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Risk factors of early-onset breast cancer: A case-control study in Eastern Morocco

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ABSTRACT

Background and aim: Breast cancer (BC) is the most common malignancy among women worldwide and a growing concern in low- and middle-income countries. In Morocco, BC occurs at younger ages compared to Western settings and is often aggressive, advanced at diagnosis, and associated with poorer survival. These challenges are particularly marked in Eastern Morocco, where socio-economic disparities and limited health-care access hinder early detection. This study aimed to identify key risk factors for BC among women under 40 years old in this region.

Methods: A case-control study included 140 women (70 cases with BC and 70 matched controls without cancer) recruited from the Reproductive Health Reference Center (RHRC) in Taza between 2020 and 2024. Data on socio-demographic, reproductive, gynecological, family, and behavioral factors were collected retrospectively from medical records. Logistic regression was used to estimate adjusted odds ratios (AOR) and 95% confidence intervals (CI).

Results: The mean age was similar between cases (33.7 ± 5.2 years) and controls (34.5 ± 3.7 years). Early menarche (< 12 years) was strongly associated with increased BC risk (AOR = 5.70; 95% CI: 1.40–23.24). Late first pregnancy (≥ 35 years) also significantly elevated risk (AOR = 5.01; 95% CI: 1.32–18.95). A positive family history of BC emerged as an independent predictor (AOR = 3.92; 95% CI: 1.71–8.95). In contrast, parity showed a protective effect (AOR = 0.31; 95% CI: 0.10–0.95), while oral contraceptive use demonstrated non-significant trends. No participant reported tobacco or alcohol use.

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Conclusion: Early menarche, late first pregnancy, and family history are major risk factors for early-onset BC in Eastern Morocco, whereas parity appears protective. These findings highlight the importance of culturally adapted prevention and early detection strategies. (www.actabiomedica.it)

Key words: breast cancer, young women, risk factors, case-control

Introduction

Breast Cancer (BC) is currently the most frequently diagnosed cancer among women worldwide and represents the leading cause of cancer-related death in women (1). Globally, its incidence is rising steadily due to demographic transitions, expanding screening practices, and rapid environmental and societal changes (2). While most cases occur in postmenopausal women over 50, early-onset breast cancer is defined as a diagnosis before the age of 40 years (<40 years) (3,4). These early-onset forms of BC are particularly concerning: they are characterized by increased biological aggressiveness, frequent diagnosis delays, rapid metastasis, and lower net survival—largely due to the prevalence of treatment-resistant molecular subtypes (5,6). The risk of BC derives from multiple factors—including hormonal, reproductive, behavioral, genetic, nutritional, environmental, occupational, radiological exposures, and contacts with endocrine-disrupting chemicals (EDCs) (7–9). However, in younger women, hormonal, reproductive, and genetic factors are particularly predominant. Factors such as early menarche, nulliparity, a late first pregnancy, and the absence of prolonged breastfeeding increase the risk. These factors are linked to prolonged exposure to endogenous oestrogens and delayed complete differentiation of breast tissue (10–12). Lifestyle behaviors such as smoking, alcohol consumption, sedentary lifestyle, and obesity also appear to increase vulnerability in this age group (7,13). In addition, genetic predisposition, particularly mutations in the BRCA1 and BRCA2 genes, are key factor in early-onset BC (14). In contrast, other factors, such as postmenopausal obesity or hormone replacement therapy, are more relevant in older women (15). From a public health standpoint, this distinction is vital. Conventional screening strategies, such as mammography, are less effective or applicable for younger women (16), making the identification of modifiable risk factors even more critical. Prevention requires understanding and targeting risk determinants that are actionable within local contexts (17). In Morocco, BC is the most common cancer among women, with a notable portion of cases diagnosed at younger ages compared to Western countries (18). Regional disparities further influence the exposure and impact of risk factors. The Taza region in Eastern Morocco exemplifies such variations: it is geographically mountainous and relatively isolated, with a predominantly rural population, limited healthcare access, lower educational attainment, and cultural norms affecting reproductive trajectories (19–21). These conditions influence age at marriage, parity, breastfeeding practices, and access to education and screening, all of which shape BC risk. Limited availability of organized screening and awareness programs further exacerbates late-stage diagnoses in this region (18,20). These structural and cultural conditions justify the focus on this region, as they highlight the need for prevention and early detection strategies tailored to local socio-economic and geographic realities rather than extrapolated from Western or urban settings (17,22). Hence, this case-control study aims to identify BC risk factors in women under 40 in the Taza region, to inform tailored prevention, awareness, and early detection strategies adapted to local realities. This approach seeks both to fill a critical evidence gap and to contribute to reducing the BC burden and improving survival among young Moroccan women.

