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ORIGINAL RESEARCH

Association of Reproductive Factors with Breast Cancer Biological Characteristics in Older Women in the Democratic Republic of the Congo

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Abstract

Introduction: Reproductive factors, including age at menarche, age at menopause, and parity, are established determinants of breast cancer risk. However, their relationships with tumor biological characteristics remain insufficiently characterized in older women, particularly in sub-Saharan Africa. This study investigated the associations of age at menarche, age at menopause, and parity with breast cancer characteristics and the *Ki-67* proliferation index among women aged ≥60 years in the Democratic Republic of the Congo (DRC). **Methods:** A prospective, multicenter analytical study was conducted from 2015 to 2023 at four medical centers in Kinshasa, DRC. Women aged ≥60 years with histologically confirmed breast cancer who underwent mammographic, ultrasonographic, histopathological, and immunohistochemical evaluation and had available reproductive history were included. Patients with nonmalignant breast diseases and male patients were excluded. Clinical, imaging, histopathological, and immunohistochemical data were collected and analyzed using IBM SPSS Statistics version 21.0. Associations between categorical variables were assessed using the Pearson chi-square test. Correlations between reproductive factors and *Ki-67* expression were also evaluated. **Results:** The study included 91 women with a mean age of 68.6 ± 5.4 years. The mean ages at menarche and menopause were 13.4 ± 1.6 and 50.5 ± 4.6 years, respectively. Most lesions were classified as BI-RADS 4 (58/91, 63.7%), followed by BI-RADS 5 (19/91, 20.9%) and BI-RADS 3 (15/91, 16.5%). Age at menopause was higher among women with BI-RADS 4 and BI-RADS 5 lesions than among those with BI-RADS 3 lesions. Age at menarche differed significantly across tumor biological subgroups, including estrogen receptor-positive tumors (13.1 ± 1.3 years; p = 0.047), HER2-overexpressing tumors (13.8 ± 1.3 years; p = 0.044), triple-negative tumors (12.9 ± 2.1 years; p = 0.004), and triple-positive tumors (13.6 ± 0.9 years; p = 0.002). Significant differences in age at menarche were also observed according to histological type (p = 0.039) and histological grade (p = 0.023). Age at menopause showed a moderate inverse correlation with *Ki-67* expression, whereas age at menarche showed a strong linear correlation that did not reach statistical significance. **Conclusion:** Among older women with breast cancer in the DRC, age at menarche was associated with several histopathological and tumor biological characteristics, while age at menopause showed an inverse relationship with *Ki-67* expression. These findings suggest that reproductive timing may be associated with tumor biology in older women. Larger, well-designed prospective studies with comprehensive and standardized assessment of reproductive history are needed to validate these findings.

Keywords: breast cancer, older women, age at menarche, age at menopause, parity; *Ki-67*, reproductive factors

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Introduction

Breast cancer is the most commonly diagnosed cancer and a leading cause of cancer-related mortality among women worldwide. Its burden is particularly concerning in sub-Saharan Africa, where breast cancer represents one of the major causes of cancer morbidity and mortality among women and increasingly contributes to the overall cancer burden in the region [1-3]. In the Democratic Republic of the Congo (DRC), several studies have reported an increasing burden of breast cancer among women of different age groups, as well as cases occurring in men [4-8].

Breast cancer is a heterogeneous disease resulting from complex interactions among genetic, hormonal, reproductive, environmental, and lifestyle-related factors. Established reproductive risk factors include early age at menarche, late age at menopause, nulliparity, and certain patterns of reproductive and hormonal exposure. Early menarche and late menopause are thought to increase breast cancer risk by extending the duration of exposure to endogenous ovarian hormones, particularly estrogen and progesterone [9-12]. Epidemiological evidence suggests that breast cancer risk increases with earlier menarche and later menopause; approximately each one-year delay in menarche has been associated with a reduction in breast cancer risk, whereas each one-year delay in menopause has been associated with an increase in risk [13, 14].

In addition to their potential role in breast cancer development, reproductive factors may be related to the biological characteristics of established tumors. Breast cancer comprises multiple histological and molecular subtypes with distinct biological behavior, prognosis, and treatment responses. Histologically, invasive ductal carcinoma and invasive lobular carcinoma are among the most common forms [15]. Molecular and immunohistochemical characterization commonly incorporates the expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (*HER2*), which are important determinants of tumor classification and therapeutic decision-making [16].

