

Risk factors of breast cancer in women referring to the surgical clinic of northern Iran Hospitals over a ten-year period (2011-2021)

Melika Hendukolai (MD)¹

Khadijeh Ezoji (MD)²

Yasser Asghari (MD)³

Majid Nabipour (MD)⁴

Sana Keshtegar (MD)¹

Aref Gholami Languri (MD)¹

Mohammad Amin Afshar (MD)¹

Abolhasan Alijanpour (MD)^{5*}

1. Student Research Committee, Babol University of Medical Sciences, Babol, Iran

2. Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

3. Department of Surgery, School of Medicine, Cancer Research Center, Health Research Institute, Shahid Beheshti Hospital, Babol University of Medical Sciences, Babol, Iran

4. Department of Internal Medicine, School of Medicine Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran

5. Clinical Research Development Unit of Rouhani Hospital, Department of Surgery, Babol University of Medical Sciences, Babol, Iran

* Correspondence:

Abolhasan Alijanpour, Clinical Research Development Unit of Rouhani Hospital, Department of Surgery, Babol University of Medical Sciences, Babol, Iran

E-mail:

abolhasanalijani@gmail.com

Tel: +98 1132238284

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Abstract

Background: Breast cancer is a major global health concern, with the highest incidence in women and the main cause of cancer-related deaths in them worldwide. The purpose of this study was to investigate the risk factors related to breast cancer in women.

Methods: This is a case-control study on breast cancer patients referred to the Surgery Clinic during the years 2011 to 2021. There were 131 participants in the case group and 131 in the control group. Patient information was collected through medical records, face-to-face or telephone interviews. This study has the ethics code IR.MUBABOL.HRI.REC.1401.226 from the National Organization for Ethics in Biomedical Research of the Ministry of Health and Medical Education of Iran.

Results: 262 participants were included in the study, 50% were in the case group (breast cancer) and 131 (50%) were in the control group. Between the case and control group in terms of demographic variables, age ($P=0.289$), height ($P=0.254$), education level ($P=0.785$), marital status ($P=0.421$), place of birth ($P=0.668$) and place of residence ($P=0.454$) have been no statistically significant difference. Presence of underlying disease ($P=0.005$), less physical activity ($p<0.001$), older age at first delivery ($P=0.003$), lower menstrual age ($P=0.001$), history of breastfeeding for at least one year ($P=0.002$) and use of oral contraceptives ($P=0.015$) can significantly predict the incidence of breast cancer.

Conclusion: OCP use, underlying disease, less physical activity, older age at first delivery, younger age at menstruation, and history of breastfeeding for at least one year are associated with the incidence of breast cancer.

Keywords: Breast cancer, Risk factors, Oral contraceptives.

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Cancer is currently ranked as one of the leading causes of death worldwide. According to GLOBOCAN 2020 data, breast cancer stands as the most frequently diagnosed cancer in women globally, with 2.26 million new cases reported in 2020 (1). Apart from its prevalence, breast cancer constitutes the primary cause of cancer-related deaths among women on a global scale. Despite the highest incidence rates being observed in developed regions, Asian and African countries accounted for 63% of all fatalities in 2020. Ongoing projections indicate that by 2030, the global count of newly diagnosed cases will reach 2.7 million annually, accompanied by a death toll of 0.87 million (1). Breast cancer risk factors are commonly classified into two distinct categories. The initial group comprises non-modifiable factors, including sex, advancing age, familial history, genetic mutations, race, and reproductive background (2). For instance, a noteworthy proportion of breast cancer patients, approximately 80%, are aged over 50 years (3).



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Moreover, an estimated 13-19% of individuals diagnosed with breast cancer possess a first-degree relative who has been afflicted by the disease (4). The highest rates of breast cancer incidence are evident among non-Hispanic white women (5). Furthermore, a history of any benign alterations within the breast, such as atypical hyperplasia, carcinoma in situ, or various other proliferative lesions, substantially augments the associated risk (6).

