examine the two groups separately. Moreover, some of our participants could not recall the exact date but the year of delivery, and thus the PABC definition may be less accurate for those on the border. We believe that having the transition period of postpartum 3-5 years helps to reduce this influence.

Identifying potential risk factors helps estimating a breast cancer risk profile for prospective mothers and identifying high risk groups among women in their late 30s to early 40s, for whom mammographic screening is controversial. Our study suggests that prospective mothers with multiple births and a positive family history of breast cancer may have an elevated risk of breast cancer during their immediate postpartum. With the global trend

towards postponed childbearing in many Western populations, the occurrence of PABC is increasing. As a starting for examining risk factors for PABC, this research should be expanded to obtain higher statistical power and replicated in Western and other populations before generalizations can be extended beyond the Nigerian population. Nigerian women culturally have high parity and long lactation, and due to the relatively short life expectancy, premenopausal breast cancer, particularly PABC, should draw more public awareness and prevention force.

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Abbreviations

BMI	body mass index
CI	confidence interval
OR	odds ratio
PABC	pregnancy-associated breast cancer
UCH	University College Hospital

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Table 1

Selected Characteristics of Breast Cancer Cases (Pregnancy Associated, and Non-pregnancy Associated) and Healthy Controls, Nigeria, 1998-2011[a]

Characteristic	PABC cases (≤2 years postpartum) N=152	Controls ≤2 years postpartum N=282	PABC cases (3-5 years postpartum) N=145	Controls within 3-5 years postpartum N=188	Non-PABC cases N=421	Controls >5 years postpartum N=525	*P* [C]
Age in years, mean ± SD[b]	35.1 ±5.4	33.5 ± 5.3	38.1 ±4.9	36.6 ± 5.9	41.0 ±6.3	37.6 ±8.6	<0.0001
Ethnicity, n (%)							
Yoruba	109 (71.7)	251 (89.3)	107 (73.8)	172 (91.5)	278 (66.0)	469 (89.3)	<0.001
Others	43 (28.3)	30 (10.7)	38 (26.2)	16 (8.5)	143 (34.0)	56 (10.7)	
Education, n (%)							
No formal	9 (6.0)	9 (3.2)	14 (9.7)	13 (6.9)	48 (11.4)	27 (5.1)	
Elementary	33 (21.9)	32 (11.4)	27 (18.6)	30 (16.0)	97 (23.0)	77 (14.7)	
Secondary	50 (33.1)	80 (28.4)	44 (30.3)	57 (30.3)	92 (21.9)	146 (27.8)	<0.001
Vocational	38 (25.2)	132 (46.8)	41 (28.3)	62 (33.0)	120 (28.5)	212 (40.4)	
Some college or above	21 (13.9)	29 (10.3)	19 (13.1)	26 (13.8)	64 (15.2)	63 (12.0)	
Family history of breast cancer, n (%)							
Yes	9 (5.9)	7 (2.5)	8 (5.6)	8 (4.3)	44 (10.5)	35 (6.7)	0.001
No	143 (94.1)	274 (97.5)	136 (94.4)	180 (95.7)	377 (89.6)	489 (93.3)	
BRCA1/2 carrier, n (%)							
Yes	12 (25.0)	n/a	4 (9.1)	n/a	16 (11.5)	n/a	0.04
No	36 (75.0)	n/a	40 (90.9)	n/a	123 (88.5)	n/a	
Benign breast disease, n (%)							
Yes	11 (7.2)	10 (3.6)	11 (7.6)	9 (4.8)	33 (7.9)	26 (5.0)	0.15
No	141 (92.8)	270 (96.4)	133 (92.4)	179 (95.2)	387 (92.1)	498 (95.0)	
Hormonal contraceptives, n (%)							
Yes	34 (22.4)	69 (25.6)	45 (31.3)	57 (30.3)	121 (28.7)	137 (26.2)	0.09
No	118 (77.6)	212 (75.4)	99 (68.7)	131 (69.7)	300 (71.3)	387 (73.8)	
Alcohol drinking, n (%)							
Yes	9 (6.0)	6 (2.1)	12(8.6)	11 (5.9)	55(13.4)	29 (5.6)	<0.001
No	141 (94.0)	275 (97.9)	128(91.4)	177 (94.2)	355(86.6)	492 (94.4)	
Height in cm, mean ± SD	161.1 ±7.3	159.9 ± 6.3	162.3 ±7.2	159.6 ± 6.0	161.5 ±7.4	159.6 ± 6.6	<0.0001
BMI, mean ± SD	24.4 ±4.8	25.0 ± 5.1	25.0 ±5.1	25.6 ± 5.1	25.7 ±5.6	25.8 ± 7.1	0.08

PABC, pregnancy-associated breast cancer; BMI, body mass index

[a] Among premenopausal women 21-50 years old (N=1,715)

[b] Cases are significantly older than their controls (≤2 years postpartum: P=0.003; 3-5 years postpartum: P=0.01; non-PABC: P<0.0001); Non-PABC cases were significantly older than PABC cases ((≤2 years postpartum: P<0.0001; 3-5 years postpartum: P<0.0001) by t-tests

