Research Article

Premenopausal Breast Cancer Risk Factors and Associations with Molecular Subtypes: A Case-Control Study

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Background. Breast cancer (BC) is the most prevalent cancer in women and the leading cause of women’s cancer-related deaths and morbidity worldwide. In Rwanda, BC incidence is increasing with an unacceptably high mortality rate in premenopausal women. Objectives. The purpose was to identify modifiable BC risk factors and assess associations between common breast cancer risks factors and molecular subtypes in premenopausal women in Rwanda. Methods. This was a case-control study. Premenopausal women with histological confirmation of BC and frequency-matched for age controls were recruited. A preestablished questionnaire was administered to both cases and controls for sociodemographics, BC probable risk factors, and health behaviors. Results. 340 participants were recruited into the study (170 cases vs. 170 controls). The median age was 39 years. The majority of cases presented at advanced stages of the disease (51.2% in stages III and IV) and had invasive ductal carcinoma (98.2%). 60.6% had subtypes of poor prognosis (HER2 enriched 14.7%, triple negative 12.9%, and unclassified 32.9%). Alcohol intake (AOR = 3.73, 95%CI 2.19–6.32, p < 0.001), obesity/overweight in adolescence or early adulthood (AOR = 10.86, 95%CI 4.82–24.4, p < 0.001), history of primary infertility (AOR = 33.8, 95%CI 3.5–321.5, p = 0.002), nulliparity (AOR = 3.75, 95%CI 1.61–8.75, p = 0.002), and a history of benign breast disease (AOR = 6.06, 95%CI 1.19–30.73, p = 0.03) were associated with the occurrence of premenopausal breast cancer. There was no significant difference between risk factor stratification per molecular subtype. Conclusion. Several reproductive, environmental, and lifestyle risk factors have been identified to be associated with premenopausal BC. Among them, alcohol intake and obesity/overweight during adolescence/early adulthood can be modified. Interventions targeting alcohol consumption and obesity/overweight in adolescents and young adults may decrease the incidence of premenopausal breast cancer.

1. Introduction

Breast cancer is the most prevalent cancer and the leading cause of women’s cancer-related deaths and morbidity worldwide. Although breast cancer is described as a disease of the elderly in developed countries, 50% of cases and 58% of deaths are occurring in developing countries within a relatively young population [1–4]. Indeed, breast cancer constitutes a major public health problem worldwide and remains a major scientific, clinical, and societal challenge generally in Africa and particularly in Rwanda. In Africa, publications on breast cancer describe a large number of patients presenting at a young age, with advanced disease and limited access to cancer education, screening, and care. We have learned from previous studies that registries are still scarce in Africa and few available data
are generally from hospital-based logs. On the continent, accurate data are generally missing [4–7].

However, there are growing evidences suggesting that clinical presentation of breast cancer in African women may significantly be different compared to their counterparts in high-income countries. Breast cancer patients in Africa may be presenting at younger age and progress rapidly to advanced stages. In fact, the average age of breast cancer diagnosis seems to be 45 years or younger, a considerable difference compared to 64 and above of Caucasian populations [7–9].

Age structure difference alone may not entirely explain the younger age of breast cancer patients in Africa. There may be involved other additional factors to be determined. These may be genetic, molecular, hormonal, and environmental factors or interplay of them [10–12]. Unfortunately, it is not yet clear whether premenopausal breast cancers have different etiologic risk factors compared to postmenopausal BC. Indeed, the existing literature remains unclear or incomplete about the factors behind early-onset and rapid progression of breast cancer in African populations.

The purpose of this study was to identify modifiable risk factors and assess the associations between common risk factors and molecular subtypes in premenopausal breast cancer in Rwanda.

2. Methods

2.1. Study Design and Setting. This was a case-control study conducted at the University Teaching Hospital of Kigali (CHUK) and Butaro Cancer Center of Excellence (BCCOE) in Rwanda from September 2019 to September 2020.