The *Ki-67* proliferation index is another important biomarker used to characterize tumor proliferative activity. In combination with hormone receptor and *HER2* status, *Ki-67* may contribute to the distinction between luminal breast cancer subtypes and provide prognostic information. In general, luminal A tumors are characterized by hormone receptor positivity, *HER2* negativity, and relatively low proliferative activity, whereas luminal B tumors generally exhibit higher proliferative activity and/or *HER2* positivity [17]. The interpretation of *Ki-67* should, however, be considered in the context of the other clinicopathological and immunohistochemical characteristics of the tumor.

Although the associations between reproductive factors and breast cancer risk have been extensively investigated in the general female population, evidence regarding their relationship with tumor biological characteristics in older women remains limited. This knowledge gap may be particularly relevant in sub-Saharan Africa, where differences in reproductive patterns, demographic characteristics, access to screening, and patterns of breast cancer presentation may influence disease characteristics.

Therefore, this study aimed to investigate the associations of age at menarche, age at menopause, and parity with clinicopathological and biological characteristics of breast cancer, as well as their relationships with the *Ki-67* proliferation index, among women aged ≥60 years in the DRC.

Materials and Methods

Study design, period, and setting

This prospective, multicenter analytical study was conducted between 2015 and 2023 in four medical centers in Kinshasa, Democratic Republic of the Congo (DRC): the Cliniques Universitaires de Kinshasa (CUK), Hôpital Général de Kinshasa (formerly Mama Yemo), Centre d'Imagerie du Congo (CEIMEC), and Centre Pilote d'Imagerie Médicale Kokolo (CEPIM).

The study population comprised women aged ≥60 years who underwent breast imaging and subsequent diagnostic evaluation for suspected or confirmed breast cancer during the study period. Mammography was performed as the primary imaging examination, with breast ultrasonography performed when clinically indicated, particularly for further characterization of lesions and guidance of ultrasound-guided core biopsy. Eligible participants were included using a convenience sampling approach.

Eligibility criteria

Women aged ≥60 years with breast cancer who were evaluated at one of the participating centers during the study period were eligible for inclusion. For the purposes of this study, women aged ≥60 years were considered older women, consistent with the age threshold used in the study protocol and the World Health Organization classification [18].

To be included, participants were required to have undergone mammographic and/or breast ultrasonographic evaluation, histopathological assessment, and immunohistochemical examination, and to have available information on at least age at menarche and parity.

Patients with breast pathologies other than breast cancer and male patients were excluded from the analysis.

Data collection and diagnostic procedures

Clinical and reproductive data were collected through direct interviews conducted by the examining physician. Information collected included age, age at menarche, age at menopause, parity, and relevant clinical characteristics.

Mammographic and ultrasonographic examinations were performed at the participating centers using imaging equipment from different manufacturers. All examinations were interpreted by experienced radiologists, with multiple readings performed according to institutional practice. Mammographic findings were classified according to the Breast Imaging Reporting and Data System (BI-RADS).

Ultrasound-guided core biopsies were performed by

experienced radiologists when indicated. Histopathological and immunohistochemical examinations were subsequently performed to establish the diagnosis and characterize tumor biological features. Pathological assessments were conducted by experienced pathologists from the University Hospitals Leuven and Ghent in Belgium and the University Clinics of Kinshasa, DRC.

Immunohistochemical assessment included evaluation of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (*HER2*), and the *Ki-67* proliferation index. Tumors were categorized according to their immunohistochemical profiles based on the available receptor and proliferation-marker results.

Data management and statistical analysis

Data were initially entered into Microsoft Excel 2016 and subsequently exported to IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) for statistical analysis.

Continuous variables were summarized using means and standard deviations when approximately normally distributed. Categorical variables were presented as absolute frequencies and percentages, with confidence intervals where appropriate.

The Pearson chi-square test was used to assess associations between categorical variables. Associations between reproductive factors and the *Ki-67* proliferation index were evaluated using correlation analysis. The specific correlation coefficient should be reported according to the distribution and measurement characteristics of the variables. A two-sided p value <0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patient confidentiality and anonymity were maintained throughout data collection, analysis, and reporting. Personal identifiers were not included in the analytical dataset or study reports.

Results

A total of 91 women aged ≥60 years with breast cancer were included in the study. The mean age of the participants was 68.6 ± 5.4 years, while the mean ages at menarche and menopause were 13.4 ± 1.6 and 50.5 ± 4.6 years, respectively (Table 1).

