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Age at Menarche and Breast Cancer Characteristics in Women in the Democratic Republic of the Congo

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ABSTRACT

Background: Early menarche has been associated with an increased risk of breast cancer, but the relationship remains poorly understood in resource-limited settings. This study aimed to explore the association between age at menarche and breast cancer in the Democratic Republic of the Congo.

Methods: We conducted a cross-sectional analysis of 401 breast cancer patients, assessing their age at menarche and clinical characteristics. Data were analyzed using ANOVA to compare the mean age at menarche across different clinical and histological subtypes, with significance set at $P < 0.05$.

Results: The mean age at menarche was 12.7 ± 3.1 years. Significant differences were observed in age at menarche between tumor subtypes, with earlier menarche associated with aggressive subtypes, such as HER2-positive and triple-negative breast cancer. Women with menarche at age ≤12 years had a higher risk of developing breast cancer, consistent with findings from other populations.

Conclusion: Our study suggests that early menarche may be a key factor in breast cancer risk in a resource-limited setting. Identifying women with early menarche could help prioritize them for targeted public health interventions and early screening, particularly in environments where advanced diagnostic tools are scarce. Further research is needed to validate these findings in larger, longitudinal studies across diverse African populations.

INTRODUCTION

Breast cancer is a major public health concern worldwide, affecting women of all ages. The disease presents with diverse biological and clinical characteristics, often varying by age at diagnosis. Among the various risk factors identified, age at menarche plays a significant role because of its influence on lifetime hormonal exposure. Early menarche, generally defined as the onset of menstruation before the age of 11 or 12, has been associated with an increased risk of breast cancer.[1,2]

Several biological mechanisms explain the relationship between the age at menarche and breast cancer risk. Primarily, early menarche extends a woman's lifetime exposure to hormones such as estrogen and progesterone, which promote the proliferation of mammary cells. This prolonged exposure, combined with an increased number of ovulatory cycles, provides additional opportunities for cell growth and division in breast tissue, thereby increasing the risk of mutations. Furthermore, early menarche is often linked to a higher body mass index

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(BMI) in adolescence, which is an independent risk factor for breast cancer. Conversely, a delayed onset of menarche is associated with a protective effect; several studies indicate that each additional year before menarche is associated with a reduced risk of breast cancer.[1–5]

Other age-related factors also influence breast cancer characteristics and detection. For instance, younger women often have dense breast tissue, which can make mammographic detection more challenging.[7] Additionally, breast cancer in younger women tends to be more aggressive and rapidly progressing, while in older women, it may follow a more indolent course.[8]

Given these variations, the role of age at menarche in breast cancer risk assessment is particularly relevant in tailoring screening and prevention strategies. The evaluation of menarcheal age in clinical settings can help estimate individual risk and inform recommendations for screening intensity and preventive interventions.

Breast cancer manifests with varying radiological and biological characteristics across different age groups. While younger women are more likely to develop aggressive subtypes, such as triple-negative or human epidermal growth factor receptor 2 (HER2)-positive cancers, older women may present with hormone receptor-positive tumors that respond to endocrine therapy.[6] In the Democratic Republic of the Congo (DRC), studies have reported an increasing incidence of breast cancer among both younger and older women, highlighting the need for targeted research and healthcare strategies.[10–14] This study aims to analyze the association between age at menarche and breast cancer characteristics among women of all ages diagnosed with the disease in the DRC. A comprehensive understanding of these relationships could contribute to more effective screening programs and personalized management approaches.

METHODS

This was a cross-sectional study from 2015 to 2023, with multicenter collection. It was carried out among patients followed at the Cliniques Universitaires de Kinshasa (CUK), the Hôpital Général de Kinshasa (formerly Mama Yemo), the Centre d'Imagerie du Congo (CEIMEC), and the Centre Pilote d'Imagerie Médicale Kokolo (CEPIM). The target population included women who had mammograms as part of breast cancer screening during the study period, with associated breast ultrasound when echo-guided microbiopsies were required. The participants were selected using a convenience sampling approach (n=401).