2.1.1. Population. Women attending breast clinics at CHUK and BCCOE have been recruited in the study. For the purpose of the study, the premenopausal period was defined based on self-rated menopausal status:

(1) Any woman who reported having seen her menses within the last month was considered premenopausal as well as those who were pregnant or breastfeeding during the study period. In addition, women who reported not having seen menses in the previous 6 months without any identifiable medical reasons (medications, diseases) were considered premenopausal if aged ≤50 years.

(2) Any women who reported not having seen menses in the previous 6 months without any identifiable medical reasons (medications, diseases) were considered postmenopausal if aged ≥50 years.
2.1.2. Study Participants’ Selection. Cases were women diagnosed with breast cancer in the premenopausal period. Potential cases were preidentified from outpatients’ breast clinics and recruited in the study after histology confirmation of breast cancer and included in the study using enumerative sampling technique. For 12 months, consecutive cases of premenopausal breast cancers have been included in the study (Figure 1).

As far as controls are concerned, we used a 1:1 ratio. Women attending the breast clinic either for breast cancer screening or any other confirmed benign breast complaints were used as controls after clinical evaluation and imaging done to investigate their breast complaints was found to be normal or benign.

Controls were recruited on a weekly basis from the same breast clinic as cases, using stratified simple random sampling technique matching the age of cases recruited the previous week.

2.1.3. Data Collection. A preestablished questionnaire was used to collect sociodemographic and potential risk factors for breast cancer. A data capture sheet was developed based on different questionnaires used in previous studies, and information on established or probable breast cancer risk factors (lifestyle, reproductive, hormonal, genetic, and medical history) was collected both for cases and controls. Clinical, histopathological, and immunohistochemistry findings were collected for cases using direct patients’ interviews, pathology registries, reports, and patients’ files.

2.1.4. Sample Size Calculation. The sample size was calculated using G∗Power 3.1.9.7 for Windows, online software for sample size calculation, assuming 85% power, minimum odds ratio to detect of 2.0, percentage of exposed controls of 30%, alpha risk of 5%, 1 : 1 ratio. Therefore, the sample size was found to be 322 individuals with 161 cases and 161 controls.

2.2. Statistical Analysis. Data analysis was done using SPSS version 25.0 (IBM Corporation, New York 10504-1722, USA). Univariate analysis was conducted to compare sociodemographic characteristics of cases and controls. The Chi-squared test was used for categorical variables and nonparametric tests (Mann-Whitney U test) for continuous variables. Bivariate and multivariate logistic regression analysis was done for associations between risk factors and premenopausal breast cancer. Risk of premenopausal breast cancer was estimated by the odds ratio. For all odds ratios, 95% confidence interval was considered. A p value less than 0.05 was considered statistically significant.

2.3. Ethical Considerations. The study was approved by the IRB of the College of Medicine and Health Sciences, University of Rwanda, and by ethical committees of the CHUK and BCCOE. Written informed consent was obtained for both cases and controls prior to prospective data collection.

| Variables | Cases (N = 170) | Controls (N = 170) |
|-----------|----------------|-------------------|
| Age       |                |                   |
| Median (Min–Max) years | 41 (18-50) | 35 (24-49) |
| Category |                |                   |
| <30 years | 6 3.5          | 6 3.5             |
| 30–40 years | 72 42.4  | 72 42.4          |
| >40 years  | 92 54.1        | 92 54.1           |
| Education |                |                   |
| No formal education | 4 2.4  | 33 19.4          |
| Primary   | 75 44.1        | 68 40             |
| Secondary | 77 45.3        | 60 35.3           |
| University | 14 8.2       | 9 5.3             |
| Ubudehe (economic) category | |                   |
| Ubudehe 1 | 9 5.3          | 7 4.1             |
| Ubudehe 2 | 39 22.9        | 81 47.6           |
| Ubudehe 3 | 119 70.0       | 81 47.6           |
| Ubudehe 4 | 3 1.8          | 1 0.6             |
| Profession |                |                   |
| Farmer    | 92 54.1        | 106 62.4          |
| Business  | 47 27.6        | 38 22.4           |
| Civil servant | 16 9.4  | 11 6.5           |
| Other     | 15 8.8         | 15 8.8            |
| Family history of breast cancer | |                   |
| Yes       | 33 19.4        | 23 13.5           |
| No        | 137 80.6       | 147 86.5          |
| Presenting symptoms |                   |                   |
| Painless breast lump | 155 45.6  |                   |
| Breast pain | 121 35.6  |                   |
| Breast swelling | 18 5.3   |                   |
| Breast discharge | 15 4.4    |                   |
| Clinical stage |                |                   |
| Stage 1   | 5 2.9          |                   |
| Stage 2   | 78 45.9        |                   |
| Stage 4   | 63 37.1        |                   |
| Stage 4   | 24 14.1        |                   |
| Disease progression |             |                   |
| Slow progression | 13 7.6     |                   |
| Intermediate | 93 54.7   |                   |
| Rapid     | 64 37.6        |                   |