Regarding mammographic findings, BI-RADS 4 was the most frequent category (58/91, 63.7%), followed by BI-RADS 5 (19/91, 20.9%) and BI-RADS 3 (15/91, 16.5%). Age at menopause differed significantly across BI-RADS categories (p = 0.033), with higher mean values among women with BI-RADS 4 and BI-RADS 5 lesions than among those with BI-RADS 3 lesions. No significant difference in age at menarche was observed across BI-RADS categories (p = 0.138) (Table 1).

Age at menarche differed significantly according to histological type (p = 0.039) and histological grade (p = 0.023) (Table 1). The mean age at menarche was 12.60 ± 1.6 years among women with adenocarcinoma, 13.42 ± 1.4 years among those with ductal carcinoma, and 14.33 ± 0.58 years among those with micropapillary ductal carcinoma. No significant associations were observed between age at menopause and histological type (p = 0.117) or histological grade (p = 0.673).

Significant differences in age at menarche were also observed according to several immunohistochemical characteristics (Table 1). The mean age at menarche was 13.8 ± 1.3 years among women with *HER2*-positive tumors (p = 0.044), 13.1 ± 1.3 years among those with ER-positive tumors (p = 0.047), 12.9 ± 2.1 years among those with triple-negative tumors (p = 0.004), and 13.6 ± 0.9 years among those with triple-positive tumors (p = 0.002). In contrast, no statistically significant association was observed between PR status and age at menarche (p = 0.091). None of the evaluated immunohistochemical characteristics was significantly associated with age at menopause (Table 1). Age at menarche also differed significantly according to tumor invasiveness (p = 0.005), whereas age at menopause did not (p = 0.573) (Table 1).

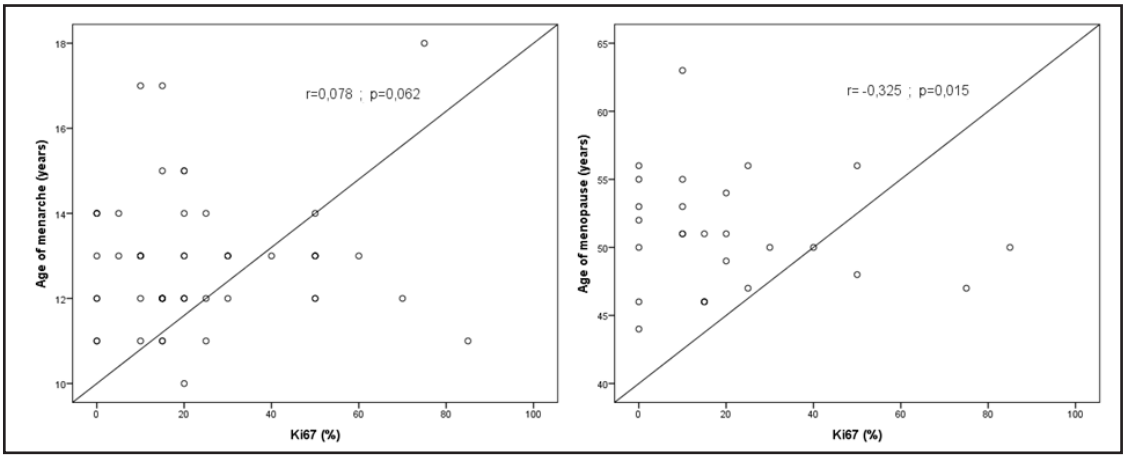

Figure 1. Correlations of Age at Menarche and Age at Menopause with the *Ki-67* Proliferation Index among Women Aged ≥60 Years with Breast Cancer. (A) Correlation between age at menarche and *Ki-67*. (B) Correlation between age at menopause and *Ki-67*.

Table 1. General Characteristics of the Study Population and Associations of Reproductive Age Variables with Clinicopathological Characteristics (N = 91)

