

# Breast Cancer Risk After Full-Term Pregnancies Among African Women From Nigeria, Cameroon, and Uganda

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**BACKGROUND:** The breast cancer (BC) risk profiles of African women differ significantly from those of women of European ancestry. African women are younger at the age of onset and tend to have high parity. The purpose of this study was to examine the relationship between full-term pregnancy (FTP) and the risk of BC. **METHODS:** A case-control study was conducted among 1995 women with invasive BC and 2631 controls in Nigeria, Cameroon, and Uganda. Odds ratios (ORs) for individual ages at FTP according to the time since delivery were calculated and adjusted for confounders. A fitted spline model was used to assess the impact of the number of pregnancies on BC risk. **RESULTS:** In comparison with a nulliparous woman, a parous woman with her first FTP at 20 years showed an OR of 0.76 (95% confidence interval [CI], 0.57-0.99) for developing BC in the following 5 years. Ten years later, this risk was 0.76 (95% CI, 0.58-0.99) and 0.76 (95% CI, 0.58-0.98) for women aged 25 and 30 years, respectively. Similarly, a parous woman with 1 pregnancy had an OR of 0.69 (95% CI, 0.49-0.96), whereas the OR was 0.66 (95% CI, 0.48-0.91) with 2 or 5 pregnancies and 0.67 (95% CI, 0.47-0.94) with 6 pregnancies in comparison with nulliparous women. **CONCLUSIONS:** In contrast to studies in women of European ancestry, this study showed no transient increase in the risk of developing BC after FTP among African women. Further studies are needed to examine the impact of reproductive factors on early-onset BC in African women. *Cancer* 2015;121:2237-43. © 2015 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

**KEYWORDS:** African, age at first full-term pregnancy, breast cancer, case-control studies, parity.

## INTRODUCTION

Breast cancer (BC) is the leading malignancy among females in many countries of Africa.<sup>1,2</sup> Worldwide, sub-Saharan Africa is one of the regions with the lowest incidence rate of the disease.<sup>1,2</sup> However, the mortality rate in this part of the world is closer to that of high-incidence countries.<sup>2</sup>

It has been shown that parity is associated with a reduction in BC risk,<sup>3</sup> and it has been suggested that the high parity among African women may contribute substantially to a lower overall burden of the disease. African women affected by BC are characterized by high parity, an average of 5 children, a mean age of 20 to 22 years at first full-term pregnancy (FFTP), and a mean age of 45 years at diagnosis.<sup>4</sup> The profile of the BC burden among these women is biphasic, with the first and highest peak in the age groups of 40 to 44 and 45 to 49 years; this is followed by a drop for the age group of 50 to 54 years and another peak (smaller) among postmenopausal women in the age group of 60 to 64 years.<sup>5,6</sup> Several hypotheses have been proposed to understand this profile. The overrepresentation of people of less than 50 years old has been suggested to be the reason for this high disease burden among younger women. However, a recent study indicates that the population structure has a minor impact on the predominance of premenopausal BC among African women; women within the same population affected by other cancers such as stomach cancer are 10 to 14 years older than women affected by BC with a median age of 55 years at diagnosis, and there is a unique peak of the burden in the age group of 65 to 69 years.

Another hypothesis is that genetic susceptibilities might play a role in the burden of early-onset BC among African women. Although common BRCA1/2 mutations have been identified among some West African and African American

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women<sup>7</sup> and some variants are unique to African Nigerian women,<sup>8</sup> the overall proportion of the disease attributable to mutations in cancer susceptibility genes among African women remains unknown.