*Ubudehe category version 2015: the category number increases with the higher socioeconomic status (government of Rwanda, community-led Ubudehe categorization) http://www.gov.rw/news_detail/?tx_ttnews[tt_news]=1054&cHash=a.

3. Results

348 participants were recruited in the study. 345 of them met inclusion criteria. Three cases and 2 controls had
multiple missing data and were excluded. For that reason, 340 (170 cases and 170 controls) were retained for final analysis.

The median age of participants was 39 years with 45.9% of them aged below 40 years. Painless breast lump was the presenting sign in 45.6% of cases. 54.7% of patients reported intermediate to rapid progression of the disease (Table 1).

In bivariate logistic regression analysis, the crude odds ratio (COR) was calculated. Alcohol intake (COR = 4.49, 95% CI 2.82-7.16, p < 0.001), obesity/overweight in adolescence or early adulthood (COR = 12.8, 95% CI 6.13-26.8, p < 0.001), history of primary infertility (COR = 16.3, 95% CI 2.13-125.2, p = 0.007), history of benign breast disease (COR = 10.5, 95% CI 2.42-46.1, p = 0.003), nulliparity (COR = 2.18, 95% CI 1.18-4.04, p = 0.012), and contraceptive use (COR = 2.89, 95% CI 1.85-4.5, p < 0.001) were found to be associated with the occurrence of premenopausal breast cancer (Table 2).

Holding other relevant variables constant, the adjusted odds ratio was calculated in a multivariate regression analysis. Alcohol intake (AOR = 3.73, 95% CI 2.19-6.32, p < 0.001), obesity/overweight in adolescence or early adulthood (AOR = 5.76, 95% CI 1.85-4.5, p < 0.001), history of primary infertility (AOR = 3.07, 95% CI 3.5-321.5, p = 0.002), nulliparity (AOR = 3.07, 95% CI 1.61-8.75, p = 0.002), and a history of benign breast disease (AOR = 2.18, 95% CI 1.19-30.7, p = 0.03) were found to be associated with the occurrence of premenopausal breast cancer (Table 3).

Table 2: Associations between exposure and premenopausal breast cancer.

| Risk factor                        | Premenopausal breast cancer | COR     | 95% CI          | p     |
|------------------------------------|-----------------------------|---------|-----------------|-------|
|                                    | Cases (n = 170)             |         |                 |       |
| Sports activity                    | No                          | 0.75    | 0.32-1.77       | 0.518 |
| Alcohol intake                     | Yes                         | 100 (58.8%) | 41 (24.1%) | 4.49  | <0.001 |
| obesity/overweight in adolescence  | No                          | 0.75    | 0.32-1.77       | 0.518 |
| Menstrual cycle regularity         | Yes                         | 77 (45.3%) | 79 (46.5%) | 12.8  | <0.001 |
| Menses quantity                    | Normal                      | 129 (75.9%) | 154 (90.6%) | 0.32  | <0.001 |
|                                    | Heavy                       | 41 (24.1%) | 16 (9.4%) |       |       |
| History of primary infertility     | Yes                         | 71 (41.8%) | 9 (5.3%) | 12.8  | <0.001 |
|                                    | No                          | 0.75    | 0.32-1.77       | 0.518 |
| Nulliparity                        | Yes                         | 157 (92.4%) | 160 (94.1%) | 0.75  | 0.32-1.77 | 0.518 |
|                                    | No                          | 13 (7.6%) | 10 (5.9%) |       |       |
| Contraception use                  | Yes                         | 100 (58.8%) | 41 (24.1%) | 4.49  | <0.001 |
|                                    | No                          | 13 (7.6%) | 10 (5.9%) |       |       |
| Radiation exposure                 | Yes                         | 100 (58.8%) | 41 (24.1%) | 4.49  | <0.001 |
|                                    | No                          | 13 (7.6%) | 10 (5.9%) |       |       |