[C] ANOVA for continuous; Chi-square test for categorical variables

Table 2

Reproductive Factors and Breast Cancer Cases (Pregnancy Associated, and Non-pregnancy Associated) and Healthy Controls, Nigeria, 1998-2011[a]

Characteristic	PABC cases (≤2 years postpartum) N=152	Controls ≤2 years postpartum N=282	PABC cases (3-5 years postpartum) N=145	Controls with 3-5 years postpartum N=188	Non-PABC Cases N=421	Controls >5 years postpartum N=525	*P* [c]
Age at menarche (years)							
10-14	44 (29.7)	100 (35.8)	61 (43.0)	72 (39.3)	164 (41.5)	204 (39.8)	
15-16	72 (48.7)	109 (39.1)	64 (45.1)	69 (37.7)	155 (39.2)	188 (36.7)	
17-18	27 (18.2)	49 (17.6)	11 (7.8)	32 (17.5)	67 (17.0)	96 (18.8)	
≥19	5 (3.4)	21 (7.5)	6 (4.2)	10 (5.5)	9 (2.3)	24 (4.7)	
mean ± SD	15.2 ±1.8	15.2 ± 2.1	14.7 ±1.9	15.0 ± 2.2	14.9 ±2.0	15.1 ± 2.1	0.08
Parity							
0	1 (0.7) [d]	0 (0)	0 (0)	0 (0)	93 (22.3)	170 (32.4)	
1-2	48 (31.6)	129 (45.7)	31 (21.4)	65 (34.6)	76 (18.2)	77 (14.7)	
3-5	86 (56.6)	137 (48.6)	89 (61.4)	101 (53.7)	182 (43.5)	224 (42.7)	
≥6	17 (11.2)	16 (5.7)	25 (17.2)	22 (1.7)	67 (16.0)	54 (10.3)	
mean ± SD [b]	3.4±1.7	2.9 ± 1.5	3.9±1.7	3.4 ± 1.7	4.1±2.1	2.6 ± 2.2	<0.0001
Age at first live birth (years)							
Nulliparous	1 (0.7) [d]	0 (0)	0 (0)	0 (0)	64 (16.5)	129 (26.7)	
<25	58 (38.2)	104 (36.9)	77 (53.1)	94 (50.0)	236 (60.8)	237 (49.1)	
25-29	64 (42.1)	123 (43.6)	47 (32.4)	73 (38.8)	71 (18.3)	95 (19.7)	
≥30	29 (19.1)	55 (19.5)	21 (14.5)	21 (11.2)	17 (4.4)	22 (4.6)	
mean ± SD	25.9 ±4.6	26.1 ± 4.4	24.5 ±5.0	24.7 ± 4.5	21.9 ±4.6	22.9 ± 4.0	<0.0001
Lifetime duration of breastfeeding (months) [b]							
≤24	35 (23.8)	95 (33.9)	21 (14.5)	37 (19.9)	76 (23.4)	238 (45.4)	
25-48	56 (38.1)	100 (35.7)	48 (33.1)	64 (34.4)	74 (22.8)	93 (17.8)	
49-72	34 (23.1)	65 (23.2)	43 (29.7)	57 (30.7)	88 (27.1)	119 (22.7)	
73-96	13 (8.8)	15 (5.4)	21 (14.5)	17 (9.1)	48 (14.8)	43 (8.2)	
>96	9 (6.1)	5 (1.8)	12 (8.3)	11 (5.9)	39 (12.0)	31 (5.9)	
mean ± SD	47.8 ±31.0	38.2 ± 24.3	55.7 ±32.2	50.0 ± 31.3	45.0 ±41.8	36.1 ± 35.0	<0.0001
Mean duration of breastfeeding per live birth (months) [b]							
<12	50 (35.0)	92 (35.1)	36 (26.3)	40 (23.4)	107 (35.0)	278 (55.2)	<0.001
≥12	93 (65.0)	170 (64.9)	101 (73.7)	131 (76.6)	199 (65.0)	226 (44.8)	
Number of abortion							
0	106 (69.7)	207 (73.4)	110 (75.9)	128 (68.1)	269 (64.7)	362 (69.8)	
1	26 (17.2)	39 (13.8)	20 (13.8)	27 (14.4)	72 (17.3)	77 (14.8)	
≥2	20 (13.2)	36 (12.8)	15 (10.3)	33 (17.6)	75 (18.0)	80 (15.4)	
mean ± SD	0.5 ± 0.9	0.5 ± 1.0	0.4 ± 0.9	0.6 ± 0.9	0.6 ±1.0	0.6 ± 1.0	0.2

[a] Among premenopausal women 21-50 years old (N=1,715)

[b] Among parous premenopausal women 21-50 years old (N=1,446)

[c] ANOVA or Wilcoxon rank-sum tests for continuous variables; Chi-square test for the categorical variable