Patients and Methods

Study design and setting

This retrospective case–control study was conducted at the Reproductive Health Reference Center (RHRC) in Taza, Eastern Morocco, between January 2020 and December 2024. The RHRC represents the second level of referral within the healthcare system, receiving women referred from primary health centers (level 1) for further diagnostic evaluation and specialized reproductive and breast health care. Diagnostic and record-keeping procedures at the RHRC are standardized, ensuring consistent and reliable data for research purposes.

Study population

The study population consisted of 140 women under 40 years of age, including 70 cases and 70 controls. Cases were defined as women under 40 years with a recent histopathological diagnosis of breast cancer recorded at the RHRC during the study period and residing within the center's catchment area. Women with incomplete records for key study variables—such as reproductive history, hormonal exposure, or family history—or with a previous history of invasive cancer were excluded. Controls were selected from women of the same age range who were referred to the RHRC for suspected breast pathology but were ultimately confirmed to be cancer-free after a complete diagnostic work-up, including repeated clinical examinations, breast imaging (ultrasound ± mammography as indicated), and histological assessment when required, according to the BIRADS classification. Controls with incomplete medical files or a past diagnosis of cancer were excluded from the study. To minimize selection bias, controls were drawn from the same referral pathway as cases. Negative diagnoses were confirmed independently by gynecologists, radiologists, and pathologists. Each case was matched to one control in a 1:1 ratio, according to age (±2 years) and, whenever possible, place of residence (urban or rural), to account for potential environmental and socioeconomic influences. This matching procedure was intended to reduce both selection and misclassification biases. Because of the retrospective design and the limited number of breast cancer cases in this age group, all eligible cases identified during the study period were included, resulting in 70 cases matched to 70 controls. No priori sample size calculation or power analysis was performed, as the study was exhaustive.

Data collection

Data were collected systematically from medical records using a standardized abstraction form. Extracted information included sociodemographic characteristics (age, place of residence, occupation, and health insurance status); reproductive and gynecological history (age at menarche, parity, age at first full-term pregnancy, and menstrual regularity); hormonal exposures (use and duration of oral contraceptives and hormone replacement therapy); personal and family medical history (presence of benign breast disease and first-degree family history of breast or ovarian cancer); and behavioral factors (tobacco and alcohol use). Certain potentially relevant variables—breast density, breastfeeding history, and physical activity level—were not available in routine clinical records. Their absence is recognized as a limitation inherent to the retrospective nature of the study and highlights priorities for future prospective data collection. To ensure data quality, identical extraction procedures were applied for cases and controls, and two independent investigators verified the accuracy of data entry. The use of matched controls from the same diagnostic stream and the confirmation of diagnoses by specialists reduced the risk of selection and classification bias. Missing data were minimal and were addressed using complete-case analysis.

Operational definitions

Early-Onset BC

Early-onset BC refers to BC diagnosed in women younger than 40 years. This cut-off is widely used in epidemiological and clinical research, as BC in this age group tends to present with more aggressive biology, advanced stage at diagnosis, and poorer outcomes compared with older women (4,23).