The second category encompasses modifiable risk factors, encompassing aspects such as medication usage, body mass index, alcohol consumption, exposure to artificial light, intake of processed foods, dietary patterns, and levels of physical activity (7). Women who engage in hormone replacement therapy, particularly for durations exceeding 5 to 7 years, face an elevated susceptibility to breast cancer development (8). The utilization of antidepressants, particularly those classified as tricyclic antidepressants and selective serotonin reuptake inhibitors, may exhibit a potential linkage to heightened breast cancer risk (9).

Consistent engagement in regular physical activity serves as a safeguarding element against the onset of breast cancer. The benefits of physical activity extend not only to women possessing a familial predisposition to breast cancer but also encompass individuals lacking a positive familial history of the condition (10).

Obesity correlates with an increased likelihood of developing breast cancer, with this association being more pronounced among postmenopausal women who are obese. Furthermore, an elevated body mass index (BMI) is linked to more aggressive tumor attributes, encompassing a greater occurrence of lymph node metastases and larger tumor dimensions. Moreover, obesity might underlie heightened mortality rates and an augmented likelihood of cancer recurrence prior to menopause (11). Notably, excessive alcohol consumption is also identified as a contributing factor to the risk of breast cancer. The elevation of estrogen levels attributed to alcohol consumption contributes to hormonal imbalances and a subsequent rise in BMI, culminating in an augmented susceptibility to breast cancer (12).

Notably, both active and passive smoking are distinctly linked to a noteworthy escalation in breast cancer risk (3). To date, comprehensive investigations into the risk factors associated with breast cancer in the northern region of Iran remain limited. Owing to the genetic and racial disparities among populations residing in distinct geographical areas, delving into the risk determinants of this ailment specific to each locale holds the potential to yield valuable insights conducive to devising targeted strategies.

Methods

This study constitutes a case-control design conducted at Babol University of Medical Sciences, executed in compliance with the ethical guidelines under code IR.MUBABOL.HRI.REC.1401.226. The case group included women in the reproductive age range (15–49 years) who had breast cancer confirmed by an oncologist and who had no history of ovarian surgery, remained premenopausal, and were considered for hysterectomy. Participants under study had to have at least one functional ovary. In addition, the diagnosis of breast cancer in these individuals was attributed exclusively to primary sources, without any metastatic spread from other neoplasms. The accuracy of the disease manifestations was confirmed through detailed pathological examinations. The study included cases who had been referred to Ayatollah Rouhani and Shahid Beheshti Hospitals in Babol for evaluation and medical care from 2011 to 2021. Exclusion due to patient death during the questionnaire visit (change of exclusion from the list and denial of inclusion as a control) and inability to access patient records.

The control group was constituted by patients from the surgical clinic who sought medical attention for concerns unrelated to cancer and fulfilled the pre-defined inclusion criteria. The control group was selected from women referring to the same departments or outpatient clinics of the same hospitals and living in the same geographical areas and in the same time period.

The process of diagnosing cancer relied upon meticulous verification through patients' pathology records. Following this pivotal confirmation, an intricate compilation of both demographic and clinical data was meticulously executed. This meticulous data compilation was facilitated through a carefully designed checklist, meticulously aligned with the insights garnered from patients' medical histories. This compilation process was conducted through a judicious combination of both face-to-face interviews and telephonic interactions with the patients. The spectrum of variables subjected to rigorous analysis encompassed a diverse array of pivotal aspects:

1. Age: The participants' chronological age at the juncture of diagnosis was meticulously noted.
2. Physical activity: Quantification followed the well-established criteria set forth by the Physical Activity Scale for the Elderly which includes information about the time spent by the person for walking, moderate and intense physical activity, and home and work environment activities during the past 7 days, which includes three parts: leisure time activities (6 questions) and home activities (6 questions) and activities related to the environment.

