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ORIGINAL PAPER

Reproductive factors and the risk of breast cancer among Nigerian women by age and oestrogen receptor status

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Abstract

Purpose of the study The aim of the study was to investigate the association between reproductive factors and breast cancer risk in Nigeria. This has not been widely investigated in sub-Saharan Africa.

Methods We conducted a hospital-based case–control study involving participants from five hospitals in Lagos and Abuja. Women were interviewed in-person between October 2016 and May 2017 using a semi-structured questionnaire. We collected data on parity, breastfeeding, age at first and last birth, age at menarche, oral contraceptive use and history of abortion. The data were analysed using multivariable logistic regression adjusting for relevant confounders.

Results Every additional 6 months of breastfeeding over a lifetime reduced breast cancer odds by: 7% (95% CI: 1%, 12%) in all women, 15% (95% CI: 5%, 24%) in women < 50 years, and 8% (95% CI: 0%, 12%, p for trend = 0.043) in oestrogen receptor negative (ER-) cases. Each additional 1-year delay before the first full-term pregnancy increased oestrogen receptor positive breast cancer odds by 9% (95% CI: 2%, 17%). Each additional 1-year delay before the last full-term pregnancy increased breast cancer odds by: 7% (95% CI: 2%, 12%) in all women, 12% (95% CI: 4%, 21%) in ER- breast cancer patients, and 14% (95% CI: 4%, 25%) in triple negative breast cancer patients. Other reproductive factors did not significantly increased breast cancer odds.

Conclusion While advanced age at first and last full-term pregnancies increased breast cancer odds, breastfeeding reduced it. These associations varied by age and oestrogen receptor status. Improved breastfeeding practices and timely births should be promoted in Nigeria.

Keywords Breast cancer · Reproductive factors · Risk factors · Women · Sub-Saharan Africa · Nigeria

Introduction

The rising incidence of breast cancer in sub-Saharan Africa (SSA) and Nigeria has been widely acknowledged [1, 2]. The increasing adoption of western lifestyle among other factors in SSA has been implicated in this rising incidence of breast cancer [3]. For example, the changing reproductive patterns such as delayed age at first birth, fewer children, reduced breastfeeding duration, early age at menarche, hormonal contraceptive use associated with high income countries (HIC) have been reported in Nigeria [4]. A few studies have examined the association between reproductive variables and the risk of breast cancer in Nigeria [5, 6] [7–10]. The findings of most of these studies were consistent that breastfeeding was associated with a reduced risk of breast cancer [6, 9, 11]. While the role of other reproductive variables such as parity, age at menarche and age at first birth were inconsistent, no study has investigated the role of age at last birth [5–10].

Moreover, the association between breast cancer and reproductive factors such as parity, breastfeeding has been shown to vary by oestrogen receptor status and age [12, 13]. To the best of our knowledge, no study in the region (except a recent study in Ghana [11]) has reported these potential variations. The need for such investigation is obvious given its relevance to appropriate intervention. Furthermore, in addition to the limited number of confounders adjusted, the available previous Nigerian studies were carried out in

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southern Nigeria. This justifies the need for a study that is more representative with respect to regional and ethnic variabilities in Nigeria. Our study investigated the association between reproductive factors and the risk of breast cancer among Nigeria women residing in the northern and southern part of Nigeria.

Materials and methods

Study design and setting

We conducted a case–control study involving participants at the University of Lagos Teaching Hospital (LUTH), Lagos State University Teaching Hospital (LASUTH), University of Abuja Teaching Hospital, Gwagwalada (UATH), National Hospital Abuja (NHA) and General Hospital, Lagos Island (GHLI). Lagos (Southern Nigeria) and Abuja (Northern Nigeria) are the two most important cities in Nigeria being the former and current federal capital city, respectively. Lagos is the largest city in sub-Saharan Africa with a population of 12.5 million in 2016 [14]. Abuja, with a population of more than 3.5 million in 2016, was listed among the world's fastest-growing cities [15]. The two cities were selected to enhance the external validity of the results owing to their rich population diversity in terms of ethnicity and socioeconomic status-SES [15]. Hospital attendance in Nigeria is not strictly guided by referral policies and catchment location because most patients bear the financial cost of their treatments in both public and private hospitals in Nigeria [16]. Available data suggest that most cases of breast cancer in Nigeria (> 86%) are diagnosed in tertiary hospitals. Moreover, some women who are initially diagnosed in private hospitals are usually referred to public tertiary hospitals owing to availability of better equipment and specialised staff.

Recruitment of participants

The cases were women with histologically confirmed invasive breast cancer who attended oncology clinics in the oncology departments of the participating hospitals between October 2016 and May 2017. All cases whose time of diagnosis has exceeded 18 months at the time of interview were excluded to reduce information bias. Controls were women seen in the outpatient clinics of the ophthalmology departments of the same hospitals during the same period except a small number participants who were recruited from the General Outpatient Departments (GOPD) to make up for the required sample size. The ophthalmology departments offer comprehensive eye services involving preventive, curative, and rehabilitative services. Hence, they attract people of all socioeconomic status (SES). We used frequency matching to match controls to cases by age (interval of 5 years). The controls had no personal history of breast cancer or breast disease. However, where a patient's close relative was selected as a control, the patient was no longer eligible, and vice versa. This was because we considered that the patients will have similar exposure patterns as their female relatives. All participants were within the age bracket of 20–80 years. The collaborating physicians considered them to be physically and psychologically able to participate in the study. These collaborating physicians did not participate in the interviewing of the participants in order to reduce interviewer bias.

