# Potential breast cancer risk factors among Saudi women aged 19–50 years in Jeddah: a case–control study

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**Background and objectives**
The Saudi cancer registry reported in 2009 that the frequency of breast cancer is the highest among all types of cancer among Saudi women aged 30–59 years. The Makkah region had the second highest frequency of reported breast cancer cases, with patients having a median age of 46 years. The objectives of this study were to explore the distribution of selected known and hypothetically claimed breast cancer risk factors among Saudi women aged 19–50 years and describe the association of breast cancer with selected risk factors.

**Design and setting**
An unmatched case–control study was conducted on breast cancer cases at three different hospitals in Jeddah.

**Patients and methods**
Online OpenEpi was used and the method of Kelsey and colleagues was selected from OpenEpi output; the calculated number of cases and controls was 134 each. Women aged 19–50 years were included and the analysis was conducted on 151 cases and 166 controls as they met the age inclusion criteria.

**Results**
The mean age of patients was 40 years. A subgroup analysis for age at menarche less than 12 years showed an odds ratio (OR) of 1.4 6 [95% confidence interval (CI) 0.88–2.44]. A high proportion of cases reported the use of exogenous estrogen and progesterone (OR=4.7, 95% CI 1.7–13.0), previous mammography screening (89% of cases vs. 11% of controls), and affected family members (4.6 vs. 1.8, OR=2.64 [95% CI 0.67–10.4]. The OR for exercise frequency in the study group was 1.45 (95% CI 0.90–2.35). The OR for breastfeeding among mothers who breast-fed for more than 12 months was 0.56 (95% CI 0.35–0.88).

**Conclusion and recommendations**
This study provides information on associative factors such as early age at menarche (<12 years), monthly income of at least 20 000 SR (5333 USD), use of exogenous estrogen and progesterone, previous biopsies/surgeries, previous clinical breast examination and mammography screening, and affected family members. Protective factors among premenopausal women, such as breastfeeding and exercising, have been described. Conducting comprehensive sessions on breastfeeding and physical education targeting young generations is highly recommended in order to reduce the risk for breast cancer among Saudi women aged 19–50 years.

**Keywords:**
breast cancer, case–control study, risk factors, Saudi women

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## Introduction

The ninth cancer incidence report pertaining to cancer incidence in 2005 by the Saudi cancer registry (2009) showed that breast cancer is ranked first in cancer frequency among Saudi women aged 30–59 years. The estimated cancer incidence in the Makkah region was 20.9/100 000, with a median age of 46 years at diagnosis [1].

Cancer is the end product of a series of DNA mutations that lead to selective growth for a particular clone of cells. Mutation in the genes occurs through three major mechanisms: environmental, chance, and hereditary [2]. In 2007, reports from the international agency for research on cancer identified 415 known or probable carcinogens [2–4]. Much of the lifetime risk for breast cancer is associated with genetic defects in breast cancer susceptibility genes BRCAI and BRCAII, but only 5–6% of all breast cancer cases are directly attributed to those genes [5–8]. Moreover, positive family history is reported by only 15–20% of women with breast cancer [8–10].

Knowledge on the distribution of breast cancer predictors among premenopausal women is of importance, as it provides us with the information needed for risk assessment. Furthermore, such evidence supports strategies for better breast cancer prevention at both individual and community levels [2].

The Gail model has been available since 1989; it has been used widely by clinicians in the USA as a tool for individual risk assessment. It includes the input of several factors, such as age of the patient, age at menarche, age at first live birth (or null parity), family history of breast cancer in first-degree relatives, history of breast biopsy, and history of breast biopsy with typical hyperplasia [11].

Previous studies on behavioral protective factors within Saudi Arabia revealed widely variable results. Those studies focused on the behavioral practice of adult women for disease prevention and early detection and showed a gap between the women's knowledge and their real practice with respect to both breast self-examination and screening mammography without commenting on clinical breast examination (CBE) [12,13].

Local case–control studies confirmed the positive association between consumption of high dietary fat and the development of breast cancer among premenopausal and postmenopausal women. The same studies showed inconclusive results on the relationship between BMI and the development of breast cancer [14,15].