A transient increase in the risk of developing BC after full-term pregnancy (FTP) has been reported in different studies. Approximately 2 decades ago, a Swedish study reported an increase in the risk of developing BC after FFTP, which was shown to persist over 15 years.<sup>9</sup> A meta-analysis and a large cohort study of French women indicated that the effective protection conferred by parity was seen only among postmenopausal women.<sup>10,11</sup> Another study reported a dual effect of parity on BC risk among African American women.<sup>12</sup>

In light of the heavy reproductive life among African women,<sup>4,6,13</sup> an increased risk of BC after FTP might be one of the explanations to consider when it comes to a better understanding of the BC profile among African women. In this study, we used a large data set to assess the effect of FTP on BC risk according to the age at diagnosis and the time since FTP among African women. The results of this study will provide new insights into a better understanding of the BC burden profile observed among African women.

## MATERIALS AND METHODS

### *Study Design*

This was a multisite, hospital-based case-control study conducted in 3 African countries with an overall sample size of 4626 subjects. The 3 sites (regions) were in Ibadan, Nigeria (West Africa), Yaounde, Cameroon (Central Africa), and Kampala, Uganda (East Africa); the sites contributed 83.49%, 8.06%, and 8.45% of the sample, respectively. The Nigeria Breast Cancer Study (NBCS) was initiated in March 1998. Its setting and design have been described in detail elsewhere.<sup>14</sup> Briefly, cases were identified through the surgical oncology and radiotherapy units of the University College Hospital (UCH) in Ibadan. UCH is the referral center for other hospitals and serves a population of approximately 3 million. UCH treats the majority of BC cases in the region. Cases were defined as women who were  $\geq 18$  years old with a histological or clinical diagnosis of invasive BC. Controls were community-based and were randomly selected to represent the diversity of UCH patients, and they were invited to visit a community clinic for the study. Additional controls were recruited through other UCH clinics. After informed consent was obtained from the cases, the interviews

were conducted by trained nurses who administered a structured questionnaire, measured height and weight, and took blood samples. The same procedure was performed for control recruitment by NBCS clerks. In 2011, the standardized NBCS concept and design were extended to the Cameroon (Yaounde) and Uganda (Kampala) sites. Since then, research at these 3 sites has been integrated and constitutes the African Breast Cancer Study. In Cameroon, cases were recruited at the Medical Oncology Service of Yaounde General Hospital; Yaounde General Hospital of the University of Yaounde I serves a population of 2.5 million people. Controls were matched to cases by age and ethnicity and were randomly recruited from the clinics of general medicine and obstetrics and gynecology departments at the same hospital. In Kampala, Uganda, cases were recruited at the Breast and Endocrine Unit of the Department of Surgery of Mulago Hospital (Makerere University). Mulago Hospital is a national referral hospital in Uganda and serves the 1.3 million residents in Kampala. Controls were randomly recruited from the general outpatient clinics and surgical ward admissions at Mulago Hospital and matched to cases by age and ethnicity. For both sites (Kampala and Yaounde), hospital controls were unselected for their medical conditions. The Nigerian site has piloted 3 different versions of the questionnaire since 1998 and has perfected the most recent version. The sites in Uganda and Cameroon have used only the most recent version of the questionnaire, which is now the standard questionnaire for the African Breast Cancer Study. All study participants provided written informed consent before their interviews, and the recruitment was highly successful with response rates  $> 90\%$ . The study protocol was reviewed and approved by the institutional review boards of the University of Chicago and the 3 study centers.

### *Statistical Analysis*

FTP was defined as a pregnancy that lasted for at least 7 months. Hence, stillbirths and live births at 7 months or longer were considered FTPs. Current pregnancies, miscarriages, tubal or ectopic pregnancies, and induced abortions were excluded from the current study. The mean duration for a live-birth pregnancy was 9.04 months, whereas that for a stillbirth pregnancy was 8.75 months.