All female patients were eligible for inclusion. Participants were followed for breast cancer within the scope of our study and had undergone mammographic, ultrasound, and immunohistochemical evaluation, with at least one recorded datum for age at menarche. Patients followed for non-cancerous breast pathology, and all male subjects were excluded.

Data collection and acquisition protocol

All mammographic and sonographic examinations were carried out using equipment of various brands, depending on the site. However, all examiners adhered to the same initial protocol to ensure procedural consistency. These examinations were read by a team of experienced radiologists, with multiple interpretations conducted according to established guidelines. Clinical data were collected by directly questioning patients, following a standardized process to ensure uniformity. Echo-guided microbiopsies were performed by radiologists, and the resulting tissue samples were analyzed by a specialized team of pathologists from KU Leuven and Ghent in Belgium, and from the Cliniques Universitaires de Kinshasa. All examiners, regardless of specialty, strictly adhered to the same protocols for sample acquisition and analysis to ensure consistency.

Data processing and analysis

Data were initially entered using Microsoft Excel 2016 and subsequently exported to IBM SPSS Statistics version 21.0 for analysis. For continuous variables following a normal (Gaussian) distribution, descriptive statistics were presented as means ± standard deviation (SD), while categorical variables were expressed as absolute frequencies (n) and percentages (%).

To assess differences in the mean age at menarche across multiple independent groups (e.g., age categories, BI-RADS classifications, histological subtypes, receptor status, and tumor grades), a one-way analysis of variance (ANOVA) was employed. This statistical test is appropriate when comparing the means of a continuous variable between 3 or more independent groups to determine whether at least 1 group mean is significantly different from the others.

ANOVA assumes normality of the dependent variable within groups and homogeneity of variances across groups. In our context, the dependent variable was the age at menarche, and the independent

variables were categorical characteristics related to the clinical, radiological, and histopathological profiles of breast cancer patients.

For each ANOVA test, the F-statistic and corresponding P-value were reported. A P-value of <0.05 was considered statistically significant, indicating that the differences observed among group means were unlikely to have occurred by chance alone. These results are presented in a comprehensive table, showing for each variable: the number of cases (n), the mean age at menarche with standard deviation, the F-value, and the associated P-value. When the ANOVA indicated statistically significant differences between group means (P<0.05), we performed Tukey's Honest Significant Difference (HSD) post-hoc test to determine which specific subgroups differed from each other. This test was chosen because it is appropriate for comparing all possible pairs of group means while controlling for the family-wise error rate. Tukey's HSD is particularly suitable when sample sizes are unequal, as was the case in several of our subgroups. This post-hoc analysis allowed us to identify the precise pairs of clinical or molecular categories (e.g., molecular subtype, histological grade) that were significantly different with respect to the continuous variable (e.g., age at menarche).

RESULTS

A total of 401 patients were recruited for our study, with a mean age of 49.6 ± 13.9 years and a mean age at menarche of 12.7 ± 3.1 years. Most patients were classified as BI-RADS 4. An analysis of variance (ANOVA) was performed to evaluate differences in the mean age at menarche according to various clinical, radiological, and histopathological characteristics of the patients with breast cancer.

Table 1. Mean Age at Menarche by Age Subtypes

Variables	Frequency, n (%) N=401, (%)	Menarche (ans), Mean ± SD	F	P
Age, (X ± SD, 49.6 ± 13.9)			1.147	0.319
<40 years	107(26.7)	13.1 ± 1.5		
41–69 years	246(61.3)	12.5 ± 3.5		
≥70 years	48(12.0)	12.9 ± 2.9		

Age at menarche according to histological type and grade

A significant difference in mean age was observed across histological grades (SBR) (ANOVA: F=3.907, P=0.002). Post-hoc Tukey analysis showed that patients with poorly differentiated tumors (SBR III) were significantly younger than those with well-differentiated tumors (SBR I) (P<0.05). No significant difference was observed between SBR II and the other grades.