The nurse's health study II concluded that BMI was inversely associated with the risk for premenopausal breast cancer, but the mechanisms for this association are poorly understood [16]. One explanation for the low risk among obese premenopausal women is the association of obesity with irregular or long cycles [17,18]. Women who are taller than 175 cm (69 inches) are 20% more likely to develop breast cancer compared with those shorter than 160 cm (63 inches), as per the pooled analysis of seven prospective cohort studies [19]. Regular physical activity has a modest effect on reducing the risk for breast cancer [20–25].

According to the results of a large pooled analysis from 47 epidemiological studies including 50 302 women with invasive breast cancer and 96 973 controls, the relative risk for breast cancer was reduced by 12 months of breastfeeding and by an additional 7% with each birth [26].

Many of the internationally developed breast cancer control strategies are working on developing evidence on the following: local etiological factors, local guidelines, international networks, and local communication.

Our study was conducted to explore the distribution of selected known and hypothetically claimed breast cancer etiological factors among Saudi women aged up to 50 years. Also, it provides a brief description of the selected breast cancer etiological factors and the protective factors among the study group. Genetic defects in breast cancer susceptibility genes BRCAI and BRCAII are beyond the scope of this study.

## Patients and methods

In 2010, the population of the Makkah region was 6 915 006, of which Saudi women accounted for 12% of the population in Jeddah, one of the major cities in the Makkah Region.

Our study was conducted in Jeddah city from April 2010 to May 2011 at three government hospitals: King Abdulaziz and Oncology center (KAA&OC), King Abdulaziz University Hospital (KAUH), and King Faisal Specialty Hospital and research center (KFSH&RC). The following women were eligibile for inclusion in the control group: Saudi women from the community and from participating hospitals excluding the oncology clinic area who were cancer-free and aged 19–50 years. With respect to cases Saudi women aged 19–50 years who were diagnosed with breast cancer during the previous 2 years were eligible to be a part of the study.

### Definitions of terms

Regular exercise was defined as a reported frequency of exercise of at least 2 h/week for more than 4 months a year.

Lifetime breastfeeding was defined as the sum of breastfeeding duration in months for each baby born to the participant.

### Sample size calculation

To calculate the appropriate sample for our unmatched case–control study, Online OpenEpi version 3.0 (Open Source Initiative; Centers for Disease Control and Prevention, Atlanta, Georgia, USA) was used with a power of 80%, assuming that the proportion of hypothetical exposure among cases is 57.14% and that for controls is 40%, and the ratio is one case to one control with the least odds ratio (OR) to be detected at 2. The method of Kelsey and colleagues was selected from OpenEpi output. The calculated number of cases and controls was 134 each.

Measures were implemented to control for selection bias while recruiting individuals between the ages of 19 and 50 years. The analysis was conducted on 151 cases and 166 controls as they met the age inclusion criteria.

### Statistical analysis

Data entry and analysis was performed using SPSS version 18.0 [27]. $\chi^2$-test was performed on dichotomous variables, independent *t*-test was performed on continuous variables, and OR calculation was used to measure the magnitude of the association between different predictors.

### Ethical considerations

Before starting the interview, verbal agreement was obtained from the participants. Ethical approval committee letters were obtained from the three participating hospitals, with the following protocol approval reference numbers: KAA&OC princes Adla clinical research unit protocol RU-0053; KAUH Ref. no. 489-11; and KFSH&RC Ref. no. Rc-J017-32 IRP2010-29. The approval was

obtained for the protocol titled 'Potential breast cancer risk factors among Saudi women up to the age of 50 in Jeddah'.

## Results

The mean age of the cases was 40.01 ± 6.3 years and that of controls was 38.93 ± 7 years. The mean age at menarche was 12.37 ± 1.66 for cases and 13.03 ± 1.98 for controls; the difference between the two groups was statistically significant (Table 1).