The study aims and the requirements for participation were explained to potential participants (both cases and controls) during clinic hours. Afterward, trained interviewers (comprising doctors, nurses, and graduates of related fields) approached the potential participants in the waiting area to confirm their eligibility and willingness to participate in the study. Cases were approached and recruited in the order in which their names appeared in the daily attendance register at the clinic; this was the process that was acceptable to the oncology departmental heads who did not permit any contact with patients outside of clinic hours.

No access was possible to the attendance registers in the ophthalmology clinics, so the interviewers approached the controls based on the order of their arrival/sitting in the waiting area.

Data collection procedure

All eligible participants were interviewed in person using a semi-structured questionnaire. The instrument was developed specifically for the study based on information from previously validated questionnaires, taking local context into consideration [17–19]. The questionnaire was used to obtain information on demographic, socioeconomic, reproductive, lifestyle, anthropometric explanatory variables. The questionnaire was pretested on 17 participants at General Hospital Lagos Island and appropriate modifications made.

There were a mix of interviewers comprising people who could speak English, the local language of the study area, as well as Pidgin English (the Nigerian version of English) which most urban dwellers in Nigeria understand. We gave the interviewers a 2–4-h training session (involving recorded mock interviews) ahead of the study. We also checked all the completed questionnaires for error and corrections made were necessary.

Measurement of relevant study variables

We examined the relationship between breast cancer risk and reproductive variables specifically parity, breastfeeding, age at first birth, and age at last birth. We also reported findings with respect to the roles of age at menarche, oral

contraceptive use and induced abortion in a separate file. A full-term pregnancy was defined as any pregnancy lasting for at least 7 months irrespective of the outcomes [20–22]. Hence, age at first full-term pregnancy as used in this study was synonymous to age at first birth. Similarly, age at last full-term pregnancy was also defined as synonymous to age at last birth—defined as the age at which a woman gave birth to her last child. Parity was defined as the number of children a woman has born irrespective of whether they survived or died. Induced abortion was defined as intentional premature termination of pregnancy resulting from clinical or non-clinical intervention with an intention other than to produce a live-born baby [23]. Total months of breastfeeding (lifetime duration of breastfeeding) was defined as the total number of months a child was offered breastmilk irrespective of whether it was only breast milk or in addition to water and other complementary food [24]. Age at menarche was defined as the age at which a woman saw her first menstrual flow. Women were considered oral contraceptive users if they had used oral contraceptives for at least one month before breast cancer diagnosis (for cases) or the time of interview (for controls) irrespective of the duration of use. We classified women as naturally postmenopausal if they indicated that their menstrual flow had completely ceased for more than six months before diagnoses [21] and could not attribute it to chemotherapy, surgery, medication, radiotherapy, or any other hormonal treatment. Cases whose menstrual flow ceased as a result of events other than natural process were considered as experiencing artificial menopause [25]. Women who provided contradictory answers or no response were classified as women with unknown menopausal status.

Confounding variables

We treated variables as potential confounders if they have been known to confound the association between the reproductive variables of interest and the risk of breast cancer according to the existing literature. These were factors known to influence both the putative risk factors of interest and breast cancer incidence while playing no mediative role [26]. Potential confounders were retained as relevant confounders for each specific association being investigated if their likelihood p values were < 0.2, or if the estimate changes by a value $> 10\%$ when such variables were dropped from the logistic regression model [26]. Nevertheless, variables judged to be important confounders based on the existing literature were purposively adjusted where necessary [26]. Furthermore, variables described as base variables—age, study sites and ethnicity were purposively adjusted to enhance similarity in age (between cases and controls) as well as the external validity of the study. Other potential confounders selected based on literature include family history of breast cancer, income, personal and maternal educational attainments, urbanicity, body mass index (BMI) physical activity, alcohol consumption as well as the relevant primary reproductive variables being investigated.

Statistical analysis

We compared the distribution of the reproductive continuous variables between cases and controls using t-tests or Mann–Whitney U (for non-normally distributed variables). That of categorical data were compared using chi square ($\chi 2$) tests. We modelled the relationship between breast cancer and reproductive variables using unconditional binary logistic regression available in the Statistical Package for Social Sciences (SPSS) version 23. Breast cancer risk was assessed as breast cancer odds. We computed adjusted odds ratios for each association of interest. All reported p values were based on likelihood ratio tests. Multicollinearity for continuous variables was assessed and assumed not to be a problem if the tolerance value was > 0.1 and the variance inflation factor < 10 (see supplementary Table 4) [27]. Pairwise deletion was applied to all missing values.

We developed three models for each associated investigated and adjusted for relevant confounders. We entered the base variables first in model 1 (minimally adjusted model) as age (continuous variable), study sites (LUTH, LASUTH, NHA, UATH, GHLI), and ethnicity (Yoruba, Igbo, Niger Deltans, other northern tribes). We further adjusted in model 2 (core model) for the effects of SES, reproductive, and lifestyle variables including education (non-formal/primary, secondary, postsecondary, first degree/HND & > first degree), income (< ₦18,000; ₦18,000—₦49,000; ₦50,000—₦100,000; > ₦100,000); urbanicity (less urbanised, more urbanised), parity (continuous variable), age at first pregnancy/birth—AAFB (continuous variable), menopausal status (premenopausal & postmenopausal), lifetime duration of breast feeding or total months of breastfeeding—TBF (continuous), age at menarche—AAM ($\leq$ 13yrs > 13yrs), oral contraceptive use-OCU (Yes &No), family history of breast cancer—FHBC (Yes & No), alcohol consumption (Yes & No). Other variables such as body mass index—BMI (continuous variables), physical activity—PA (tertiles) were adjusted for in model 3, (fully adjusted model). We considered that since BMI and PA reported here were recent, they have the potential to act both as confounders (based on their correlation with previous BMI and PA) or mediators of the relationship between some of the putative risk factors of interest (such as parity and breastfeeding) and breast cancer. Hence, they were adjusted in model 3. In such cases, interpretation of the findings was based on model 2. Other variables considered as having stronger mediative than confounding roles (for example parity with respect to the relationship between age at first birth and breast cancer

odds) were also adjusted in model 3 to ascertain if such relationship (where significant) could be said to be independent of such mediators.