Variables	n (%)	Age at menarche (years)	***p*-value**	Age at menopause (years)	***p*-value**
		Mean ± SD		Mean ± SD	
Age					
Overall age	91 (100)	68.6 ± 5.4	—	—	—
Mammographic classification					
BI-RADS 3	15 (16.5)	14.3 ± 1.2	0.138	48.2 ± 3.2	0.033
BI-RADS 4	58 (63.7)	13.33 ± 1.5	—	53.6 ± 2.5	—
BI-RADS 5	19 (20.9)	13.8 ± 1.7	—	53.4 ± 5.7	—
Histological type					
Adenocarcinoma	17 (18.7)	12.60 ± 1.6	0.039	54.3 ± 6.6	0.117
Ductal carcinoma	36 (39.6)	13.42 ± 1.4	—	50.3 ± 3.7	—
Micropapillary ductal carcinoma	3 (3.3)	14.33 ± 0.58	—	50.3 ± 8.02	—
Lobular carcinoma	2 (2.2)	13	—	Not available	—
NOS carcinoma	18 (19.8)	13.6 ± 1.5	—	50.1 ± 3.9	—
Immunohistochemical characteristics					
HER2-positive	20 (21.9)	13.8 ± 1.3	0.044	50.1 ± 4.3	0.571
ER-positive	55 (60.4)	13.1 ± 1.3	0.047	51.5 ± 4.8	0.39
PR-positive	57 (62.6)	13.2 ± 1.5	0.091	50.5 ± 4.9	0.616
Triple-negative	11 (12.1)	12.9 ± 2.1	0.004	50.4 ± 5.6	0.57
Triple-positive	13 (14.3)	13.6 ± 0.9	0.002	50.3 ± 5.4	0.566
Tumor invasiveness					
Invasive carcinoma	—	13.15 ± 1.4	0.005	50.88 ± 4.8	0.573
Carcinoma in situ	—	14.67 ± 3.1	—	47.00 ± 4.6	—
Histological grade					
SBR I (well differentiated)	5 (5.5)	12.20 ± 0.45	0.023	54.0 ± 4.6	0.673
SBR II (moderately differentiated)	62 (68.1)	13.15 ± 1.6	—	50.4 ± 4.6	—
SBR III (poorly differentiated)	24 (26.4)	13.86 ± 1.5	—	51.30 ± 5.7	—

BI-RADS, Breast Imaging Reporting and Data System; ER, estrogen receptor; PR, progesterone receptor; *HER2*, human epidermal growth factor receptor 2; NOS, not otherwise specified; SBR, Scarff–Bloom–Richardson grading system; SD, standard deviation.

The correlations between reproductive timing and the *Ki-67* proliferation index are presented in Figure 1. Age at menopause showed a moderate inverse correlation with *Ki-67* expression, whereas age at menarche showed a positive linear correlation with *Ki-67* that did not reach statistical significance (Figure 1). The corresponding correlation coefficients and p-values are presented in the figure.

Discussion

This study investigated the relationships between reproductive timing and clinicopathological and biological characteristics of breast cancer among women aged ≥60 years in the Democratic Republic of the Congo (DRC). The principal findings were that age at menarche was significantly associated with several tumor characteristics, including histological type, histological grade, ER status, *HER2* status, triple-negative and triple-positive profiles, and tumor invasiveness. Age at menopause was significantly associated with BI-RADS category but was not significantly associated with the evaluated histological or immunohistochemical characteristics. In addition, age at menopause showed a moderate inverse correlation with *Ki-67* expression, whereas the association between age at menarche and *Ki-67* did not reach statistical significance.

Age at menarche and breast cancer characteristics

Early menarche is a well-established risk factor for breast cancer, generally attributed to a longer cumulative exposure to endogenous ovarian hormones over the reproductive lifespan [9-12]. Previous epidemiological studies have reported an inverse relationship between age at menarche and breast cancer risk. Brinton et al. reported a substantially lower risk among women whose menarche occurred at a later age compared with those who experienced menarche at a younger age [19]. The mean age at menarche in our study was 13.4 ± 1.6 years, which is broadly comparable with values reported in previous populations [10-18].

In the present study, however, the relevance of age at menarche extended beyond breast cancer risk itself. Significant differences were observed according to histological type and grade, as well as several

immunohistochemical characteristics. In particular, women with triple-negative tumors had a lower mean age at menarche than the other tumor subgroups. Significant differences were also observed among women with ER-positive, *HER2*-positive, and triple-positive tumors. These findings may indicate that reproductive timing is related not only to the occurrence of breast cancer but also to the biological heterogeneity of tumors diagnosed in older women.

The biological plausibility of such associations is supported by the role of endogenous hormones in mammary epithelial proliferation. Estrogen promotes proliferation of mammary epithelial cells through estrogen receptor-mediated signaling and may increase the number of cellular divisions during which DNA replication errors and other genomic alterations can occur. Estrogen metabolites may also contribute to carcinogenesis through mechanisms involving oxidative stress and DNA damage [20, 21]. Nevertheless, these mechanisms should be interpreted cautiously in the context of the present study because the observed associations do not establish a causal relationship between age at menarche and tumor phenotype.