Demographic factors and potential confounding variables were compared between cases and controls with *t* tests or Wilcoxon rank sum tests for continuous variables and with chi-square tests for categorical data. Logistic

regression models were used to examine the relationship of BC risk with reproductive factors. To investigate whether there is a transiently increased risk after FTPs, we used the model proposed by Pathak and Whittemore,<sup>15</sup> in which the occurrence and timing of full-term pregnancies, the age at menarche (AAM), and the age at menopause are considered. The mathematical forms of the models are listed here:

$$\begin{aligned} \text{logit}(Y=1) &= \alpha + \beta_1 x_1 + \rho_1 z_1 + \delta_1 t_1 + \rho_2 z_2 \\ &\quad + \delta_2 t_2 + \dots + \rho_n z_n + \delta_n t_n + \rho_m Z_m + \delta_m T_m \\ &\quad + \beta_2 \text{ALC} + \beta_3 \text{OC} + \beta_4 \text{BMI} + \beta_5 \text{BBD} \\ &\quad + \beta_6 \text{FH} \\ x_1 &= \log(\text{age} - \text{AAM} + 1) \\ z_1 &= 1 \text{ if at least 1 FTP, } z_1 = 0 \text{ if nulliparous} \\ t_1 &= \log(\text{age} - \text{AAM} + 1) - \log(\text{age at FFTP} - \text{AAM} + 1), \\ &\quad t_1 = 0 \text{ if } z_1 = 0 \\ z_2 &= 1 \text{ if at least 2 FTPs, } z_2 = 0 \text{ if otherwise} \\ t_2 &= \log(\text{age} - \text{AAM} + 1) - \log(\text{age at second FTP} \\ &\quad - \text{AAM} + 1), t_2 = 0 \text{ if } z_2 = 0 \\ z_n &= 1 \text{ if at least } n \text{ FTPs, } z_n = 0 \text{ if otherwise} \\ t_n &= \log(\text{age} - \text{AAM} + 1) - \log(\text{age at } n\text{th FTP} - \text{AAM} + 1), \\ &\quad t_n = 0 \text{ if } z_n = 0 \\ Z_m &= 1 \text{ if postmenopausal, } Z_m = 0 \text{ if premenopausal} \\ T_m &= \log(\text{age} - \text{AAM} + 1) - \log(\text{age at menopause} \\ &\quad - \text{AAM} + 1), T_m = 0 \text{ if } Z_m = 0 \end{aligned}$$

where ALC is alcohol use, OC is oral contraceptive, BMI is body mass index, BBD is benign breast disease, and FH is family history of BC. Here, we modeled the odds of BC as a function of the joint effect of the occurrence and time of pregnancies since menarche on a log-log scale after conditioning for several risk factors. Parameter  $\rho_1$  indicates the change in the overall level of BC risk after FFTP, whereas parameter  $\delta_1$  indicates the change in the slope of BC risk after FFTP. In other words, if both parameters are significant,  $\rho_1$  is the magnitude of the transient change, and  $\delta_1$  models the long-term change after first pregnancy. Parameter  $\rho_2$  indicates the change in the overall level of BC risk after the second FTP in addition to FFTP, whereas  $\delta_2$  indicates the change in the slope of BC risk after the second FTP in addition to first BC. Using a backward selection procedure, we modeled up to 12 FTPs (ie,  $n = 12$ ). In brief, we first tested whether parameters  $\rho_{12}$  and  $\delta_{12}$  were significantly different from zero. If not, they were removed from the model, and we further tested whether parameters  $\rho_{11}$  and  $\delta_{11}$  were significant. The backward procedure was stopped when parameters  $\rho$  and  $\delta$  were significant.

In addition, we examined the effect of parity on BC risk in logistic regressions by including parity as a categorical variable (1, 2, . . . , 6, 7 or more) or as a continuous

variable. We used a linear spline function with a knot at 1 FTP to assess the effect of FFTP and the trend after FFTP. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed as measures of association from the logistic models. All statistical analyses were conducted with Stata 12 (StataCorp, College Station, Texas).