For the purpose of this analysis, we categorised parity first as nulliparous versus parous, then as nulliparous, uniparous, 2–3 births and ≥ 4 births- taking into consideration the median number of births (3 births) among controls. Breastfeeding was categorised first as 'having ever breastfed' versus 'never breastfed', then as never breastfed, 1–24 months, 25–48 months, > 48 months of breastfeeding taking into consideration the World Health Organisation's minimum breastfeeding duration recommendation for a baby (1–2 years or longer) [28]. Age at first full-term pregnancy was categorised as < 22 years, 22–27 years, and ≥ 28 years taking into consideration the mean age at last birth (22 years) for urban female population of Nigeria in 2013 [29]. Age at last full-term pregnancy was categorised as tertiles. Age at menarche was categorised based on the median age at menarche among urban Nigerian girls (13–14 years) [30]. With respect to stratified analysis based on oestrogen receptor status, we categorised parity and breastfeeding based on their median values in view of small sample of participants with known oestrogen receptor status. Throughout $p < 0.05$ (two-sided) was considered statistically significant for trend tests. The significance of the odds ratio reported for the categorical variables were based on 95% confidence interval. Age group variation in the findings were assessed in line with literature [11–13].

We conducted sensitivity analyses restricted to: (1) participants resident within the geographic boundaries of Lagos and Abuja (to ascertain the potential influence of externally referred cases), (2) cases diagnosed not more than 12 months prior to the date of interview (to ascertain the potential influence of cases diagnosed between 12 to 18 months before interview who were included to meet the sample size requirement), (3) controls (patients/visitors) seen in the ophthalmology department (to ascertain the potential influence of controls recruited from the GOPD.

Results

Distribution of the characteristics of participants

We recruited 372 cases. Of these, 317 (84.6%) were diagnosed 12 months prior to the time of interview while the remaining 62 (16.4%) cases were diagnosed 12 to 18 months prior to the time of interview. For controls, 387 participants (96%) were recruited from the Ophthalmology clinics, while 16 participants (4%) were recruited from the GOPD. With an estimated 545 potential cases and 1186 potential controls seen, and 415 (cases) and 428 (controls assuming those who declined were not eligible) eligible participants confirmed, the cooperation rate (number of completed interviews among eligible participants was 84.1% for cases and 88.1% for controls.

We showed the distribution of the characteristics of the participants (both cases and controls) in Table 1. The distribution of reproductive characteristics of cases and controls were shown in Table 2. While the median number of births as well as the mean age at last birth were similar among cases and control, the mean duration of breastfeeding per pregnancy and mean age at first full-term pregnancy were higher among controls than cases (Table 2).

Potential of roles Parity and breastfeeding in breast cancer risk

According to Table 3, the odds of breast cancer between nulliparous and parous women was not significantly different in any of the models. However, following adjustments for the base variables and the core confounders (except breastfeeding), having 2–3 births was associated with a reduced odds of breast cancer compared to having no birth-nulliparity (OR 0.53, 95% CI: 0.30, 0.92). The estimate, however, was attenuated and not significant among women with ≥ 4 births. All the estimates attenuated and became non-significant after adjustment for breastfeeding (Table 3). The results were consistent with findings based on sensitivity analysis (Supplementary file, Table 3). Although the age-stratified multivariable analysis restricted to parous women showed a tendency for an effect modification, none of the results were significant (Table 4).

Women who have ever breastfed had a significantly reduced odds of breast cancer (compared with women who have never breastfed) after adjustment for the base variables and the core confounders including parity (OR 0.52, 95% CI: 0.29, 0.93). The estimate, however, attenuated after further adjustments for BMI (OR 0.66, 95% CI: 0.35, 1.24). (Table 3). The finding was consistent with the observation based on the sensitivity analyses (supplementary file, Table 3). Moreover, every additional 6 months of breastfeeding over lifetime was associated with a 5% (95% CI: 1%, 7%) reduction in breast cancer odds which attenuated and became barely significant after adjustment for BMI. The interpretation did not change in an analysis based on mean number of months of breastfeeding per pregnancy (Table 3 & supplementary file, Table 4). Table 4 shows that among women < 50 years, those who breastfed for > 48 months (compared to women who have never breastfed) had a significantly reduced odds of breast cancer (OR 0.18, 95% CI: 0.05, 0.67). Every additional 6 months of breastfeeding was associated with a 15% (95% CI: 5%, 24%) reduction in breast cancer odds among women < 50 years. No significant results were observed among women aged ≥ 50 years (Table 4). The