**Table 1. Age distribution and monthly income among cases and controls**

| | Mean for cases ($N=151$) | Mean for controls ($N=166$) | $P$-value |
|---|---|---|---|
| Age | | | |
| Age of the study group | 40.01 ± 6.3 | 38.93 ± 7.0 | <0.0001 [+] |
| Age at first birth | 21.19 ± 5.10 | 20.87 ± 5.35 | 0.62 |
| Age at menarche | 12.37 ± 1.66 | 13.03 ± 1.98 | 0.002 [+] |
| Income per month | Frequency (%) for cases ($N=151$) | Frequency (%) for controls ($N=166$) | |
| <10 000 SR | 55 | 67.4 | – |
| 10 000–20 000 SR | 30 | 28.3 | 0.02 [#] |
| >20 000 SR | 15 | 4.3 | – |

[+] Independent $t$-test.
[#] $\chi^2$-test.

**Table 2. Disease association to parity, lifetime breastfeeding, and family history**

| Factor | Cases ($N=151$) | Controls ($N=166$) | OR [95% CI] | $P$-value [@] |
|---|---|---|---|---|
| Total number of reported pregnancy | | | | |
| <4 | 73 (51) | 62 (44.9) | 1.3 [0.8–2.0] | 0.30 |
| ≥4 | 70 (49) | 76 (55.1) | | |
| No response/ missing | 8 (5.3) | 28 (16.9) | | |
| Lifetime breast feeding ≥12 months | | | | |
| Yes | 81 (54) | 112 (67.9) | 0.56 [0.35–0.88] | 0.01* |
| No | 69 (46) | 53 (32.1) | | |
| No response/ missing | 1 (0.7) | 1 (0.6) | | |
| History of affected family member | | | | |
| Yes | 7 (4.6) | 3 (1.8) | 2.64 [0.67–10.4] [a] | 0.13 |
| No | 144 (95.4) | 163 (98.2) | | |

CI, confidence interval; OR, odds ratio.
[a] Fisher's exact test.
[@] $P$-value calculated for the valid response.
*Significant at $P<0.05$.

The majority of participants were married; the divorce rate was 8.6% for cases and 4.8% for controls. Almost two-thirds of the study group were educated below the secondary school level. The monthly income for the majority of participants was less than 10 000 SR ($2666). Cases were relatively older than controls at first birth.

Higher parity (≥4 pregnancies, including abortion and ectopic pregnancy) was noticed among controls. Breast-feeding practice was higher among controls (67.9% vs. 54%). The proportion of a family history of affected family members was higher among cases (4.6%) than among controls (1.8%); however, the difference was not significant (Table 2).

The use of exogenous estrogen and progesterone for contraception was significantly higher among cases (OR = 4.7, 95% CI 1.7–13.0) (Table 3).

Active smoking was reported among 6 and 13% of cases and controls, respectively.

A significant proportion of cases reported higher rates of CBEs and screening mammography. Previous breast biopsies or surgeries accounted for 89% of cases but only 11% of controls (Table 4).

The frequency of exercise was low in both groups but slightly higher among cases (35.1%) than among controls (27.1%) (Fig. 1). The mean BMI was 29.86 and 29.45 for cases and controls, respectively. Mean height was relatively higher among cases (Table 5).

## Discussion

The contributing factors to breast cancer among premenopausal Saudi women aged 19–50 years were as follows: early age at menarche (<12 years), monthly income of at least 20 000 SR (≥5333 USD), use of exogenous estrogen and progesterone, and previous breast biopsies or surgeries irrespective of the diagnosis. The mean age of cases was 40 years, which was relatively lower than the reported median age of breast cancer at the Saudi cancer registry [1]; this could be attributed to the limited age range of our study population.