## RESULTS

This study included a sample of 4626 subjects: 1995 cases and 2631 controls recruited from March 1998 to September 2013 in 3 African countries. The mean age at diagnosis (or at interview) was 48 years for cases, which was more than that of controls at 43 years ( $P < .05$ ). Significant differences in BMI, parity, age at menopause, alcohol consumption, and contraceptive use were observed between cases and controls. No differences were observed between the 2 groups for the mean ages at menarche (15 years), FFTP (23 years), second FTP (26 years), third FTP (28 years), or fourth FTP (30 years; Table 1).

Table 2 presents the regression parameters estimated in the logistic regression model that examined whether there was a transiently increased risk after pregnancy. After backward selection of different parameters related to pregnancies, only FFTP was statistically significant and was kept. As expected, alcohol consumption, a previous history of BBD, and a positive FH were significantly associated with an increase in the risk of developing BC. Interestingly, BMI (increase per unit) and contraception use were significantly associated with a reduction in BC risk. FFTP was associated with an overall reduced BC risk with an OR of 0.73 ( $e^{-0.31}$ ), but the slope for the risk of change was not significant; this suggests that there is no transient increase in the risk of developing BC after FFTP. As illustrated in Figure 1 (estimated from the model in Table 1), there was a constant reduction in BC risk after FFTP, regardless of the age at FFTP. A parous woman whose FFTP occurs at 20 years has an OR of 0.76 (95% CI, 0.57-0.99) for the next 5 years (Supporting Table 1 [see online supporting information]), and as illustrated in Figure 1, the reduction of risk is similar across the different ages at FFTP. For example, women who have given birth at 25 or 30 years can receive almost the same protection from pregnancy; it is 0.76 (95% CI, 0.58-0.99) and 0.76 (95% CI, 0.58-0.98), respectively, more than 10 years after delivery (Supporting Table 1 [see online supporting information]).

Because the effect of FFTP on a transiently increased risk of developing BC could be hidden by multiple FTPs,<sup>9</sup> we restricted our analysis to nulliparous and uniparous women. Although few of these results were statistically significant because of the considerable reduction of