3. The total score is obtained by multiplying the amount of time spent in each activity by the scores obtained from the questionnaire (PASE) (13).
4. **Residential status:** Participants' domiciles were systematically classified, distinguishing between urban and rural settings.
5. **Educational attainment:** The participants' educational accomplishments were meticulously classified, spanning from illiteracy to advanced diploma and higher education levels.
6. **Anthropometric measurements:** Rigorous recording of height and weight measurements formed the foundation for subsequent Body Mass Index (BMI) calculations.
7. **Underlying medical conditions:** Thorough scrutiny encompassed discerning underlying health concerns, including, but not limited to, historical instances of high blood pressure, ischemic heart disease, heart failure, diabetes, and thyroid disorders.
8. **Obstetric and reproductive history:** A comprehensive assessment embraced factors such as the age at first pregnancy, cumulative pregnancies and deliveries, along with an in-depth one-year history of breastfeeding. Concurrently, instances of pregnancy-related complications, including gestational hypertension, gestational diabetes, eclampsia, and abortion, were meticulously recorded.
9. **Occupational status:** Participants' vocational roles were carefully categorized as either freelance or employee-based.
10. **Familial medical history:** A rigorous exploration was undertaken to discern the presence of breast cancer or other malignancies within immediate family members.
11. **Age at menarche:** Participants' age at the onset of their initial menstrual cycle was meticulously documented.
12. **Oral contraceptive Pill usage:** Scrutiny extended to evaluate historical patterns of oral contraceptive pill (OCP) usage.

Concurrently, dietary patterns were analyzed, encompassing dominant food consumption. This involved categorizations of high fat, high salt, high sugar, or regular dietary preferences. Additionally, participants' physical exercise routines were assessed, with specific attention to daily engagement in physical activities for a minimum of thirty minutes. This methodically executed data collection process attests to the robustness and comprehensiveness of our study in effectively capturing nuanced associations within this distinct patient population. The collected data were subjected to analysis utilizing SPSS Version 22 software. Quantitative data were presented through measures of central tendency, including mean and standard deviation, while qualitative data were characterized by

frequency and percentage distributions. To explore relationships between variables, chi-square and t-tests were employed. The predictive factors of breast cancer were investigated through logistic regression analysis. A p-value of less than 0.05 was deemed statistically significant. The determination of the appropriate sample size was informed by a reference study titled "Reproductive Risk Factors Associated with Breast Cancer Molecular Subtypes among Young Women in Northern China (14)." Considering a positive family history prevalence of 14.1% in the case group and 1.2% in the control group, with an alpha value of 0.02 and a power of 0.95, the following formula was employed. As a result, a minimum of 131 participants were ascertained for each group, culminating in a total of at least 262 individuals.

$$N_1 = \left\{ Z_{1-\alpha/2} * \sqrt{p * q * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + \left(\frac{p_2 * q_2}{k} \right)} \right\} / \Delta^2$$

Results

To examine the correlation between demographic factors and disease within two distinct groups, the chi-squared test was employed for qualitative variables, while the t-test was applied for quantitative variables. However, statistically significant differences were not observed. The outcomes of this analysis are presented in table 1 and table 2.

Table 1. Demographic profile of the participants

variable	Case group	Control group	P-value
	Mean±SD	Mean±SD	
Age	56.25±8.13	8.13	0.289
Height	165.34±5.63	5.63	0.254
Weight	80.11±80.11	14.04	0.239

SD: Standard deviation

To investigate the history of cigarette and alcohol consumption, oral contraceptive pill (OCP) usage, breastfeeding history, physical activity, and underlying medical conditions, encompassing hypertension, diabetes, thyroid disorders, and autoimmune diseases within the scope of our study, the chi-square test was employed. Based on our analysis, no significant association was observed between cigarette and alcohol consumption and the incidence of breast cancer. These findings are presented in table-3 along with their corresponding p-values. However, within the case group, the number of individuals with a history of OCP usage and underlying medical conditions has been significantly higher statistically (table 3).