Health insurance

In Morocco, health insurance is organized into several schemes reflecting socio-economic diversity. RAMED/AMO-Tadamon offers free or subsidized care to economically disadvantaged groups. CNOPS covers public sector employees and their families, while CNSS serves private sector employees through contributions. Since the merger of social security funds, CNSS now manages the system (24). Two types of Compulsory Health Insurance (AMO) exist: a paid AMO (AMO-Achamil) for formal workers and self-employed individuals, and a non-paying AMO (AMO-Tadamon), where the State pays contributions for vulnerable households based on a vulnerability score (HS), which replaced RAMED (25).

Family history of BC

Family history of BC refers to the presence of this disease among first-degree relatives (mother, sister, daughter), and sometimes extended to second-degree relatives (aunt, grandmother). Its presence is associated with an increased individual risk, particularly when the relative was diagnosed at a young age or when multiple cases occur within the same family line (26,27).

Early menarche

Early menarche is defined as menarche before the age of 12 years, a well-established risk factor for BC. indeed, each one-year earlier onset of menarche is associated with a 5–9% higher risk of BC (28).

Late pregnancy

Late pregnancy refers to the occurrence of a first full-term childbirth at the age of 35 years or older. Epidemiological evidence shows that postponing the first childbirth beyond this age is associated with a higher risk of BC compared with earlier pregnancies (23).

Ethical considerations

The study received approval from the ethics committee under code CERBO.REF.01.2025, dated 11 June 2025. Data collection was conducted with respect for patient confidentiality and anonymity, without direct contact with the participants. All necessary measures were taken to protect personal information in accordance with the ethical principles outlined in the Declaration of Helsinki (29).

Data analysis

Extracted data were entered and analyzed using statistical software (SPSS version 22). Descriptive analyses were performed to characterize the study population, followed by univariate and multivariate logistic regression analyses to identify independent risk factors while adjusting for confounding variables. Results were expressed as odds ratios (OR) with 95% confidence intervals. A p-value < 0.05 was considered statistically significant.

Bias control

Selection bias was minimized by recruiting both cases and controls from the same source population—women referred to the Reproductive Health Reference Center (RHRC) from primary health facilities within the same catchment area. This design ensured comparability in referral pathways and diagnostic access. Cases were defined as women with a recent histopathological diagnosis of breast cancer, whereas controls were those with negative clinical and imaging assessments (ultrasound ± mammography) confirmed by specialists, thereby reducing selection and misclassification biases. Information bias was limited by relying exclusively on medical records, avoiding recall bias and ensuring that exposure data preceded the diagnosis. Data were extracted using standardized forms, and only complete records on core variables (sociodemographic, reproductive, hormonal, familial, and behavioral factors) were included. Confounding was addressed through the inclusion of key covariates identified in the literature and adjusted for using multivariable logistic regression. Data reliability was reinforced through double data entry, internal consistency checks, and independent validation of extracted variables. Despite these precautions, the possibility of residual confounding or information

bias inherent to retrospective studies cannot be entirely excluded.

Results

Characteristics of the participants

The main socio-demographic characteristics of the study population are summarized in Table 1. The mean age of the participants was comparable between the two groups: 33.66 ± 5.19 years for the cases and 34.49 ± 3.71 years for the controls. Regarding place of residence, 30% of women with BC lived in rural areas compared to 18.6% in the control group. Conversely, urban residence was more frequent among controls (31.4%) than among cases (20%). In terms of professional status, the majority of women in both groups were housewives, accounting for 48.6% of the cases and 45% of the controls, respectively. Only a small proportion were employed (5% of controls and 1.4% of cases). Concerning health insurance coverage, a large proportion of the participants were affiliated with Ramed or AMO-Tadamoun, representing 45% of cases and 35.7% of controls. Coverage through CNOPS or CNSS was reported in 14.3% of cases, but in only 5% of controls.