Table 3: Predictors of breast cancer in premenopausal women.

| Predictor                        | Category | z     | AOR     | 95% CI          | p     |
|----------------------------------|----------|-------|---------|-----------------|-------|
| Alcohol intake                   | Yes      | 4.88  | 3.73    | 2.19-6.32       | <0.001|
| Obesity/overweight in past       | Yes      | 5.76  | 10.86   | 4.82-24.4       | <0.001|
| History of primary infertility   | Yes      | 3.07  | 33.8    | 3.5-321.5       | 0.002 |
| Nulliparity                      | Yes      | 3.07  | 3.75    | 1.61-8.75       | 0.002 |
| History of benign breast disease | Yes      | 2.18  | 6.06    | 1.19-30.73      | 0.03  |
|                                    | No       |       |         |                 |       |

COR = crude odds ratio.
AOR: adjusted odds ratio.
By stratifying risk factors by molecular subtypes, there was no significant difference between risk factors stratified per molecular subtype (Table 4).

Invasive ductal carcinoma was the main histology type in 98.2% of patients while invasive lobular carcinoma and ductal carcinoma in situ represented 0.6% each (Table 5).

The most frequent molecular subtype was luminal A with 26.5% with subtypes of poor prognosis in 60.6% (HER2 enriched 14.7%, triple negative 12.9%, and unclassified 32.9%) (Table 6).

4. Discussion

This study identified risk factors for premenopausal breast cancer in Rwanda and stratified them per molecular subtypes. Indeed, the majority of patients with breast cancer in Rwanda and in sub-Saharan Africa may be young premenopausal women, presenting with advanced stages of the disease and having poor outcomes [6, 8, 13–15]. The reasons why it happens like that are not yet fully understood. Marie Swanson et al. clearly demonstrate the existence of differences in age-specific incidence, risk factors, and outcomes, when comparing young African-Americans and White-Americans [10]. However, what they do not explain is why these epidemiological differences exist.

Table 4: Associations between risk factors and molecular subtypes.