Furthermore, in terms of statistical significance, breastfeeding history and physical activity have been more pronounced within the control group (table-3). To investigate the influential factors contributing to the occurrence of breast cancer, we employed logistic regression analysis (table-4). According to the results of this analysis, the presence of an underlying medical condition

($P=0.016$, $OR=0.042$), lower levels of physical activity ($P=0.005$, $OR=4.0$), advanced age at first childbirth ($P=0.013$, $OR=1.031$), earlier menarche age ($p<0.001$, $OR=0.635$), and a history of breastfeeding for at least one year ($P=0.006$, $OR=2.332$) significantly demonstrated predictive capabilities for breast cancer incidence.

Table 2. Comparison of demographic characteristics between two study groups

	Variable	Case group	Control group	P-value
Education	Below diploma	94 (71.8%)	92 (70.2%)	0.785
	diploma, and above	37 (28.2%)	39 (29.8%)	
Occupation	Homemaker	99 (75/6%)	102 (77.9%)	0.661
	Employed	32 (24.4%)	29 (22.1%)	
Marital status	Married	105 (80.2%)	110 (84%)	0.421
	Single	26 (19.8%)	21 (16%)	
Place of birth	Rural	97 (74%)	100 (76/3%)	0.668
	City	34 (26%)	31 (23/7 %)	
Place of Residence	Rural	72 (55%)	78 (59/5%)	0.454
	City	59 (45%)	53 (40/5 %)	

Table3. Comparison of risk factors in case and control groups

	Variable	Case group	Control group	p-value
Smoking history	Yes	21 (16%)	11 (8.4 %)	0.059
	No	110 (84%)	120 (91.6 %)	
Alcohol consumption history	Yes	2 (1.5%)	1 (0.8%)	1/00
	No	129 (98.5 %)	130 (99.2%)	
OCP consumption history	Yes	57 (43.5 %)	38 (29 %)	0.015
	No	74 (56.5%)	93 (71%)	
Physical activity	Yes	25 (19.1 %)	51 (38.9 %)	0.001
	No	106 (80.9 %)	80 (61.6 %)	
Breastfeeding history	Yes	66 (50.4 %)	91 (69.5 %)	0.002
	No	65 (49.6 %)	40 (30.5 %)	
Underlying disease	Yes	60 (45.8 %)	38 (29 %)	0.005
	No	71 (54.2 %)	93 (71%)	

OCP: Oral Contraceptive Pill

Table 4. Risk factors affecting the occurrence of breast cancer

variables	ADJ				Crude			
	P-value	OR	95% CI for EXP (B)		P-value	OR	95% CI for EXP (B)	
			Lower	Upper			Lower	Upper
Age	0.288	0.988	0.967	1.01	0.711	0.995	0.970	1.021
BMI (kg/m²)	0.104	1.038	0.992	1.086	0.117	1.043	0.990	1.100
Education	0.785	0.929	0.544	1.584	0.565	0.835	0.451	1.544
Occupation	0.667	1.137	0.641	2.017	0.437	1.299	0.672	2.508
Marital status	0.421	1.297	0.688	2.446	0.435	1.349	0.636	2.864
Place of birth	0.668	1.131	0.645	1.982	0.954	1.019	0.535	1.939
Place of residence	0.454	1.206	0.739	1.969	0.302	1.364	0.765	2.369
Underlying disease	0.005	2.068	1.241	3.446	0.016	2.042	1.143	3.648
Physical activity	<0.001	0.370	0.211	0.647	0.003	0.390	0.209	0.728
Age at first birth	0.003	1.108	1.034	1.187	0.013	1.103	1.021	1.191
Menstrual age	0.001	0.709	0.575	0.874	<0.001	0.635	0.500	0.807
Breastfeeding	0.002	2.241	1.351	3.714	0.006	2.233	1.257	3.969
OCP	0.015	1.885	1.130	3.144	0.112	1.610	0.895	2.897
Alcohol	0.569	2.016	0.181	22.503	0.786	1.429	0.109	18.726
Smoking	0.063	2.083	0.960	4.516	0.100	2.103	0.867	5.102

BMI: Body Mass Index, OCP: Oral Contraceptive Pill, ADJ: Adjusted analysis. EXP: Exponential.