Table 1 Participants characteristics

Characteristics	Control n (%)	Case n (%)
Age		
< 50.00 yrs	247 (61.3)	225 (59.4)
≥ 50.00 yrs	156 (38.7)	154 (40.6)
Mean ± SD	46.8 ± 10.8	47.1 ± 10.7
Ethnicity		
Yoruba	192 (47.9)	155 (41)
Igbo	100 (24.9)	128 (33.9)
Hausa/Fulani	14 (3.5)	13 (3.4)
Niger Deltans	51 (12.7)	42 (11.1)
Other Northern ethnic groups	44 (11)	40 (10.6)
Missing values[μ]	2 (0.5)	1 (0.3)
Marital status		
Never Married	33 (8.3)	36 (9.5)
Widowed	32 (8.0)	26 (6.9)
Divorced/separated	9 (2.3)	14 (3.7)
Married	325 (81.5)	301 (79.8)
Missing values[μ]	4 (1)	2 (0.5)
Religion		
Christianity	315 (78.8)	310 (82.9)
Islam	85 (21.3)	64 (17.1)
Missing values[μ]	4 (1)	2 (0.5)
Ever consumed alcohol?		
No	235 (58.9)	225 (59.4)
Yes	164 (41.1)	154 (40.6)
Missing values	4 (1)	0 (0)
Family history of BC (FHBC)		
No	381 (95.3)	339 (89.4)
Yes	19 (4.8)	40 (10.6)
Missing values[μ]	3 (0.7)	0 (0)
Urbanicity of area of residence?		
More urbanized	348 (86.6)	299 (79.1)
Less urbanized/rural	54 (13.4)	79 (20.9)
Missing values[μ]	1 (0.2)	1 (0.3)
Body mass index-BMI (kg/m^2)		
Median (IQR)	27.77 (7.29)	26.76 (7.26)
Missing values	36.00 (8.9)	37.00 (9.8)
Education		
Non formal/Primary	37 (9.3)	63 (16.6)
Junior/Senior secondary	96 (24)	109 (28.8)
Post-secondary	73 (18.3)	71 (18.7)
1st degree / HND	134 (33.5)	110 (29)
> 1st degree	60 (15)	26 (6.9)
Missing values[μ]	3 (0.7)	0 (0)
Respondents' income		
< ₦18,000	71 (18.9)	100 (28.7)
₦18,000—₦49, 000	106 (28.3)	128 (36.7)
₦50,000 -₦100,000	123 (32.8)	77 (22.1)
> ₦100,000	75 (20.0)	44 (12.6)
Missing values[μ]	28 (6.9)	30 (7.9)
Physical activity-PA (MET-hr/wk)		
< 128.20	134 (36.9)	112 (29.5)
128.20—184.29	118 (32.5)	131 (34.5)
≥ 184.30	111 (30.6)	137 (36.1)
Missing values[μ]	23 (5.7)	16 (4.2)

*Missing values includes 'not applicable' results

[μ]Missing values were not considered in the computation of percentages associated with the samples of variable groups

Table 2 Comparison of the distribution of the reproductive characteristics of the participants between cases and controls

Reproductive variables	Control n (%)[δ]	Case n (%)[δ]
Ever been pregnant?		
No	47 (11.9)	46 (12.2)
Yes[a]	349 (88.1)	332 (87.8)
Missing	11 (2.7)	6 (1.6)
Multiparity*		
1 birth (uniparous)	27 (7.8)	28 (8.6)
2–3 births[b]	173 (50)	136 (41.6)
≥ 4 births	146 (42.2)	163 (49.8)
Missing	3 (0.9)	5 (1.5)
Median (IQR)	3.0 (2)	3.0 (2)
Ever breastfed?		
No	49 (12.5)	58 (15.5)
Yes[a]	343 (87.5)	315 (84.5)
Missing	11 (2.7)	6 (1.6)
Total months of Breast Feeding		
Never breastfed	51 (13.0)	59 (15.8
1–24 months	81 (20.7)	68 (18.2)
25–48 months	145 (37.0)	126 (33.8)
> 48 month[a]	115 (29.3)	120 (32.2)
Missing	2 (0.6)	1 (0.3)
Mean duration per child	13.4 ± 5.8	13.0 ± 5.9
Age at menarche		
≤ 13yrs	127 (33.1)	129 (35.1)
> 13yrs	257 (66.9)	239 (64.9)
Missing	19 (4.7)	11 (4.7)
Menopausal Status		
Premenopausal	229 (56.8)	161 (42.5)
Unknown/artificial	20 (5.0)	64 (16.9)
Natural menopause	154 (38.2)	154 (40.6)
Ever used oral contraceptive		
No	312 (80.1)	282 (76.8)
Yes	77 (19.8)	85 (23.2)
Missing	14 (3.5)	12 (3.2)
Induced abortion		
No	310 (80.3)	269 (75.1)
Yes	76 (19.7)	89 (24.9)
Missing	14 (3.5)	12 (3.2)
Age at 1st full-term pregnancy		
< 23	99 (28.7)	110 (33.3)
23–27	120 (34.8)	112 (33.9)
≥ 28	126 (36.5)	108 (32.7)
Missing[μ]	58 (14.4)	49 (12.9)
Mean ± SD	25.5 ± 4.8	25.3 ± 5.1
Age at last full-term pregnancy		
< 23	117 (34.4)	85 (26.2)
23–27	109 (32.1)	100 (30.9)
≥ 28	114 (33.5)	139 (42.9)
Missing[μ]	63 (15.6)	55 (14.5)
Mean ± SD	33.4 ± 4.8	34.4 ± 5.7

*Includes parous women only

[δ]Computation of percentages for variables categories did not include missing values

[μ]Missing values include women with 'not applicable' results

observation was consistent with the analysis based on menopausal status (supplementary file, Table 4).

In line with observations in previous studies [11–13], we stratified the roles of parity and breastfeeding by oestrogen receptor status based on the available data. Table 5 suggests that while each additional full-term pregnancy beyond the first experience was associated with a non-significantly reduced odds of oestrogen receptor positive (ER +) breast cancer, it was associated with a non-significantly increased odds of oestrogen receptor negative (ER-) and triple negative (TN) breast cancer subtypes. In contrast, every additional 6 months of breastfeeding was associated with an 8% (95% CI: 0%, 15%, p for trend = 0.043) reduced odds of ER- breast cancer following adjustments of relevant confounders. A reduced odds of breast cancer was also observed with respect to ER + breast cancer for every additional 6 months of breastfeeding but the result was not significant (Table 5).