**TABLE 1.** Demographic Characteristics of Subjects Included in the Study

| Characteristic                                   | Controls<br>(n = 2631) | Cases<br>(n = 1995) |
|--|------------------------|---------------------|
| Study site, No. (%)                              |                        |                     |
| Nigeria (Ibadan)                                 | 2253 (85.63)           | 1607 (80.55)        |
| Cameroon (Yaounde)                               | 182 (6.92)             | 192 (9.62)          |
| Uganda (Kampala)                                 | 196 (7.45)             | 196 (9.82)          |
| Age at diagnosis/interview, No. (%) <sup>a</sup> |                        |                     |
| <30 y  | 383 (14.62)            | 74 (3.73)           |
| 30-39 y  | 719 (27.45)            | 442 (22.31)         |
| 40-49 y  | 702 (26.80)            | 639 (32.26)         |
| ≥50 y  | 815 (31.13)            | 826 (41.70)         |
| Age at diagnosis/interview, mean ± SD, y         | 43.1 ± 13.0            | 47.6 ± 11.65        |
| Age at menarche, No. (%)                         |                        |                     |
| ≤12 y  | 255 (9.95)             | 181 (9.86)          |
| 13-14 y  | 703 (27.44)            | 527 (28.72)         |
| 15-16 y  | 1013 (39.54)           | 759 (41.36)         |
| ≥17 y  | 591 (23.07)            | 368 (20.06)         |
| Age at menarche, mean ± SD, y                    | 15.2 ± 2.2             | 15.1 ± 2.03         |
| Body mass index, No. (%) <sup>a</sup>            |                        |                     |
| <18.5 kg/m <sup>2</sup>                          | 134 (5.19)             | 131 (6.87)          |
| 18.5-24.9 kg/m <sup>2</sup>                      | 1014 (39.26)           | 816 (42.81)         |
| 25.0-29.9 kg/m <sup>2</sup>                      | 810 (31.36)            | 556 (29.17)         |
| ≥30 kg/m <sup>2</sup>                            | 625 (24.19)            | 403 (21.15)         |
| Body mass index, mean ± SD, kg/m <sup>2</sup>    | 26.5 ± 6.06            | 25.9 ± 6.60         |
| Parity, No. (%) <sup>a</sup>                     |                        |                     |
| 0  | 273 (10.39)            | 184 (9.28)          |
| 1-2  | 559 (21.29)            | 352 (17.75)         |
| 3-4  | 804 (30.62)            | 588 (29.65)         |
| 5-6  | 622 (23.69)            | 550 (27.74)         |
| ≥7   | 368 (14.01)            | 309 (15.58)         |
| Parity, mean ± SD                                | 4.3 ± 2.30             | 4.5 ± 2.23          |
| Age at full-term pregnancy, No., mean ± SD       |                        |                     |
| First  | 2336, 23 ± 4.81        | 1771, 23 ± 4.93     |
| Second   | 2052, 26 ± 4.88        | 1591, 26 ± 4.99     |
| Third  | 1743, 28 ± 4.82        | 1392, 28 ± 4.96     |
| Fourth   | 1373, 30 ± 4.92        | 1126, 30 ± 5.07     |
| Fifth  | 942, 32 ± 4.93         | 821, 32 ± 5.12      |
| Breastfeeding, No. (%)                           |                        |                     |
| Yes  | 2313 (88.96)           | 1752 (88.31)        |
| No   | 287 (11.04)            | 196 (11.69)         |
| Alcohol consumption, No. (%) <sup>a</sup>        |                        |                     |
| Yes  | 343 (13.09)            | 402 (20.26)         |
| No   | 2278 (86.91)           | 1582 (79.74)        |
| Contraception, No. (%) <sup>a</sup>              |                        |                     |
| Yes  | 902 (34.67)            | 576 (29.33)         |
| No   | 1700 (65.33)           | 1388 (70.67)        |
| Menopause, No. (%)                               |                        |                     |
| Yes  | 813 (30.97)            | 858 (43.12)         |
| No   | 1812 (69.03)           | 1132 (56.88)        |
| Age at menopause, No. (%) <sup>a</sup>           |                        |                     |
| <50 y  | 311 (46.21)            | 356 (50.14)         |
| ≥50 y  | 362 (53.79)            | 354 (49.86)         |
| Age at menopause, mean ± SD, y                   | 49.3 ± 4.98            | 48.5 ± 5.19         |

Numbers in the table are not always added up to the sum due to missing data. Abbreviation: SD, standard deviation.

<sup>a</sup>There was a statistically significant difference between cases and controls ( $P < .05$ ).

the sample size, the results showed a trend of the risk of developing BC being reduced after FTP (Supporting Table 2 [see online supporting information]).

The effect of the number of FTPs among parous women versus nulliparous women was examined in this study. We found a clear protective effect of parity across different numbers of pregnancies; there was a significant reduction in BC risk after FFTP, whereas there was only a slight risk reduction for each additional pregnancy (Fig. 2 and Supporting Table 3 [see online supporting information]). In comparison with nulliparous women, parous women with 1 pregnancy had an OR of 0.69 (95% CI, 0.49-0.96), whereas parous women with 7 or more pregnancies had an OR of 0.54 (95% CI, 0.38-0.75; Fig. 2 and Supporting Table 3 [see online supporting information]).