Discussion

Among the multitude of factors scrutinized, certain variables demonstrated predictive capacity for breast cancer occurrence. Notably, the utilization of oral contraceptive pills (OCPs), the presence of underlying medical conditions, reduced physical activity, advanced age at initial childbirth, lower age at menarche, and a history of breastfeeding for a minimum of one year emerged as significant predictors. Conversely, no discernible correlations were established between the incidence of breast cancer and factors encompassing age, education level, and marital status, place of residence, as well as smoking and alcohol consumption. In respect to the age at first childbirth (termed as age at first term pregnancy), our findings align harmoniously with prior investigations, which underscored an elevated breast cancer risk among individuals experiencing their inaugural pregnancy at an

advanced age (typically 30 or older) (15-17). Interestingly, our study corroborates the association between lower menarche age and breast cancer incidence. This noteworthy discovery is in harmony with results derived from several comprehensive meta-analyses, encompassing Shamshirian's investigation conducted in Iran (17), as well as LI et al.'s (18) and Hamajima et al.'s (19) respective studies. The confluence of these findings underscores the consistency of our results with established research, thereby reinforcing the existing body of knowledge concerning the interplay of these pivotal factors in breast cancer etiology. Our investigation has yielded a compelling revelation: breastfeeding for a duration surpassing one year (ranging from 13 to 24 months) exerts a protective influence against breast cancer. Remarkably, this finding diverges from the outcomes of several meta-analyses conducted across disparate populations (20-23), wherein contrary results

were observed. However, an intriguing contrast emerges when considering one of the most expansive studies encompassing "breast cancer and breastfeeding." This extensive research amalgamates insights from 47 epidemiological investigations spanning 30 nations. Notably, a notable reduction of 42% in breast cancer incidence is observed, particularly in developing countries. This protective effect is attributed to the prolonged breastfeeding practices prevalent in these regions. In stark contrast, shorter durations of breastfeeding, prevalent among women in developed countries characterized by smaller family units, engender an elevated risk of breast cancer within these contexts (24).

These disparate findings underscore the intricate interplay between breastfeeding practices and breast cancer susceptibility, intricacies which are further shaped by socio-economic dynamics and cultural norms. The report of "Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective" in 2007 recommended physical activity as a protective factor against cancers, especially postmenopausal breast cancer (25). Also, physical activity for cancer prevention is recommended by "American Cancer Society Guidelines on nutrition and physical activity for cancer prevention (26). Our findings also support this hypothesis as a preventive factor for breast cancer. In fact, physical activity affects the risk of cancer through mechanisms such as metabolic, hormonal and immune strengthening effects, etc. (27). A study by Steven C Moore et al entitled "Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults" reported a significant association for high physical activity and a lower risk of breast cancer (28).

In our study, although there were active smokers in breast cancer patients compared to the control group, this difference was not significant. In two meta-analyses, passive smokers were shown to have a higher risk of breast cancer, but no such association was observed for active smokers (17, 29). In addition, some other studies also reported a significant association between passive smoking and the risk of breast cancer (30, 31). The results of this study showed a significant relationship between OCP consumption and breast cancer, which is consistent with several other studies (32, 33). The association between OCP use and breast cancer is associated with duration, dose, pattern of use, type of oral contraceptive pill, and age of first use (34). There are several hypotheses regarding the relationship between OCP use and breast cancer. The most important thing is that breast cancer is caused by the increase of estrogen in the body, which is stimulated by two factors. One of these factors is oral contraceptives, which

are mainly composed of estrogen and progesterone, another factor is multiple pregnancies that expose a woman to more female hormones. so, these pills may increase estrogen levels and therefore increase the risk of breast cancer (7). It is possible to reduce and control estrogen levels by doing physical activities. Those who exercise while using these pills are less prone to increased estrogen levels and also the occurrence of breast cancer (35, 36). In our study, we encountered limitations such as lack of access to patients in some areas of the Caspian Sea and considering the reproductive age range up to 49 years. Therefore, to make the data more generalizable and increase the accuracy of the impact of risk factors, we suggest that other researchers interested in this field evaluate wider age groups and, if available, a larger population.

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