Potential roles of other reproductive variables in breast cancer

According to Table 3, the elevated odds of breast cancer associated with having a first full-term pregnancy after 27 years (compared to a first full-term pregnancy before the age of 22) was not significant. No significant observations were also made in the age-stratified analysis (Table 4). However, among ER + breast cancer patients, every additional 1-year increase in age at first full-term pregnancy was associated with a 9% (95% CI:2%, 17%, p for trend = 0.017) increased odds of breast cancer following adjustments for relevant confounders. A non-significant modest elevated odds were observed for ER- and TN breast cancer subtypes (Table 5). Older age at last full-term pregnancy ≥ 36 years compared to an older age at last full-time pregnancy < 32 years was associated with an increased odds of breast cancer in all the three models (Table 3). The association was more marked among older/postmenopausal women than young/premenopausal women (Table 4 & supplementary file, Table 6). The result was consistent even when uniparous women were excluded from the model (p for trend = 0.001)(Supplementary Table 5)[31]. Each additional 1-year delay before last full-term pregnancy increased breast cancer odds by: 7% (95% CI: 2%, 12%) in all women, 12% (95% CI: 4%, 21%) in ER- breast cancer patients, and 14% (95% CI: 4%, 25%) in TN breast cancer patients. The association was not significant among women with ER + breast cancer (Table 5). No significant association was observed with respect to induced abortion, oral contraceptive use and age at menarche (supplementary file, Table 3).

Discussions

Our findings suggest that neither being parous nor multiparity was significantly associated with a reduced odds of breast cancer. On the other hand, having a history of breastfeeding and longer lifetime duration of breastfeeding significantly reduced the odds of breast cancer especially among younger women and women with ER- breast cancer. While advanced age at last full-term pregnancy was significantly associated with an increased odds of breast cancer which was more marked among older women, women with ER- and TN breast cancer; an advanced age at first full-term pregnancy was associated with a significantly increased odds of ER + breast cancer only. Older age at menarche, history of induced abortion and history of oral contraceptive use were not significantly associated with increased odds of breast cancer.

A few studies in SSA [6, 32], and other parts of the world [33–35] have observed a reduced risk of breast cancer with being parous or having multiple births [6, 32, 33, 35]. A reduced risk of breast cancer has also been observed among women with history of breastfeeding or longer lifetime duration of breastfeeding [6, 9, 32, 34, 36]. The non-significant reduction in breast cancer odds associated with being parous or multiparity compared with nulliparity among all women in our study was consistent with observations in other indigenous African studies (although they were smaller in sample size) that did not observe a significantly reduced risk of breast cancer with high parity compared with nulliparity or low parity [7–10]. It was, however, inconsistent with two large case control studies that observed a significant reduction in breast cancer risk with multiparity in comparison with nulliparity [6, 32]. These latter two studies did not adjust for the effect of breastfeeding (an important confounder) which we adjusted for. Hence, their results were not independent of the effect of breastfeeding. Our observation with respect to the role of breastfeeding was consistent with previous indigenous studies where reduced odds/risk of breast cancer was associated with having a history of breastfeeding or longer duration of breastfeeding when compared with having no breastfeeding history, or shorter duration of breastfeeding [6, 8, 9].

However, contrary to the higher reduction in breast cancer odds among younger/premenopausal women in our study (which was consistent with a Tanzanian study [8]), a Ghanaian study observed a higher reduction in breast cancer risk among postmenopausal women [10]. This could be due to a higher proportion of older women in that study (50% compared to 40.6% in our study).

The non-significantly increased odds of breast cancer reported for advanced age at first full-term pregnancy in our study was

Table 3 Relationship between reproductive variables and breast cancer risk (Multiple regression analysis)

Main effects	Model 1 [a]OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Ever given birth			
No (Nulliparous)	1.00 (ref)	1.00 (ref)[b]	1.00 (ref)[c]
Yes	1.00 (0.63, 1.57)	0.76 (0.43, 1.33)	0.80 (0.44, 1.45)
P for categories	0.982	0.334	0.559
Multiparity			
Nulliparous	1.00 (ref)	1.00 (ref)[d1]	1.00 (ref)[d2]
1 birth (uniparous)	0.93 (0.47, 1.83)	0.77 (0.36, 1.65)	0.82 (0.38, 1.79)
2–3 births	0.72 (0.45, 1.17)	**0.53 (0.30, 0.92)**	0.70 (0.38, 1.29)
≥ 4 birth[s]	1.01 (0.61, 1.66)	0.66 (0.37, 1.19)	1.12 (0.52, 2.42)
Per each additional birth	1.05 (0.97, 1.14)	0.97 (0.88, 1.07) [d1]	1.14 (0.96, 1.34)
P for trend	0.219	0.130	0.156
Ever breastfed			
No	1.00 (ref)	1.00 (ref)[e]	1.00 (ref)[c]
Yes	0.79 (0.51, 1.21)	**0.52 (0.29, 0.93)**	0.66 (0.35, 1.24)
P for categories	0.277	**0.028**	0.192
Breast feeding duration			
Never breastfed	1.00 (ref)	1.00 (ref)[f]	1.00 (ref)[c]
1–24 months	1.00 (0.62, 1.63)	0.62 (0.33, 1.15)	0.70 (0.36, 1.36)
25–48 months	0.73 (0.47, 1.13)	**0.47 (0.24, 0.95)**	0.56 (0.27, 1.18)
> 48 months	0.78 (0.54, 1.13)	**0.41 (0.17, 0.99)**	0.52 (0.20, 1.34)
Per each additional 1 month average breastfeeding/birth	1.00 (0.98, 1.02)	**0.96 (0.93, 0.99)**	**0.97 (0.94, 1.00)[c]**
Per each extra 6 months of breastfeeding	1.01 (0.98, 1.04)	**0.93 (0.88, 0.99) [f]**	**0.94 (0.89, 1.00)[c]**
P for trend	0.560	**0.012**	**0.033**
Age at first birth (Yrs)			
< 22	1.00 (ref)	1.00(ref)[g]	1.00(ref)[h]
22—27	0.81 (0.55, 1.19)	1.03(0.66, 1.59)	1.04(0.67, 1.62)
> 27	0.75 (0.51, 1.10)	1.14(0.70, 1.85)	1.19(0.72, 1.98)
P for trend	0.32	0.840	0.761
Per each additional 1 yr delay	0.99 (0.98, 1.02)	1.02 (0.98, 1.06)	1.02(0.98,1.07)
Age at last birth (Yrs)			
< 32	1.00 (ref)	1.00 (ref)[i]	1.00 (ref)[j]
32—35	1.28 (0.86, 1.90)	**1.65 (1.02, 2.65)**	**1.74 (1.03, 2.94)**
≥ 36	**1.72(1.17, 2.53)**	**2.17(1.29, 3.66)**	**2.53 (1.41, 4.53)**
P for trend	**0.022**	**0.014**	**0. 007**
Per each additional 1-year delay	**1.04 (1.01, 1.07)**	**1.06 (1.01, 1.10)[i]**	**1.07 (1.02,1.12)[j]**