Table 2. Comparison of mean age at menarche according to histological type and grade (SBR)

Histological type	Frequency, n (%)	Mean age ± SD (years)	Post-hoc comparison (Tukey HSD)
Adenocarcinoma	36 (9.0)	11.8 ± 1.6	–
Ductal carcinoma	175 (43.6)	12.5 ± 1.8	–
Micropapillary ductal carcinoma	8 (2.0)	12.2 ± 1.3	–
Lobular carcinoma	48 (12.0)	13.8 ± 0.9	Higher than adenocarcinoma (P<0.05)
NOS carcinoma	134 (33.4)	13.2 ± 1.3	–
Carcinoma in situ	15 (3.7)	14.7 ± 3.1	Excluded from post-hoc (small n)
ANOVA test			F=0.990, P=0.452
SBR Grade	Frequency (n, %)	Mean age ± SD (years)	Post-hoc comparison (Tukey HSD)
SBR I (Well differentiated)	23 (5.7)	12.5 ± 2.1	–
SBR II (Moderately differentiated)	171 (42.6)	12.1 ± 3.5	–
SBR III (Poorly differentiated)	207 (51.6)	11.8 ± 2.8	Lower than SBR I (P<0.05)
ANOVA test			F=3.907, P=0.002

Comparison of mean age at menarche according to BI-RADS classification (mammography)

Analysis of variance (ANOVA) showed a statistically significant difference in the mean age across BI-RADS categories on mammography (F=6.812; P=0.017). Post-hoc Tukey HSD testing revealed that patients with BI-RADS 4 lesions were significantly younger compared to those with BI-RADS 3 and 5 (P<0.05). No significant difference was found between BI-RADS 3 and 5 categories.

Table 3. Comparison of mean age according to BI-RADS classification (mammography)

BI-RADS category	Frequency (n, %)	Mean age ± SD (years)	Post-hoc comparison (Tukey HSD)
BI-RADS 3	103 (25.7)	13.3 ± 2.4	Not significantly different
BI-RADS 4	222 (55.4)	12.2 ± 3.4	Lower than BI-RADS 3 and 5 (P<0.05)
BI-RADS 5	76 (18.9)	13.3 ± 2.2	Not significantly different from BI-RADS 3
ANOVA test			F=6.812, P=0.017

Comparison of mean age at menarche across molecular subtypes of breast cancer

A one-way analysis of variance (ANOVA) revealed a statistically significant difference in the mean age across molecular subtypes of breast cancer (F=10.124; P<0.001). Post-hoc analysis using Tukey's Honestly Significant Difference (HSD) test showed that patients with triple-negative breast cancer were significantly younger compared to those with HER2 overexpression and Luminal B HER2-positive subtypes (P<0.01). No significant difference was observed between estrogen receptor (ER)-positive and progesterone receptor (PR)-positive subtypes. Carcinoma in situ did not show statistically significant differences, likely due to the small sample size (Table 4).

Table 4. Comparison of mean age across molecular subtypes of breast cancer

Molecular subtype	Frequency (n, %)	Mean age ± SD (years)	Post-hoc comparison (Tukey HSD)
HER2 overexpression	57 (14.2)	13.7 ± 1.4	Higher than Triple-negative (P<0.01)
ER positive	201 (50.1)	12.2 ± 3.6	Not significant vs PR; lower than Triple-negative (P<0.05)
PR positive	196 (48.9)	12.8 ± 2.5	–
Triple-negative	50 (12.5)	12.0 ± 0.9	Lower than $HER2^+$ and Luminal B (P<0.01)
Luminal B HER2-positive	38 (9.5)	13.7 ± 1.5	Higher than Triple-negative (P<0.01)
ANOVA test			F=9.7, P<0.001

DISCUSSION

Several studies have implicated early menarche as a risk factor for breast cancer; the earlier it occurs, the greater the risk, due to prolonged lifetime exposure to endogenous estrogens.[9–12] In our series, the mean age at menarche was 12.7 ± 3.1 years, which is consistent with findings reported by several other authors.[10–17] However, precise retrospective recall of age at menarche is challenging, particularly among older women in our population, which may limit the accuracy of this variable.