The association between early menarche and breast cancer risk has not been entirely consistent across populations. Some epidemiological studies have reported increased breast cancer risk among women with menarche before 12 years of age [22], whereas other studies have failed to demonstrate a significant association [23]. Differences in study populations, sample size, study design, reproductive patterns, and methods of assessing age at menarche may partly explain these discrepancies. Such differences are particularly relevant in the present study because reproductive history was obtained retrospectively from older women.

Age at menopause and BI-RADS classification

Later menopause is also recognized as a risk factor for breast cancer, presumably because it extends lifetime exposure to endogenous ovarian hormones [19]. Previous epidemiological evidence suggests that breast cancer risk increases with increasing age at menopause, whereas earlier menopause may have a protective effect.

In our study, women with BI-RADS 4 and BI-RADS 5 lesions had higher mean ages at menopause than women with BI-RADS 3 lesions, and the difference was statistically significant. This finding is consistent with the biological rationale that prolonged exposure to endogenous hormones may contribute to breast carcinogenesis. However, BI-RADS categories represent radiological assessments of the likelihood of malignancy rather than biological or molecular tumor subtypes. Therefore, the observed association should not be interpreted as evidence that age at menopause determines mammographic lesion category.

The lack of significant associations between age at menopause and most histological and immunohistochemical characteristics in our study may also reflect the relatively small sample size and limited statistical power. In addition, menopausal age is influenced by genetic, nutritional, environmental, and reproductive factors, which were not comprehensively assessed in the present study.

Reproductive timing and Ki-67 expression

An important finding was the moderate inverse correlation between age at menopause and *Ki-67* expression. *Ki-67* is a marker of cellular proliferation and is commonly used as an indicator of proliferative activity in breast tumors. The observed inverse relationship may suggest that reproductive timing is related to proliferative characteristics in breast cancer among older women. However, the underlying biological mechanisms remain uncertain.

The relationship between age at menarche and *Ki-67* was positive and linear but did not reach statistical significance. The absence of statistical significance should be interpreted cautiously, particularly given the limited sample size. A lack of statistical significance does not necessarily indicate the absence of a biological association; rather, the study may have had insufficient power to detect a modest effect. Larger studies with standardized *Ki-67* assessment are therefore required to clarify these relationships.

Strengths and limitations

The principal strength of this study is its focus on an understudied population of women aged ≥60 years in the DRC. Older women are frequently underrepresented in clinical research, and data concerning the relationship between reproductive history and breast tumor biology in sub-Saharan African populations remain limited. The multicenter design and incorporation of imaging, histopathological, and immunohistochemical data also provide a multidimensional assessment of tumor characteristics.

Several limitations should be considered. First, the sample size was relatively small, which limits statistical power and the precision of the observed associations. Second, reproductive information, particularly age at menarche and age at menopause, was obtained retrospectively and may therefore be affected by recall error. This limitation may be particularly relevant among older participants. Third, the use of a convenience sample may limit the generalizability of the findings to the broader population of older women with breast cancer in the DRC. Fourth, potential confounding factors, including family history, body mass index, breastfeeding history, age at first pregnancy, use of exogenous hormones, and other socioeconomic or lifestyle factors, were not comprehensively incorporated into the analysis. Finally, multiple comparisons were performed, increasing the possibility of chance findings. The results should therefore be regarded as exploratory and hypothesis-generating rather than definitive.

Despite these limitations, the findings provide preliminary evidence that reproductive timing may be associated with selected biological and clinicopathological characteristics of breast cancer in older women in the DRC. These observations support the need for larger, adequately

powered studies incorporating standardized reproductive histories, pathological assessment, and multivariable analyses to determine whether these associations persist after adjustment for potential confounders.

In conclusion, in this multicenter study of women aged ≥60 years with breast cancer in the DRC, age at menarche was associated with several histopathological and immunohistochemical characteristics, whereas age at menopause was associated with BI-RADS category and showed a moderate inverse correlation with *Ki-67* expression. Because of the small sample size, retrospective assessment of reproductive history, and potential for confounding and multiple-comparison effects, these findings should be interpreted as preliminary. Larger prospective studies with standardized assessment of reproductive factors and tumor biomarkers are warranted to confirm these associations and clarify their clinical and biological significance.

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All authors contributed to the conception, preparation, and writing of the manuscript. TKM performed the data processing and statistical analysis. All authors reviewed and approved the final version of the manuscript.

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