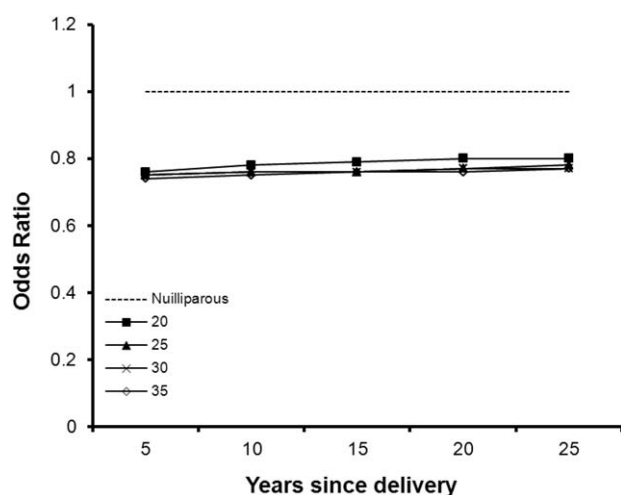
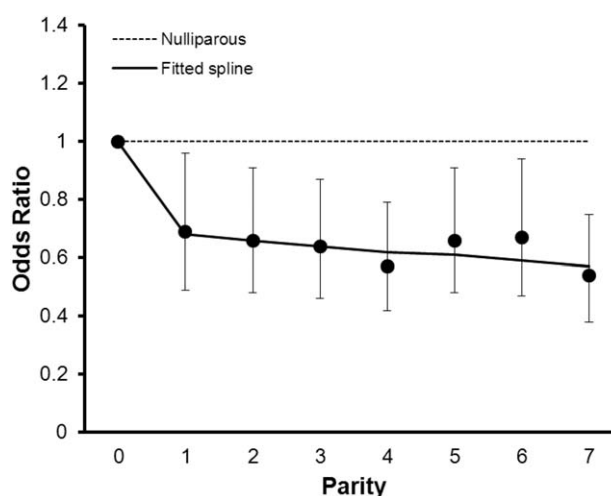
## DISCUSSION

Using a large data set of African women, we assessed whether there was a transient increase in BC risk after FTPs among African women and whether its existence could be an explanation for the high proportion of young-onset BC among these women. A study conducted on a Swedish population that compared nulliparous women to uniparous women showed that childbirth correlated with a transient increase in the risk of developing BC, and this risk was reduced in later years.<sup>9</sup> In contrast, in the current study, we found a strong protective effect after FFTP, regardless of the age at pregnancy, and a strong protection resulting from pregnancy, regardless of the number of FTPs. These data suggest that the protective effect of parity is exhibited immediately after FFTP and that the transiently increased risk after pregnancy observed in previous studies may not be applicable to African populations. It could be argued that the previous studies strictly compared nulliparous women with uniparous women and that multiple births could have hidden the transient increase in the risk of BC. However, our study employed the same cutoff parameters, and the results did not show any increase in the risk of BC after FTPs. Furthermore, the past studies that have reported a transient increase in the risk of BC were not adjusted for confounders.<sup>5,9</sup> Nevertheless, similar studies that adjusted their results for confounders found a marginal increase in the risk of developing BC after the first pregnancy (adjusted OR, 1.07; 95% CI, 1.01-1.13).<sup>16</sup> Although several studies have reported a transient increase in the risk of developing BC, the risk was limited to women at an older age at FFTP.<sup>12,16-19</sup> Our study did not find an increase in the risk with any delay in the age at FFTP as reported in one study performed among Estonian women.<sup>17</sup> It has been suggested that the age of approximately 35 years represents an important transition point for BC risk. Before



**TABLE 2.** Regression Parameters Estimated With Fitted Logistic Regression Model

| Parameter                       | Interpretation                         | Log Odds Ratio | Standard Error | P     |
|---------------------------------|--|----------------|----------------|-------|
| Year since menarche             | Increase per log(year)                 | 1.35           | 0.13           | <.001 |
| Parity                          |  |                |                |       |
| $\rho_1$                        | Change in the level after first birth  | -0.31          | 0.14           | .029  |
| $\delta_1$                      | Change in the slope after first birth  | 0.05           | 0.05           | .31   |
| Menopause                       |  |                |                |       |
| $\rho_m$                        | Change in the level after menopause    | -0.08          | 0.12           | .49   |
| $\delta_m$                      | Change in the slope after menopause    | -1.27          | 0.36           | <.001 |
| Alcohol consumption             | Yes vs no                              | 0.24           | 0.11           | .03   |
| Contraception use               | Yes vs no                              | -0.24          | 0.08           | .002  |
| Body mass index                 | Increase per unit (kg/m <sup>2</sup> ) | -0.03          | 0.01           | <.001 |
| Benign breast diseases          | Yes vs no                              | 0.27           | 0.13           | .03   |
| Family history of breast cancer | Yes vs no                              | 0.45           | 0.12           | <.001 |

