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Breast Cancer Risk Factors in Patients With Endometriosis

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ABSTRACT

Background: Endometriosis is a common chronic inflammatory, estrogen-dependent disease with characteristics similar to cancer. Epidemiological studies of the association between endometriosis and breast cancer have yielded inconsistent results. The present study aimed to investigate the association between endometriosis and breast cancer risk factors.

Methods: This case-control study (with 222 persons in each group) was conducted in Arash Women's Hospital from 2014 to 2017. Women with laparoscopically proven endometriosis were considered as cases. Controls were selected from women who had previous laparoscopic surgery due to any reason, and the absence of endometriosis was confirmed in them.

Results: Multivariate logistic regression analysis by considering the risk factors (age, body mass index, gravidity, age at first pregnancy, age at menarche, history of breast-feeding, history of oral contraceptive and hormone use, history of miscarriage and induced abortion, breast cancer in first-degree relatives, and physical activity) revealed that endometriosis was positively association with age at first pregnancy (OR = 1.16, 95% CI: 1.08-1.25; P < 0.001), history of oral contraceptive use (OR = 3.91, 95% CI: 1.92-7.95; P < 0.001), and history of hormone use (OR = 5.82, 95% CI: 2.70-12.56; P < 0.001), and negatively associated with gravidity (OR = 0.61, 95% CI: 0.42-0.91; P = 0.01), and history of breast-feeding (OR = 0.37, 95% CI: 0.16-0.86; P = 0.02).

Conclusion: Women with endometriosis have some of the breast cancer risk factors in their history, and these risk factors (gravidity, age at first pregnancy, history of breast-feeding, and OCP or hormone use) can change the risk of endometriosis as they increase or decrease the risk of breast cancer.

Introduction

Cumulative exposure of a woman to exogenous

estrogens causes hormonal abnormalities that will accompany her during reproductive life cycle and is considered an established risk factor for breast cancer.

Endometriosis is a common chronic inflammatory, estrogen-dependent disease which affects approximately 10%-15% of women of reproductive age. However, its prevalence may be as high as 25%-30% in infertile women.^{1, 2} Many women are asymptomatic, while others experience varying

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degrees of chronic pelvic pain, dysmenorrhea, or dyspareunia. Endometriosis has characteristics similar to cancer, including cell invasion, unrestrained growth, development of new blood vessels, and a decrease in the number of cells undergoing apoptosis.³ Furthermore, endometriosis, like cancer, is characterized by metastasis and recurrence, and the 5-year recurrence rate of endometriosis after laparoscopy has been reported to be 40%-50%.⁴ However, endometriosis is not categorized as a malignant disorder, and malignant transformation of endometriosis occurs only in 1% of cases.⁵

Several studies have shown a possible association between ovarian cancer and endometriosis.⁶⁻⁸ A 1997 study in Sweden, with a large sample size and long-term (11.4 years) follow-up, reported that ovarian cancer rate in patients with endometriosis was about two times higher than the general population. They also found these women to have a 30% increased risk of breast cancer.⁸ However, subsequent epidemiological studies examining the association between endometriosis and breast cancer provided inconsistent results.⁸⁻¹⁴

Therefore, the aim of this study was to evaluate the association between breast cancer risk factors and endometriosis.

Methods

Study Population

This case-control study was approved by the Ethics Committee of Tehran University of Medical Sciences. Oral informed consent was obtained from all participants. The study was performed in Arash Women's Hospital during the period 2014-2017. Women with endometriosis were considered as cases, providing us with a case group of 222 women. The diagnosis was confirmed using laparoscopic surgery. An equal number of controls were selected from women who had previously undergone laparoscopic surgery due to any reason (pelvic pain, dysmenorrhea, unknown infertility, etc.), and the absence of endometriosis was confirmed in them.

Women with a history of any type of cancer, history of head and neck radiotherapy, and positive genetic test for breast cancer (*BRCA1*, *BRCA2*) were excluded. Demographic information and breast cancer risk factors [age, body mass index (BMI), gravidity, age at first pregnancy, age at menarche, history of breast-feeding, history of oral contraceptive and hormone use, history of abortion, history of breast cancer in first-degree relatives, and weekly physical activity (hours)] were obtained by a trained midwife through face-to-face interview. BMI is defined as weight divided by height squared (kg/m^2). Weekly physical activity was the total hours per week that a woman exercised.

Statistical Analysis

Categorical and continuous variables are

presented as N (%) and mean \pm standard deviation, respectively. Pearson's chi-square test and independent t test were used to assess differences between baseline demographic and clinical characteristics of the study groups. Multivariate logistic regression with backward selection mode was used to examine the association between endometriosis and the possible risk factors selected based on the prior knowledge. In this model, a P value of 0.2 was used as the criteria for entering a variable in the model, whereas a P value of 0.1 was considered the threshold for a variable to stay in the model. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). Statistical analysis was performed using SPSS software (version 18, Chicago, IL, USA).