[a]Adjusted for study sites, age, ethnicity

[b]Additionally adjusted for personal education, maternal education, menopausal status, oral contraceptive use, TBF (continuous), family history of breast cancer

[C]Additionally adjusted for BMI

[d1]Additionally adjusted for personal education, income, maternal education, and menopausal status

[d2]Additionally adjusted for TBF (continuous)

[e]Additionally adjusted for personal education, maternal education, menopausal status, parity (continuous)

[f] Additionally adjusted for personal education, income, menopausal status, parity(continuous). [h] Additionally adjusted for BMI, & PA. [g] Additionally adjusted for personal education, income, menopausal status, AAM

[h] Additionally adjusted for parity. [i]Adjusted for FHBC, education, menopausal status, AAFB, AAM, parity, TBF. [n] Additionally adjusted for BMI and PA

[s]Indicates grand multiparity

Bold indicates significant results

Table 4 Relationship between reproductive factors and breast cancer risk stratified by age

Reproductive factor	Cases N (%)	Controls N (%)	< 50yrs OR (95% CI)	Cases N (%)	Controls (%)	≥50yrs OR (95% CI)
Total months of breastfeeding						
Never breastfed	49(22.0)	39(16.3)	1.00(ref)	10(6.7	12(7.8)	1.00(ref)
1–24months	46(20.6)	48 (20.1)	0.59(0.26, 1.33)	22(14.7)	33(21.6)	0.76(0.23, 2.66)
25–48months	73(32.7)	92(38.5)	0.31(0.11, 0.82)	53(35.3)	53(34.6)	1.23(0.34, 4.46)
> 48 months	55(24.7)	60 (25.1)	**0.18(0.05, 0.67)[a,β]**	65(43.3)	55(35.9)	1.33(0.30, 6.01)
Per every additional 6 months breastfed			**0.85 (0.76, 0.95)[a]**			0.96 (0.90,1.03)
Per each additional average of 1 month breastfed/pregnancy			**0.95 (0.91, 0.99)[a]**			0.98 (0.94,1.03)[a]
P for trend			**0.012**			0.402
Multiparity[β]						
1 birth	18 (9.9)	21 (10.4)	1.00 (ref)	10 (6.9)	6(4.2)	1.00(ref)
2–3 births	95(52.2)	115(56.9)	1.56(0.61, 3.99)	41(28.3)	58(40.3)	0.54(0.15, 1.98)
≥ 4 birth	69(37.9)	66 (32.7)	3.38(0.98, 11.62)	94(64.8)	80(55.6)	1.03(0.26, 4.11)
Per each additional birth			1.26(0.95, 1.67)			1.15(0.92,1.42)
P for trend			0.113			0.204
Age at first birth						
< 23	42(22.2)	57(27.7)	1.00(ref)[d]	52(36.6)	58(42.0)	1.00(ref)[d]
23–27	68(36.0)	74(35.9)	0.90 (0.47, 1.73)	50(35.2)	40(29.0)	1.15(0.62, 2.15)
≥ 28	79(41.8)	75(36.4)	1.05(0.52, 2.10)	40(28.2)	40(29.0)	1.02(0.49, 2.12)
P for trend			0.835			0.882
Age at last birth						
< 32	61(33.3)	72(36.5)	1.00(ref)[e1]	24(17.0)	45(31.5)	1.00(ref)[e2]
32–35	54(29.5)	66(33.5)	1.68(0.79, 3.59)	46(32.6)	43(30.1)	**2.67(1.07, 6.67)**
≥ 36	68(37.2)	59(29.9)	**2.95(1.16, 7.52)**	71(50.4)	55(38.5)	**3.74(1.47, 9.59)**
P for trend			0.071			**0.018**

[a]Adjusted for study site, ethnicity, age (continuous), education, income, menopausal status, parity

[c]Adjusted for study site, age(continuous), ethnicity, education, income, maternal education, menopausal status, TBF

[d]Adjusted for age study site, ethnicity, FHBC, income, menopausal status, AAM, BMI

[e1]Adjusted for study site, age (continuous), ethnicity, FHBC, education, menopausal status, AAFB, AAM, TBF, BMI &total PA

[e2]Adjusted for study site, age(continuous), ethnicity, FHBC, income, menopausal status, AAFB, AAM, TBF, BMI &total PA

[β]Restricted to parous women owing to small sample of nulliparous women.