Gynecological, Reproductive, Hormonal, and Behavioral Risk Factors

Regarding gynecological, reproductive and behavioral risk factors, Table 2 presents their distribution among participants. Early menarche was significantly more frequent among women with BC (9.3%) compared to controls (2.1%), with a p-value of 0.08. Marital status did not differ significantly between the two groups; 76.4% of participants were married (p = 0.319). Most women reported having a regular menstrual cycle (83.6%), with no statistically significant difference between cases and controls (p = 0.820). Regarding reproductive history, parity was significantly associated with BC; 17.1% of cases had never been pregnant compared to only 5.7% of controls (p = 0.001). Late first pregnancy (≥ 35 years) was also more frequent among women with BC (8.6%) compared to controls (2.9%), with a statistically significant association (p = 0.034). The use of oral contraception was significantly more common among controls (34.3%) than among cases (20%) (p = 0.001). Although long-term use (more than 10 years) appeared slightly more frequent among cases (6.4%) than controls (4.3%), this difference was not statistically significant (p = 0.076). Hormone replacement therapy was rarely reported in the sample (1.4%) and showed no association with cancer status (p = 1.000). Personal history of benign breast disease was present in 3.6% of participants and was not significantly associated with BC (p = 0.172). The main reported types included mastosis, phyllodes tumors, and fibroadenomas. Family history of cancer was reported by 22.9% of BC cases compared to 11.4% of controls, showing a statistically significant association (p = 0.004). None of the participants reported current or past tobacco or alcohol consumption.

Risk Factors Associated with BC

In the bivariate analysis, early menarche was significantly associated with BC risk (COR =5.09; 95%

Table 1. Socio-demographic of participants.

Variables		Breast cancer		
		Cases	Controls	Total
Mean age		33.66 ± 5.19	34,49 ± 3,71	
Residence	Rural	18,6%	30%	48,6%
	Urban	31,4%	20%	51,4%
Patient's profession	Housewife	45%	48,6%	93,6%
	Worker	5%	1,4%	6,4%
Health insurance	Ramed/Amo-Tadamon	35,7%	45%	80,7%
	CNOPS/CNSS	14,3%	5%	19,3%

Table 2. Gynecological, Reproductive, Hormonal, and Behavioral Risk Factors.

Variables		Breast cancer			p-value
		Cases	Controls	Total (%)	
Early menarche	No	40,7	47,9	88,6	0,003
	Yes	9,3	2,1	11,4	
Marital status	Single	13,6	10	23,6	0,319
	Married	36,4	40	76,4	
Menstrual cycle	Regular	41,4	42,1	83,6	0,820
	Irregular	8,6	7,9	16,4	
Parity	No	17,1	5,7	22,9	0,001
	Yes	32,9	44,3	77,1	
Late first pregnancy ≥ 35 years	No	41,4	47,1	88,5	0,034
	Yes	8,6	2,9	11,5	
Oral contraception	No	30	15,7	45,7	0,001
	Yes	20	34,3	54,3	
Duration of contraceptive use	No	30	21,4	51,4	0,076
	<5 years	9,3	17,1	26,4	
	6–10 years	4,3	7,1	11,4	
	>10 years	6,4	4,3	10,7	
Hormone replacement therapy	No	49,3	49,3	98,6	1,000
	Yes	0,7	0,7	1,4	
History of breast Disease	No	47,1	49,3	96,4	0,172
	Yes	2,9	0,7	3,6	
Type of breast disease	No	47,1	49,3	96,4	0,381
	Mastosis	1,4	0	1,4	
	Phyllodes tumor	0,7	0	0,7	
	Fibroadenoma	0,7	0,7	1,4	
Family history of BC	No	27,1	38,6	65,7	0,004
	Yes	22,9	11,4	34,3	
Tobacco use	No	50	50	100	NA
	Yes	0	0	0	
Alcohol consumption	No	50	50	100	NA
	Yes	0	0	0	

Note: NA: Chi-square test not applicable because some expected cell frequencies are less than 5.