Early age at menarche of less than 12 years was shown to be a statistically significant contributing factor to the disease (Table 1). Subgroup analysis comparing cases and controls for age at menarche less than 12 years and at least 12 years reported an OR of 1.4 6 [95% confidence

**Table 3. The association of hormonal treatment, contraceptive use, and age at menarche with breast cancer**

| Factor | Response | Cases ($N=151$) [$N$ (%)] | Controls ($N=166$) [$N$ (%)] | OR [95% CI] | $P$-value [@] |
|---|---|---|---|---|---|
| The use of exogenous hormones and/or contraception | Yes | 12 (7.9) | 3 (1.8) | 4.7 [1.3–17] | 0.005* |
| | No | 139 (92.1) | 163 (98.2) | | |
| Age at menarche | <12 years of age | 46 (32.4) | 37 (24.7) | 1.46 [0.88–2.44] | 0.07* |
| | ≥12 years of age | 96 (67.6) | 113 (75.3) | | |
| | No response/missing | 9 (6.0) | 16 (9.6) | | |

CI, confidence interval; OR, odds ratio.
[@] $P$-value calculated for the valid response.
*Significant at $P<0.5$.

**Table 4. The reported breast cancer screening behavior in the study group**

| Factor | Response | Cases ($N=151$) [$N$ (%)] | Controls ($N=166$) [$N$ (%)] | OR [95% CI] | $P$-value[@] |
|---|---|---|---|---|---|
| Clinical breast examination | Yes | 92 (60.9) | 57 (34.3) | 3 [1.9–4.7] | <0.001* |
| | No | 59 (39.1) | 109 (65.7) | | |
| Screening mammography | Yes | 96 (65.8) | 33 (22.2) | 7.7 [4.6–12.9] | <0.001* |
| | No | 50 (34.2) | 133 (68.1) | | |
| | No response | 5 (3.3) | | | |

CI, confidence interval; OR, odds ratio.
[@]*P*-value calculated for the valid response.
*Significant at $P<0.5$.

interval (CI) 0.88–2.44], with no significant difference (Tables 1 and 3).

A significantly higher proportion of cases reported frequent use of exogenous estrogen and progesterone (OR = 4.7, 95% CI 1.7–13) (Table 3). The result is consistent with a prospective study (2002) that observed an increased risk of oral contraceptives at young age among current users [28]. In contrast, another large case–control study confirmed the absence of any association with past use or after discontinuation [29].

Screening mammography and CBE were reported to be significantly higher among cases (OR = 3 at 95% CI 1.9–4.7 and OR = 7.7 at 95% CI 4.6–12.9 for CBE and screening mammography, respectively) (Table 4). Information bias is a possibility, as some of the cases reported CBE and mammography after disease suspicion and for diagnostic purposes. Although the interviewer asked specifically about both CBE and screening mammography for screening purposes, the reply was often not guaranteed. The issue could be resolved by conducting a review on individual electronic health records to obtain more reliable data. This was not possible as the electronic health records are not well implemented in most of the centers from where the data were collected. The OR for previous breast aspiration and/biopsies was 23.1 (95% CI 11.7–45.5).

Cases reported higher proportions of affected family members (4.6%) compared with controls (1.8%) but the difference was not statistically significant. This could be a reflection of the response bias associated with the nature [30] of case–control studies. Our cases reported markedly smaller proportion of affected family members, which could be attributed to response bias in the sense of concealment and/or under-reporting as a result of cultural stigmatization.

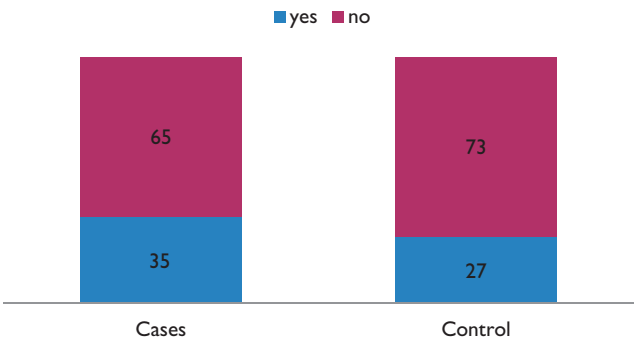
For breastfeeding, the OR was 0.38 (95% CI 0.22–0.67), especially among mothers who exceeded the lifetime breastfeeding duration of more than 12 months. Our study conveyed a significant difference in breastfeeding in favor of the control group (Table 2). Moreover, further analysis showed a statistically significant protective effect of 12 months of breastfeeding (OR = 0.56, 95% CI 0.35–0.88). In one study, the parous women who reported ever breastfeeding had a slightly significant reduction in the risk for breast cancer (OR = 0.83, 95% CI 0.63–1.09). Women who breast-fed their babies for more than 13 months had risk reduction by 0.47 (95% CI 0.23–0.94) compared with those who never breast-fed. Stratification conducted by the same study according to menopausal status showed a risk reduction related to breastfeeding for both premenopausal and postmenopausal women [31].