Bold indicates significant results

not consistent with the significantly increased odds of breast cancer associated with advanced age at first birth in a previous Nigerian study and other international studies [37] [35, 38, 39]. The discrepancy with that Nigerian study could be due to differences in the variable categories and cut offs used. Nevertheless, our finding contradicted the significant reduction in breast cancer risk associated with advanced age at first birth reported in a study involving Malian and Gambian women [10] possibly due to unadjusted confounders such as SES variables which were not available to the authors of that study. Our finding, however, was consistent with the non-significant observations in two previous African studies especially a recent study in Ghana [6, 11]. Nevertheless, the increased odds of ER + breast cancer associated with each additional 1-year delay before a first full-term pregnancy observed in our study was not consistent with the non-significant observation reported in that Ghanaian study- which happened to be the only indigenous study that has investigated this association [11]. This could be due to differences in the covariates adjusted. Notably, our finding was consistent with findings in Asia and North America [25, 38, 40]. The role of age at last birth has not been previously investigated in Africa. Nevertheless, our result was consistent with the observation in a recent metanalysis of studies outside Africa that carried out such investigations [41]. The non-significant associations between breast cancer odds and increased age at menarche, induced abortion and history of oral contraceptive use in our study were consistent with reports of other indigenous studies [6, 9, 11, 37]. However, most of these studies were based on small sample size [9, 37].

Table 5 Relationship between reproductive variables and breast cancer stratified by oestrogen receptor status

Variables	Oestrogen receptor + VE		Oestrogen receptor -Ve		Triple negative	
	N(%)	OR (95% CI)	N(%)	OR (95% CI)	N(%)	OR (95% CI)
Parity						
Parity 1–3	29 (50.9)	1.00 (ref)	28 (43.8)	1.00 (ref)	18 (42.9)	1.00 (ref)
Parity ≥ 4	28 (49.1)	0.78 (0.31, 1.93)[a]	36 (56.3)	1.28 (0.52, 3.17)[a]	24 (57.1)	1.51 (0.51, 4.47)[a]
Per each additional birth		0.95 (0.70, 1.27)		1.08 (0.82, 1.42)		1.04 (0.73, 1.48)
Lifetime duration of breastfeeding/Total months of breast feeding (TBF)						
TBF ≤ 36 months	20 (35.1)	1.00 (ref)	26 (42.6)	1.00 (ref)	27 (41.5)	1.00 (ref)
TBF > 36 months	37 (64.9)	1.15 (0.46, 2.86)[b]	35 (57.4)	0.53 (0.22,1.29)[b]	44 (58.5)	0.48 (0.17,1.39)[b]
Per each additional 6 months		0.95 (0.88, 1.04)		**0.92 (0.85, 1.00)**		0.92 (0.83,1.02)
P for trend		0.261		**0.043**		0.099
Age at first birth (AFB)						
< 25yrs	20 (35.1)	1.00(ref)	29(45.3)	1.00(ref)	19(45.2)	1.00(ref)
> 25yrs	37 (64.9)	1.97 (0.94, 4.10)[c]	35(54.7)	1.19 (0.62, 2.29)[c]	23(54.8)	1.07 (0.50, 2.32)[c]
Per each additional 1 yr delay		**1.09 (1.02, 1.17)**		1.04(0.98, 1.11)		1.01(0.93, 1.10)
P for trend		**0.017**		0.226		0.806
Age at last birth						
≤ 34	26(45.6)	1.00 (ref)[d]	25(39.7)	1.00 (ref)[d]	15(36.6)	1.00 (ref)[d]
≥ 35	31(54.4)	1.34 (0.63, 2.85)	38 (60.3)	**2.65 (1.25, 5.60)**	26(63.4)	**3.00 (1.26, 7.29)**
Per each additional 1 year delay		1.07 (0.99, 1.15)		**1.12 (1.04, 1.21)**		**1.14 (1.04, 1.25)**
P for trend		0.094		**0.004**		**0.005**
Age at menarche						
< 13yrs	24 (37.5)	1.00(ref)	24(32.4)	1.00(ref)	13(27.1)	1.00(ref)
> 13yrs	40 (62.5)	0.93 (0.52, 1.67)[e]	50(67.6)	1.00 (0.57, 1.76)[e]	35(72.9)	1.36 (0.68, 2.71)[e]

[a]Adjusted for age, study location, ethnicity, menopausal status, personal education, TBF, AAFB, AAM

[b]Adjusted for age, study location, ethnicity, menopausal status, income (below N50,000, N50,000 -N100,000, ≥ 100,000) parity, AAFB

[c]Adjusted for age, ethnicity, study location(Lagos, Abuja), personal educational attainment (below senior secondary, below first degree, first degree and above), maternal educational attainment (Non formal, primary/junior secondary, secondary and above), AAM

[d] age, study location, ethnicity, education, menopausal status, parity, TBF, AAFB, AAM, BMI

[e]Adjusted for age, study location, ethnicity, height. All adjusted reproductive confounders were based on categories shown on the table

Bold indicates significant results

Our finding with respect to the role of parity requires further investigation based on a study with sufficient sample of patients with known oestrogen receptor status. The only available population based SSA study [11] in Ghana found a non-significant effect modification consistent with our finding. The observation, however, was made among younger women only. Nevertheless, the tendency for parity to increase the risk of ER- and TN breast cancers while reducing that of ER + breast cancer has been reported among African Americans [13]. Notably, the role of parity in breast cancer has been described as controversial (with tendency to both increase and reduce breast cancer risk [42]). Since the prevalence of ER- breast cancer, TN breast cancer, and total fertility rate is high in Nigeria compared to the experience in high income countries, it will be necessary to clarify the nature of their relationships. This will be necessary for appropriate intervention.