CI: 1,38–18.76). Women who had ever been pregnant showed a significant protective effect, with about a 76% reduction in BC risk (COR = 0.24; 95% CI: 0.10–0.6).Late first pregnancy (≥ 35 years) was associated with a higher risk (COR = 3.41; 95% CI: 1.04–11.16), as were family history of cancer (COR = 2.84; 95% CI: 1.37–5.89) and oral contraceptive use (COR = 0.3; 95% CI: 0.15–0.61), which appeared to have a protective effect in crude analysis. After adjustment for potential confounders in the multivariate logistic regression model, several associations remained statistically and clinically relevant. Precocious menarche

Table 3. Risk Factors Associated with BC: Results from Univariate and Multivariate Analyses.

Variables		COR	95% CI		AOR	95% CI	
Early menarche	No	-Ref	-Ref	-Ref	-Ref	-Ref	-Ref
	Yes	5.09	1.38	18.76	5.70	1.40	23.24
Parity	No	-Ref	-Ref	-Ref	-Ref	-Ref	-Ref
	Yes	0.24	0.10	0.6	0.31	0.10	0.95
Late first pregnancy ≥ 35 years	No	-Ref	-Ref	-Ref	-Ref	-Ref	-Ref
	Yes	3.41	1.04	11.16	5.01	1.32	18.95
Oral contraception	No	-Ref	-Ref	-Ref	-Ref	-Ref	-Ref
	Yes	0.30	0.15	0.61	0.54	0.22	1.32
Family history of breast cancer	No	-Ref	-Ref	-Ref	-Ref	-Ref	-Ref
	Yes	2.84	1.37	5.89	3.92	1.71	8.95

Note: -Ref: Reference category.

remained a strong independent risk factor for BC (AOR = 5.70; 95% CI: 1.40– 23.24). Similarly, late first pregnancy (≥ 35 years) was independently associated with increased risk (AOR = 5.01; 95% CI: 1.32–18.95). Family history of cancer also remained a significant predictor (AOR = 3.92; 95% CI: 1.71–8.95). The association between parity and BC risk, which showed a protective effect in the unadjusted analysis (COR = 0.24), remained statistically significant in the adjusted model, although its effect was diminished (AOR = 0.31; 95% CI: 0.10–0.95). Likewise, the protective effect of oral contraceptive use was attenuated after adjustment (AOR = 0.54; 95% CI: 0.22–1.32), with the confidence interval including the value of 1, which rendered the association non-significant (Table 3).

These findings indicate that early menarche, late age at first pregnancy, and a family history of BC are significant independent predictors of BC risk in the study population. Conversely, parity appears to be a significant protective factor against disease (Figure 1).

Discussion

This study identifies several notable risk factors for BC in young Moroccan women (under 40 years) from the eastern Morocco region, marked by socio-economic disparities and limited access to care. Young patients represent a disproportionately large share of BC cases in this context, and cultural dynamics significantly shape both exposure to risk factors and health behaviors. A marked homogeneity was observed in the socio-demographic characteristics of women with BC and controls, reflecting patterns commonly reported in low-resource settings. The mean age in our cohort was around 34 years, almost identical between groups, which is consistent with Moroccan studies that have similarly reported a mean diagnostic age ranging from 32 to 36 years (30,31). With respect to residence, a slightly higher proportion of cases lived in rural areas, although the overall urban–rural distribution remained comparable across groups. In terms of professional activity, the majority of participants were housewives in both groups. This finding echoes broader socio-economic dynamics in Morocco, where limited educational opportunities, particularly in rural areas, restrict women's access to formal employment (32,33). Finally, health insurance coverage mirrored the regional socio-economic structure: both groups were predominantly affiliated with public or subsidized schemes (RAMED, AMO-Tadamoun), a pattern in line with national data showing that unemployed women from lower-income strata are more frequently covered by such programs (34). In addition to these socio-demographic characteristics, reproductive and hormonal factors were examined, and Early menarche before age 12 years emerged as a strong independent risk factor (AOR = 5.70; 95% CI: 1.40– 23.24), affirming findings linking prolonged endogenous