| Risk factor                          | Luminal A (n = 45) | p   | Luminal B (n = 22) | p   | HER2 enriched (n = 25) | p   | Triple negative (n = 22) | p   |
|--------------------------------------|-------------------|-----|--------------------|-----|-----------------------|-----|-------------------------|-----|
|                                      | OR (95% CI)       |     | OR (95% CI)        |     | OR (95% CI)           |     | OR (95% CI)             |     |
| Sports activity                      |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 2.07 (0.44-9.74)  | 0.355| 1.24 (0.25-6.03)   | 0.785| 2.16 (0.26-17.4)      | 0.468| 1.74 (0.31-9.62)        | 0.526|
| No                                   |                   |     |                    |     |                       |     |                         |     |
| Alcohol intake                       |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 1.79 (0.87-3.70)  | 0.112| 1.26 (0.49-3.19)   | 0.624| 1.05 (0.44-2.51)      | 0.897| 1.29 (0.50-3.36)        | 0.591|
| No                                   |                   |     |                    |     |                       |     |                         |     |
| Obesity/overweight in past           |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 1.25 (0.62-2.52)  | 0.527| 0.47 (0.17-1.29)   | 0.146| 0.74 (0.31-1.74)      | 0.495| 2.35 (0.91-6.07)        | 0.077|
| No                                   |                   |     |                    |     |                       |     |                         |     |
| Menstrual cycle regularity           |                   |     |                    |     |                       |     |                         |     |
| Regular                              | 1.07 (0.54-2.13)  | 0.829| 1.92 (0.74-4.99)   | 0.179| 1.06 (0.45-2.49)      | 0.888| 1.06 (0.41-2.73)        | 0.899|
| Irregular                            |                   |     |                    |     |                       |     |                         |     |
| Menses quantity                      |                   |     |                    |     |                       |     |                         |     |
| Normal                               | 0.60 (0.25-1.42)  | 0.249| 0.82 (0.30-2.27)   | 0.826| 0.78 (0.30-2.04)      | 0.624| 0.99 (0.32-3.01)        | 0.992|
| Heavy                                |                   |     |                    |     |                       |     |                         |     |
| History of infertility               |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 1.01 (0.30-3.35)  | 0.986| 0.55 (0.14-2.16)   | 0.399| 0.39 (0.04-3.10)      | 0.374| —                       |     |
| No                                   |                   |     |                    |     |                       |     |                         |     |
| Nulliparity                          |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 1.2 (0.40-4.15)   | 0.666| 2.12 (0.63-7.17)   | 0.224| 1.78 (0.46-6.92)      | 0.399| 1.08 (0.21-5.41)        | 0.921|
| No                                   |                   |     |                    |     |                       |     |                         |     |
| Contraception use                    |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 1.98 (0.99-3.96)  | 0.052| 1.01 (0.41-2.47)   | 0.987| 240 (0.94-6.08)       | 0.066| 1.05 (0.41-2.67)        | 0.914|
| No                                   |                   |     |                    |     |                       |     |                         |     |
| History of benign breast disease     |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 2.05 (0.56-7.41)  | 0.271| 0.76 (0.20-2.88)   | 0.695| 0.31 (0.10-0.91)      | 0.035*| 0.66 (0.13-3.22)        | 0.614|
| No                                   |                   |     |                    |     |                       |     |                         |     |
| Family history of breast cancer      |                   |     |                    |     |                       |     |                         |     |
| Yes                                  | 3.09 (1.02-9.37)  | 0.045*| 0.45 (0.16-1.23)   | 0.121| 0.52 (0.14-1.86)      | 0.317| 0.61 (0.19-1.19)        | 0.399|
| No                                   |                   |     |                    |     |                       |     |                         |     |

Table 5: Histology type distribution (n = 170).

| Histology type                        | n  | %   |
|---------------------------------------|----|-----|
| Invasive ductal carcinoma             | 167| 98.2|
| Invasive lobular carcinoma            | 1  | 0.6 |
| Ductal carcinoma in situ              | 1  | 0.6 |
| Other                                 | 1  | 0.6 |

95%CI 1.19 – 30.73, p = 0.03) were retained in the final fitting model as predictors of premenopausal breast cancer (Table 3).
Table 6: Prevalence of different breast cancer molecular subtypes (n = 170).

| Molecular subtype classification | n  | %  |
|----------------------------------|----|----|
| Luminal A                       | 45 | 26.5 |
| Luminal B                       | 22 | 12.9 |
| HER2 enriched                   | 25 | 14.7 |
| Triple negative                 | 22 | 12.9 |
| Unclassified*                   | 56 | 32.9 |

Luminal A: ER+/PR+, HER2/Neu negative; luminal B: ER+/PR+, HER2/Neu positive; HER2 enriched: ER-/PR-, HER2/Neu positive; triple negative: ER-/PR-, HER2/Neu negative. *Unclassified: any other combination and equivocal HER2/Neu. It is important to note that for the purpose of this study, tumors with equivocal HER2/Neu status were considered "unclassified." In fact, if the IHC result is 3+, the cancer is HER2/Neu positive. If the IHC result is 1+, the cancer is HER2/Neu negative. However, if the result is 2+, the HER2/Neu status is not clear (equivocal) and needs further testing by FISH to clarify the result. Unfortunately, FISH technology is not available in the country.

In our study, the median age of participants was 39 years with 45.9% of them aged below 40 years, aligning with previous studies [14, 16, 17]. On the one hand, population age structure and younger populations in Rwanda and African countries may explain partially the findings. However, age structure may give a false impression that breast cancer patients in Africa are predominantly young [18–21]. On the other hand, breast cancer heterogeneity may also support the hypothesis of BC younger age and aggressive presentation in premenopausal women as seen in this study. Indeed, breast cancer is not a single disease; it is rather a heterogeneous disease with different molecular subtypes behaving differently in clinical presentation, progression, and outcome [12, 22, 23]. Apparently, more aggressive breast cancer subtypes like triple negative or HER2/Neu-enriched tumors are mainly found in black populations and may present early [24–27].