With respect to breastfeeding, the reduced odds of breast cancer associated with having ever breastfed, and a longer duration of breast breastfeeding (especially among younger women) suggest that improved breast-feeding practices such as longer duration of breeding could help reduce the risk of breast cancer in Nigeria especially those of ER- and TN breast cancer subtypes. This was further supported by the fact that similar observations have been made among African Americans [12, 13]. Moreover, the fact that younger women, ER- and TN breast cancer subtypes constitute a greater proportion of breast cancer cases seen in Nigeria and in most SSA black population makes our finding interesting and important[6, 9] [43–46]. Several mechanisms by which breastfeeding could reduce breast cancer risk especially among younger or premenopausal women has been postulated [47–49]. One of these hypotheses suggests that glandular involution which occurs following weaning and its associated programmed cell death could decrease cell proliferation rate while enhancing the differentiation of mammary duct epithelial cells. This reduces the number of these cells exposed to malignant transformation [47, 48].

Our observation with respect to advanced age at first and last full-term pregnancies may reflect the changing trend toward late marriage and postponement of childbearing to a later age among young people in Nigeria and other SSA countries. This has been attributed to the increasing quest for education, as well as poverty and lack of employment opportunities which discourage timely marriage and birth among young people [5, 50]. In an environment like Nigeria where total fertility is still high (owing to high cultural value for children, poor access to contraceptives and gender inequality), late age at first birth implies that some women will give birth to their last children at an older date. Notably, our result concerning age at last full-term pregnancy, was adjusted for that of age at first full-term pregnancy. It is interesting that our finding suggests that completing childbirth early could protect against ER- and TN breast cancer subtypes given their high prevalence in the region. Unfortunately, we did not come across any existing study locally or internationally that has done such investigation. We, therefore, recommend that the finding be further investigated. Biologically, the higher risk of breast cancer associated with late age at first and last pregnancies could be attributed to a cumulative effects of increased proportion of latent initiated tumour cells following pregnancies at older ages [51, 52]. Pregnancy at an older age could increase the vulnerability of susceptible cells to malignancy owing to increased or cumulative exposure to oestrogen and progesterone [52]. Although some studies have de-emphasized the role of age at last pregnancy as having little contribution beyond that of age at first pregnancy [53], our findings support other studies that have observed its importance [41, 52]. Although our findings need replication since the role of age at last birth has not been previously reported in Africa, it may have implication for family planning in favour of completing child birth early among Nigerians, and other SSA women in view of breast cancer prevention in the region.

Our study has strengths. It is more generalisable to Nigerian female urban population than previous studies having included participants from the northern region of Nigeria. Unlike previous studies we reported the role parity after accounting for that of that of breastfeeding. The mean number of children (3.02) among women aged < 50 years in our study was consistent with the 3.06 reported for Nigerian women in 2013. Similarly, the median age at first birth in our study (25) was consistent with 24.05 average reported for Lagos and Abuja (although higher than the 22 years average reported for female urban population in 2013) [29]. These makes a case for generalisability. Our study has some novelties. It is the first study to report the effect of age at last full-term pregnancy in Africa as well as the differential role of age at first full-term pregnancy depending on oestrogen receptor status. Our study also has limitations. it has potentials for selection bias since it was not based on probability sampling technique. We, however, recruited participants in the order in which they arrived or seated during clinic hours. Moreover, our methodology has been applied in a previous study [6]. While women may remember accurately the number of pregnancies or children they have had, they do not show the same accuracy with breastfeeding and age at menarche. Hence, this type of information bias may not be ruled out in our study. Moreover, our finding with respect to the age at last birth did not account for the potential effect of time since last childbirth. This was because we did not consider it as a confounder although they may be correlated. Our study lacked sufficient data to fully establish how these factors varied by oestrogen receptor status. This is an important investigation that should be carried out in the future.

Conclusion

Our findings suggest that poor breastfeeding practices such as shorter lifetime duration of breastfeeding, older age at first and last full-term pregnancies could increase the risk of breast cancer in Nigeria and SSA. Circumstances that encourage good breastfeeding practices (such as improved awareness and support) and timely birth (such as timely marriage, family planning and favourable socioeconomic conditions) should be promoted. Our finding further emphasised the need to clarify the observed associations based on studies with sufficient sample of oestrogen receptor status information. The need to further investigate the contributions of oral contraceptive use, induced abortion, age at menarche based on larger sample studies in view of changing socioeconomic and reproductive trends especially in the urban communities is also suggested.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10552-022-01629-z.

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Author contributions SO conceived the study, contributed to study design, data acquisition, analysis, interpretation of results, preparation of the first draft, subsequent revision and final report.RM and LH contributed in the study design, data acquisition, analysis, interpretation, revision of the draft, and final report. LS contributed to the study design, data analysis, interpretation, revision of the draft paper, and the final report. All authors agreed to be accountable for all aspects of

the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability The data generated and analysed during the current study are not publicly available because other related contents of the data sets are still being analysed for possible publications but are subsequently available from the corresponding author on reasonable request.

Declarations

Competing interest The authors declare that they have no conflicts of interests.

Ethical approval The study protocol and data collection instruments were approved by the Ethics Committees of the five participating hospitals (NHA/EC/085/2016; FCT/UATH/HREC/PR/537; ADM/DCST/HREC/APP/1108; NRECC04/04/2008; SUB/GHL/1288/19) described earlier as well as those of Newcastle University, United Kingdom (1031/2016) and Lagos State Health Services Commission, Lagos, Nigeria (LSHSC/2222/Vol. XIX/48).

Informed consent Informed consent was obtained in writing from all participants using a consent form specifically prepared for the purpose. In the case of the aged and illiterate participants, it was obtained by proxy through a relative they trusted and designed to act on their behalf. The study was performed per the Declaration of Helsinki.

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