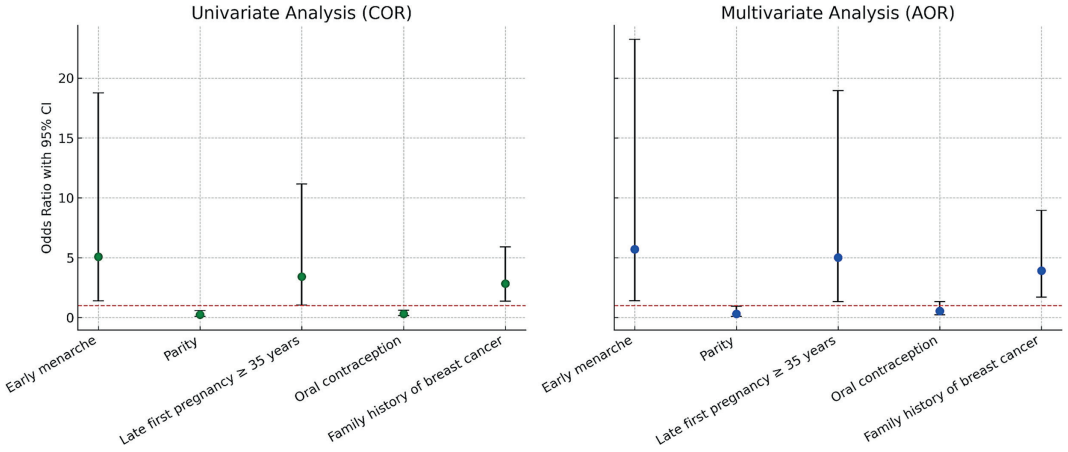

Figure 1. Distribution of crude (COR) and adjusted (AOR) odds ratios with confidence Intervals for factors associated with early-onset breast cancer. *(Note: The red dashed horizontal line marks OR = 1.0, the null value (no association). Points above this line indicate higher odds of breast cancer; points below indicate lower odds.)*

estrogen exposure to elevated BC risk (35,28). This association is consistent with studies from other North African countries, including Algeria and Egypt, where early menarche (<12 years) or younger pubertal timing has been linked with higher breast cancer risk and unfavorable profiles (36,37). More recent studies also implicate environmental exposure to endocrine-disrupting chemicals in the trend of declining age at menarche (38,39). In our study, the first pregnancy at the age of 35 years or older was identified as a significant risk factor for BC (AOR = 5.01; 95% CI: 1.32–18.95), in line with previous evidence highlighting the protective effect of earlier pregnancies through more complete breast tissue differentiation (12). Comparable findings are reported in North African populations: Algerian and Tunisian datasets emphasize the adverse impact of delayed first birth and reduced parity on risk (37,40). This finding is particularly relevant in the current Moroccan context, where demographic behaviors are undergoing profound changes. Indeed, recent data from the High Commission for Planning in Morocco indicate that the mean age at first marriage has stabilized around 24–25 years among women in recent years, reflecting a trend toward delayed entry into marital life and, consequently, delayed childbearing. At the same time, the total fertility rate (TFR) has declined significantly, reaching 1.97 children per woman in 2024—below the replacement level of 2.1—compared with 2.2 in 2014. This decrease is more pronounced in urban areas (1.77) than in rural settings (2.37) (32). The association between delayed motherhood and increased BC risk, therefore, emerges as a major public health concern, amplified by the ongoing socio-demographic transformations in Morocco. Family history of breast cancer remains a critical predictor (AOR = 3.92; 95% CI: 1.71–8.95), reflecting hereditary predisposition (e.g., BRCA1/2 mutations) (27,41). Similar associations have been reported across North African countries such as Algeria, Tunisia, and Libya, where familial aggregation of breast cancer is well documented, and BRCA1/2 pathogenic variants have been identified despite limited genetic screening infrastructure (40,42,43). Given that genetic testing remains largely inaccessible in most parts of the region, the clinical identification and surveillance of high-risk families become particularly important for early detection and tailored prevention strategies. Regarding oral contraceptives, a protective effect was observed on univariate analysis (COR = 0.3; 95% CI: 0.15–0.61); however, the association lost significance after adjustment (AOR = 0.54; 95% CI: 0.22–1.32), suggesting confounding factors. Literature on this subject remains inconsistent: some studies report increased risk with prolonged use (43–45), while others note no association or even a protective effect against certain cancer subtypes (46). In our sample, no significant duration-related difference was found between cases and controls