[d] Currently pregnant with first baby while breast cancer was diagnosed

Table 3

Multivariable Logistic Regressions on Risk Factors for Three Types of Breast Cancers among *Parous* Premenopausal Women, Nigeria (N=1,446), 1998-2011[a]

	PABC		Non-PABC	
	≤2 years postpartum	**3-5 years postpartum**	**>5 years postpartum or nulliparous**	***P* for heterogeneity**
Sample Size: Cases	**N=152**	**N=145**	**N=421**	
Controls	**N=282**	**N=188**	**N=525**	
Odds ratio: Case vs. Control (95% confidence interval)				
Parity				
1-2	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
3-5	1.79 (0.80-4.00)	1.20 (0.44-3.28)	0.86 (0.46-1.60)	
≥6	2.12 (0.50-9.04)	1.87 (0.39-9.00)	0.66 (0.26-1.66)	0.097
P for trend	*0.2*	*0.4*	*0.4*	
Per birth	1.20 (0.92-1.57)	1.13 (0.83-1.55)	0.92 (0.76-1.11)	
Age at first live birth (years)				
<25	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
25-29	1.15 (0.59-2.20)	1.05 (0.53-2.05)	0.83 (0.53-1.29)	0.6
≥30	1.06 (0.42-2.69)	1.18 (0.40-3.51)	0.79 (0.36-1.73)	
P for trend	*0.9*	*0.8*	*0.4*	
Lifetime duration of breastfeeding (months)				
≤24	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
25-48	1.12 (0.55-2.29)	0.92 (0.37-2.31)	0.82 (0.46-1.46)	
49-72	0.56 (0.21-1.50)	1.05 (0.37-3.00)	0.75 (0.39-1.43)	0.8
73-96	0.54 (0.13-2.25)	1.92 (0.48-7.75)	0.99 (0.42-2.35)	
>96	1.03 (0.16-6.85)	1.37 (0.20-9.42)	0.97 (0.33-2.82)	
P for trend	*0.4*	*0.5*	*0.9*	
Mean duration of breastfeeding per live birth (months)				
<12	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	0.3
≥12	0.75 (0.44-1.30)	0.90 (0.47-1.73)	1.01 (0.70-1.45)	
Number of abortion				
0	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
1	1.14 (0.59-2.21)	0.96 (0.44-2.09)	0.92 (0.57-1.49)	0.6
≥2	0.95 (0.45-2.04)	0.55 (0.25-1.22)	0.84 (0.52-1.36)	
P for trend	*0.99*	*0.2*	*0.5*	

PABC, pregnancy-associated breast cancer

[a]Independent variables include parity, age at first live birth, breastfeeding duration (lifetime or per live birth, in separate models), number of abortion, age in 3-year category, ethnicity, education, family history of breast cancer, previous benign breast diseases, hormonal contraceptive use, alcohol drinking, height, and body mass index.

Table 4

Multivariable Logistic Regression on Risk Factors for Three Types of Breast Cancers among Premenopausal Women (N=1,715), Nigeria, 1998-2011[a]

	PABC		Non-PABC	
	≤2 years postpartum	3-5 years postpartum	>5 years postpartum or nulliparous	*P* for heterogeneity
Sample Size: Cases	**N=152**	**N=145**	**N=421**	
Controls	**N=282**	**N=188**	**N=525**	
Odds ratio: Case vs. Control (95% confidence interval)				
Age at menarche (years)				
10-14	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
15-16	1.18 (0.67-2.10)	1.00 (0.55-1.81)	1.02 (0.71-1.47)	
17-18	0.94 (0.45-1.93)	0.32 (0.12-0.80)	0.75 (0.48-1.19)	0.7
≥19	0.32 (0.09-1.13)	0.49 (0.13-1.82)	0.40 (0.16-0.98)	
p-value for trend	*0.2*	*0.05*	*0.06*	
Family history of breast cancer				
No	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	0.3
Yes	3.28 (1.05-10.3)	1.35 (0.39-4.64)	1.84 (0.86-2.75)	
Benign breast disease				
No	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	0.6
Yes	2.30 (0.82-6.41)	1.73 (0.57-5.27)	1.49 (0.80-2.77)	
Hormonal contraceptives (%)				
No	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	0.7
Yes	0.87 (0.49-1.53)	0.96 (0.53-1.73)	0.92 (0.65-1.30)	
Alcohol drinking				
No	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	0.3
Yes	1.14 (0.27-4.84)	0.96 (0.32-2.89)	1.76 (0.99-3.13)	
Anthropometry				
Height (per 5 cm)	1.07 (0.89-1.28)	1.32 (1.07-1.62)	1.11 (0.99-1.26)	0.9
BMI (per 5 kg/m^2)	0.73 (0.56-0.95)	0.75 (0.56-1.01)	0.82 (0.70-0.95)	0.3

PABC, pregnancy-associated breast cancer; BMI, body mass index

[a]Model controlled for age in 3-year category, ethnicity, education, parity, age of first live birth, breastfeeding, and number of abortion, in addition to variables listed in the table.