Generally, premenopausal breast cancer is underdocumented. So far, the majority of available studies on breast cancer are conducted on postmenopausal breast cancers and suggest that premenopausal breast cancer may share the same risk factors with postmenopausal breast cancer [28]. However, there are growing evidences that premenopausal breast cancer may be having different risk factors. For example, extremely dense breasts and having a family history of breast cancer appear to be increasing specifically the risk of premenopausal breast cancers [28–30]. Furthermore, obesity and pauciparity seem to have no effect on premenopausal breast cancer while they are found to be increasing postmenopausal breast cancer [31, 32]. However, contrary to the latter findings, our study found an association between history of obesity/overweight in adolescence and early childhood and the developing breast cancer in the premenopausal period.

While our study found no differences in risk factor distribution among different molecular subtypes in premenopausal women with breast cancer, studies on etiologic heterogeneity of breast cancer linking environmental exposures to somatic mutations caused by smoking, exposures to infectious agents, or exposure to other known carcinogens supported the existence of distinct epigenetic profiles of breast cancer in general [22, 25, 33]. In addition, many studies have suggested that estrogen positive premenopausal breast cancer has distinct molecular characteristics compared to postmenopausal cancers and behaves differently with distinct integrin/laminin and EGFR signalling pathways [34–36]. Further studies on this subject are still needed.

Indeed, there are not yet enough evidences to conclude that premenopausal breast cancer is totally different to justify specific treatment guidelines, screening, and early detection strategies [37–39]. Breast cancer heterogeneity has been documented not only among different patients (inter-tumor heterogeneity) but also within each individual tumor (intra-tumor heterogeneity). The existence of different molecular subtypes of breast cancer indicating intratumor heterogeneity creates diagnostic and therapeutic challenges but has improved the classification of breast cancer patients into the low, intermediate, and high risk groups for personalized treatments [36, 40–43].

In our study, the majority of molecular subtypes identified in premenopausal women are estrogen negative molecular subtypes (basal-like and HER2/Neu-enriched). Even if young women with breast cancer are more likely to have genetic predisposition with BRCA1 and BRCA2 mutations, the expression of key biomarkers ER, PR, and HER2/Neu and proliferation markers like Ki67 appears to be different compared to postmenopausal cancers, confirming the above findings [11, 44, 45].

This study had some limitations. As in all case-control studies, we attempted to find correlations between past events and current status. Hence, due to its retrospective nature, there is room for potential recall bias, as there is an increased likelihood that those with outcomes will recall and report the exposure better compared to controls due to subject imperfect memories of past exposure. Furthermore, we may have failed to identify all confounding variables as there is no exhaustive list of probable risk factors for premenopausal breast cancer.

Lastly, we have not been able to conduct further analysis for equivocal HER2/Neu results. In fact, FISH technology is not available in the country. For the purpose of this study, tumors with equivocal HER2/Neu status were considered “unclassified”; this may have increased the number of unclassified tumors.

5. Conclusion

This study identified risk factors for premenopausal breast cancer in Rwanda and stratified them per molecular subtypes. Among the identified risk factors, alcohol intake and obesity/overweight during adolescence/early adulthood can be modified. Interventions targeting alcohol intake and obesity/overweight in young women may decrease the incidence of premenopausal breast cancer. Large-scale studies are still needed, to define whether premenopausal breast cancer is totally different from postmenopausal BC, to justify specific treatment guidelines, screening, and early detection strategies.
Data Availability
The datasets used during the current study are available from the corresponding author on request.

Disclosure
The statements made and views expressed are solely the responsibility of the authors.

Conflicts of Interest
The authors declare that they have no conflict of interests.

Authors’ Contributions
FN designed the study; FN, GB, and JDT performed data extraction and analysis; FN and BR interpreted the results; FN wrote the initial draft. FN, GB, JDT, BR, and SR contributed to subsequent drafts. All authors critically reviewed and approved the final version.

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