Brinton et *al.* [18] reported a 23% reduction in breast cancer risk in women whose menarche occurred after the age of 15 compared to those before the age of 12. This observation aligns with the biological plausibility that earlier exposure to hormonal cycles, particularly estrogens, may increase the cumulative mitotic activity in mammary epithelial cells, thereby raising the risk of genetic mutations and malignant transformation. During puberty, breast development accelerates, with rapid epithelial proliferation under the influence of endogenous and exogenous estrogens.[19] These hormones can promote tumorigenesis via both receptor-dependent and receptor-independent mechanisms, including errors in DNA replication and sustained mitotic stimulation.[19]

In this regard, our ANOVA analysis revealed significant differences in age at menarche across various clinical and molecular characteristics. Notably, lower mean menarchal age was significantly associated with certain aggressive biological subtypes, including HER2 overexpression (P<0.001), triple-negative breast cancer (P<0.001), and high histological grade (SBR III) tumors (P=0.002). These results support the hypothesis that early menarche may be linked not only to increased risk but also to the development of more biologically aggressive tumor forms.

Some epidemiological studies report a 10–25% increased risk of breast cancer in women who had menarche before the age of 12.[20] According to Indonesia's National Health Research data[20], most women in that setting begin menstruating at age 13, and early menarche (≤12 years) appears to confer a higher risk. In one study, 26.5% of women had menarche at or before 12 years, with a high proportion of those developing breast cancer. However, other authors, such as Endah Zuraidah *et al.*[21] found no significant association between menarche and breast cancer, highlighting the heterogeneity of findings across populations.

Relevance in a resource-limited setting

The implications of these findings are especially critical in low-resource countries such as the DRC, where early detection and personalized care remain limited. Breast cancer is frequently diagnosed at late stages due to constrained access to mammographic

screening, financial barriers, and sociocultural factors delaying medical consultations.

Understanding the association between early menarche and breast cancer risk could aid in the identification of high-risk individuals in such contexts. In the absence of widespread imaging infrastructure, targeted awareness campaigns and low-cost screening approaches (e.g., clinical breast exams and education on self-examination) could be directed toward women with known early menarche.

Moreover, modifiable factors influencing early puberty, such as childhood nutrition and increasing obesity, warrant investigation in the Congolese context. Evidence suggests that improved nutrition may be leading to an earlier onset of puberty, possibly raising future breast cancer incidence. Community-based nutritional education and health promotion strategies may help mitigate this trend.

Treatment disparities also pose a major challenge. While high-income countries tailor therapies based on immunohistochemistry and molecular profiling, such approaches are often inaccessible in the DRC. Consequently, patients frequently receive generalized treatment protocols that may not be optimal. Further research is needed to evaluate whether the associations between menarcheal age and tumor subtypes observed in Western populations hold true in African settings.

Despite its limitations, including the retrospective collection of self-reported menarcheal age, our study remains one of the few to explore this relationship in a Central African population. This underscores the need for larger, prospective studies to elucidate hormonal and genetic risk factors relevant to breast cancer in sub-Saharan Africa.

Ultimately, while the biological plausibility of the link between early menarche and breast cancer is widely accepted, findings remain variable. More research stratified by age and tumor characteristics is essential to improve our understanding and guide prevention and treatment strategies adapted to local realities.

Study limitations

This study has several limitations. First, its retrospective nature and reliance on anamnesis data, particularly age at menarche and menopause, may introduce recall bias, especially among older participants. Second, as the sample is hospital-based, it may not be representative of the general population, thus limiting the generalizability of the findings.

CONCLUSION

This study highlights the potential association between early menarche and an increased risk of breast cancer in a resource-limited setting. The findings suggest that early menarche may serve as an important factor for identifying women at higher risk of developing breast cancer, particularly those with aggressive tumor subtypes. Given the challenges of early detection in low-resource environments like the DRC, targeting high-risk groups, such as women with early menarche, could improve early screening and prevention efforts.

Further research, including larger, longitudinal studies, is needed to understand better the role of hormonal and genetic factors in breast cancer development in sub-Saharan African populations. Ultimately, the implementation of cost-effective interventions and public health campaigns, alongside improvements in healthcare infrastructure, could contribute to better breast cancer management and outcomes in resource-constrained settings.

ETHICAL CONSIDERATIONS

Data were collected, processed, and presented in accordance with the Helsinki recommendations. Patient anonymity and confidentiality were respected. Ethics committee approval code: cirimed-/ETH/008/024.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY

The data supporting the findings of this study are available upon request.

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