**Figure 1.** Odds ratios for developing breast cancer by individual ages at the first full-term pregnancy among parous women versus nulliparous women.**Figure 2.** Odds ratios and 95% confidence intervals for developing breast cancer among parous women according to the number of full-term pregnancies versus nulliparous women.

that age, any birth appears to be protective, whereas the opposite effect is observed after that age.<sup>18</sup> In our study, only 6.8% of the subjects experienced their FFTP after 35 years, and this age was not associated with an increased risk of BC.

To date, no study has assessed the impact of a potential transient increase in BC risk after FTP among African women. Available studies that compared the age at FFTP among African women found that a later age at FFTP (>20 vs ≤20 years) correlated with stronger protection against BC in premenopausal women (OR, 0.41; 95% CI, 0.18-0.89) and postmenopausal women (although the data were not statistically significant). One of our studies conducted among Nigerian women found no difference in BC risk with an increasing age at FFTP.<sup>4</sup>

Several factors could explain why our results contradict those of previous studies. First, the reported transient increase in the risk of developing BC after FFTP or any

pregnancy has been mostly reported among Western Caucasian women who are known to have fewer children than African women. Studies that have included several populations from Europe, Asia, Latin America, and the United States of America have found that the increased risk of developing BC after FTP is restricted with a delayed age at FFTP<sup>15,18-22</sup> (see Supporting Table 4 [see online supporting information]).

Second, when we consider that there are several BC subtypes and that some of them are less likely to be influenced by reproductive factors, it is possible that our results could be the reflection of a different BC subtype. For example, it has been shown that the increased BC risk with an older age at FFTP is more frequent in hormone-dependent BC, which is more prevalent among Caucasian women.<sup>23-27</sup> If we consider the context of African women with an overrepresentation of hormone receptor-negative

BC and the fact that this subtype is known to be more prevalent among younger women with a younger age at FFTP or with high parity<sup>28-32</sup> and if we hypothesize that high parity confers an overall short-term exposure to estrogen, younger women with high parity might then be protected against hormone-dependent BC but not against hormone receptor–negative BC. It has been reported that the protection conferred by multiparity and an early age at FFTP is restricted to hormone receptor–positive BC and that women at higher risk for hormone receptor–positive BC are more likely to be older at their FFTP, whereas women affected by hormone receptor–negative BC are frequently younger at their FFTP.<sup>23,33,34</sup> One limitation of this study is the lack of annotated data on the hormone receptor status of all the cases involved in the study. In contrast to women involved in previous studies, the subjects of our study had high parity, which is known to be strongly protective against hormone-dependent BC but has not been demonstrated against hormone receptor–negative BC.<sup>35,36</sup> Therefore, the fact that our results do not support previous reports might be due to the predominance of non–hormone-dependent BC among African women.

In agreement with previous studies stating that parity is protective against BC,<sup>4,37</sup> our results indicate that parity is strongly protective against BC, and this protection seems to be stable or slightly stronger with an increased number of pregnancies. The absence of a transient increase in the risk of developing BC after FFTP suggests that in addition to the probably higher proportion of hormone receptor–negative BC, inherited genetic susceptibilities could play a role in the observed pattern and need to be evaluated.

One could also argue that a recall bias for the age at FTP might have introduced mistakes into the accuracy of the ages provided. However, a study assessing the impact of differential recall on the results of case-control studies has shown that it has a minor impact on the result of the study.<sup>38</sup>

In conclusion, our results support the hypothesis that the overall lower burden of BC among African women versus Western women might be in part due to the protection conferred by their heavier reproductive life.

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## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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