(p = 0.076), which precludes inference a dose-response relationship. Unlike nulliparity, the association between pregnancy and BC risk remained statistically significant in our adjusted model. This aligns with biological models where pregnancy induces protective cellular differentiation in breast tissue (12,36,40). Given that our cohort is relatively young, the full protective effect of pregnancy may not yet be clearly exhibited. Notably, no participants reported smoking or alcohol consumption, consistent with the conservative cultural context of the study population. National surveys estimate smoking prevalence among Moroccan women at only 1–2%, with substantial regional variability, while alcohol consumption remains negligible, particularly in rural and conservative settings. Similar findings have been consistently reported in other North African countries such as Algeria, Tunisia, and Egypt, where tobacco and alcohol use among women remain exceptionally low due to comparable socio-cultural and religious norms (47). These patterns contrast sharply with those observed in Western populations, where tobacco and alcohol are established risk factors in young women (7,13,48). Hence, prevention strategies should prioritize locally relevant risk profiles rather than importing ill-suited Western models (17). Among the strengths of this study are its focus on a young population from a scarcely studied region, as well as the consideration of often overlooked local socio-cultural factors. The use of a rigorous methodology allowed for the identification of independent risk factors despite a complex healthcare environment. However, several limitations must be acknowledged. The limited access to genetic testing restricts precise characterization of familial risk, while the absence of assessment or reporting of passive smoking exposure may have led to an underestimation of this potential contributor. Another limitation concerns the unavailability of molecular and immunohistochemical profiling at the Reproductive Health Reference Center (RHRC), which functions as a second-level facility. Following a positive histopathological diagnosis, patients are referred to the University Hospital Center or, when available, to private clinics for complementary investigations—including molecular and immunohistochemical profiling (ER, PR, HER2)—and for comprehensive treatment planning. A structured coordination pathway between the RHRC and tertiary-level institutions is being developed to facilitate data sharing, ensure continuity of care, and enable future integration of molecular data and strengthen clinicopathological analyses. Finally, the lack of longitudinal follow-up limits the ability to infer causal relationships and to monitor changes in risk factors over time.

Conclusion

This study highlights several major risk factors for BC among young women in eastern Morocco, a region marked by socio-economic inequalities and limited access to healthcare. Early menarche and late first pregnancy are key determinants, confirming the role of prolonged exposure to sex hormones in tumor development. Family history remains an important predictive factor, emphasizing the need for clinical identification of high-risk patients in a context where genetic screening is scarcely available. In contrast, parity emerged as a significant protective factor, which supports biological models where it induces protective cellular differentiation in breast tissue. These findings underscore the importance of prevention and management strategies tailored to the local social and cultural specificities to ensure their effectiveness. Therefore, it is essential to strengthen awareness of hormonal and reproductive risk factors, develop clinical tools to identify women with a high familial risk, and incorporate cultural realities into prevention efforts. Finally, establishing early screening programs targeting this young population and promoting local research on environmental risk factors are crucial.

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Conflict of interest: Each contributor has confirmed that they have no commercial affiliations (such as consultancy agreements, stockholdings, equity stakes, or patent/licensing agreements, among others) that could potentially create a conflict of interest regarding the submitted article.

Authors' contributions: BN: Concept, Design, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript. EF: Concept, Design, Supervision, Critical review. EE: Concept, Design, Literature Search. HK: Analysis and Interpretation, Literature Search. BS: Design, Supervision. All authors read and approved the final version of the manuscript.

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