With respect to lifestyle risk factors, our study concluded that current active smoking was significantly associated with disease-free individuals (OR = 0.44, 95% CI 0.19–0.98). Our results contradict those of the study conducted on premenopausal Japanese women with a hazard ratio of 3.9 with 95% CI (1.5–9.9) and also the conclusions drawn from eight Japanese case–control studies, which showed a direct effect of smoking on the development of breast cancer [30,32]. However, these contradicting results can be resolved by the frequently observed, antiestrogenic properties of smoking. If the carcinogenic effects of tobacco are counterbalanced by its antiestrogenic effect, the result is a nil or very small effect of tobacco on breast cancer. Also, second-hand smoking (SHS) was not associated with the disease as an outcome in our case–control study. In contrast, a report of the Canadian Expert Panel on Tobacco smoke and breast cancer risk concluded a 65% increase in premenopausal breast cancer risk among never smokers exposed to SHS and that the association between SHS and breast cancer among younger premenopausal women who never smoke is consistent with causality [33].

The odds for exercise frequency among the cases and controls was 1.45 (95% CI 0.90–2.35) (Fig. 1). The reported frequency of exercise ($\geq 2$ h/week for more than 4 months a year) was slightly more among cases (35.1%) than among controls (27.1%). The results were not comparable to the results reported from the nurses' health study II (17 and 21–26). Maruti *et al.* [34] reported a 23% lower lifetime risk for invasive premenopausal breast cancer among women who are engaged in relatively high levels of physical activity, especially during the ages of 12–22 years. The culturally rare exposure to exercise among Saudi women made it difficult to conclude on the protective effect of exercise. Conducting a 5-year prospective study on premenopausal Saudi women with focus on the currently observed changing pattern of physical activities is expected to uncover the subtle relation between physical activity and premenopausal breast cancer.

Our study did not conclude any significant relations between body weight and height and premenopausal breast cancer (Table 5). Those results were matched with another local case–control study [15].

**Figure 1.**




The percentage of reported regular exercise in the study group.

**Table 5. The association of participants' height and BMI with breast cancer**

| Factor | Mean for cases ($N=151$) | Mean for controls ($N=166$) | Mean difference [95% CI] | *P*-value |
|---|---|---|---|---|
| BMI | 29.86 ± 6.61 | 29.45 ± 6.60 | 0.41 [−1.1 to 1.9] | 0.6$^{+}$ |
| Height | 158.9 ± 7.54 | 158.6 ± 7.43 | 0.38 [−1.5 to 2.1] | 0.7$^{+}$ |

$^{+}$Independent *t*-test.
CI, confidence interval.

## Conclusion and recommendations

Considering the nature of the case–control study in providing the OR, this study provided us with information regarding the most frequently reported associating factors with breast cancer, such as early age at menarche (<12 years), monthly income of at least 20 000 SR (≥5, 333 USD), use of exogenous estrogen and progesterone, previous breast biopsies or surgeries, previous CBE and mammography screening, and presence of affected family members. Also, it provided a description of some of the hypothetically protective factors, such as breastfeeding duration and frequent exercising. Finally, this study explored the debatable relationships of BMI, weight, height, and smoking with premenopausal breast cancer.

### Recommendations

We recommend conducting comprehensive sessions on breastfeeding and physical education targeting our young generations, with a focus on evaluating the effective duration and frequency of breastfeeding in reducing the risk for breast cancer among Saudi women aged 19–50 years. We also recommend conducting qualitative research to uncover the stigma associated with breast cancer reporting.

A cohort study is suggested to explore the temporal relationship between BMI, smoking, and breast cancer with consideration given to the length of the menstrual cycle, estrogen blood level, and ovulation.

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### Conflicts of interest

There are no conflicts of interest.

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