Results

Demographic and clinical characteristics of the subjects are shown in Table 1. The mean age of the subjects was 33.11 ± 5.88 (range: 19-45) years. Only three women were in postmenopausal status (one in the case and 2 in the control group). Independent t test showed no significant difference in age at menarche and physical activity between the case and the control groups ($P > 0.05$). However, other variables were significantly different between the two groups ($P < 0.05$) (Table 1). After univariate logistic regression analysis by considering the P value of < 0.2 , the variables age, BMI, gravidity, age at first pregnancy, history of breast-feeding, history of miscarriage and induced abortion, and history of oral contraceptive and hormone use were selected for further analysis (data not shown in the table). Multivariate logistic regression results are presented in Table 2. The results revealed that endometriosis was positively associated with age at first pregnancy (OR = 1.16, 95% CI: 1.08-1.25; $P < 0.001$), history of oral contraceptive use (OR = 3.91, 95% CI: 1.92-7.95; $P < 0.001$), and history of hormone use (OR = 5.82, 95% CI: 2.70-12.56; $P < 0.001$), and negatively associated with gravidity (OR = 0.61, 95% CI: 0.42-0.91; $P = 0.01$) and history of breastfeeding (OR = 0.37, 95% CI: 0.16-0.86; $P = 0.02$).

Discussion

Breast cancer is the most common cancer in women. Therefore, many researchers are interested in early detection of breast cancer risk factors in high risk population. The risk of cancer development in patients with endometriosis has been investigated. We evaluated the breast cancer risk factors in endometriotic cases compared with a control group. The results of the present study showed that some of the risk factors for breast cancer, such as gravidity, age at first pregnancy, history of breast-feeding, and OCP or hormone use have the same effect on endometriosis as they have on breast cancer. It means the association of these risk factors with

**Table 1.** Comparison of demographic characteristics of the case and the control

Variables	Cases (n = 222)	Controls (n = 222)	P value*
Age (y)	32.03 ± 5.22	34.17 ± 6.25	<0.001
BMI (kg/m ²)	24.03 ± 3.75	26.25 ± 4.49	<0.001
Duration of education (y)	15.13 ± 3.02	12.56 ± 4.00	<0.001
Gravidity (n)	0.53 ± 8.60	1.59 ± 1.35	0.002
Age at first pregnancy (y)	26.94 ± 4.98	22.81 ± 4.70	<0.001
Age at menarche (y)	13.08 ± 1.51	13.10 ± 1.57	0.85
Physical activity (h/wk)	3.76 ± 13.56	3.22 ± 7.18	0.60
History of miscarriage	23 (10.4)	41 (18.5)	0.02
History of induced abortion	7 (3.2)	31 (14)	<0.001
History of breast-feeding	51 (23)	147 (66.2)	<0.001
History of OCP usage	160 (72.1)	92 (41.4)	<0.001
History of hormone use	88 (39.6)	36 (16.2)	<0.001
Breast cancer in first-degree relatives			0.60
Yes	31 (13.9)	29 (13.1)	
No	191(86.1)	193 (86.9)	

* Statistically significant at 0.05 level.

BMI: body mass index; OCP: oral contraceptive pills.

Table 2. Adjusted odds ratio for endometriosis according to known risk factors in multivariate analysis

Parameters	Adjusted OR	Lower 95% CI	Higher 95% CI	P value
Gravidity	0.61	0.42	0.91	0.01
Age at first pregnancy	1.16	1.08	1.25	<0.001
History of breast-feeding	0.37	0.16	0.86	0.02
History of OCP use	3.91	1.92	7.95	<0.001
History of hormone use	5.82	2.70	12.56	<0.001

* Statistically significant at 0.05 level. Model includes age, body mass index (BMI), gravidity, age at first pregnancy, history of breast-feeding, history of OCP use, history of hormone use, history of miscarriage, and history of induced abortion. OCP: oral contraceptive pills; CI: confidence interval.

endometriosis and breast cancer is similar. Therefore, such results indicate the possibility of an increased risk of breast cancer in these patients. The predominant risk factors were the use of oral contraceptives and other hormones and age at first pregnancy. However, gravidity and history of breast-feeding were associated with protective effects.

Consistent with our findings, two cohort studies, both based on hospital records of endometriotic patients, have reported overall increased risk of breast cancer after a diagnosis of endometriosis.^{8,9} However, the findings of Schairer *et al.* were based on a limited number of breast cancer case,⁸ and Brinton *et al.* didn't find any apparent difference in risk according to the age of diagnosis.⁹

A large case-cohort study by Bertelsen *et al.* reported the increased risk of breast cancer in women whose endometriosis were diagnosed at an older age.¹⁰ A recent publication by Kokcu *et al.* discussed about the possible mechanisms of increased risk of malignancy in patients with endometriosis and the contributions of genetic and epigenetic variations of endometriosis and universal carcinogens that may be potential risk factors of breast or other cancers in women with endometriosis.²

However, the results of this study are not consistent with other studies.¹¹⁻¹⁴ The study by Brinton *et al.*,⁸ with longer follow-up, was not able to confirm the previous finding of the association between endometriosis and breast cancer.¹¹ Furthermore, the positive association was not

manifested in two case-control studies^{12,13} and one cohort study.¹⁴ It is worth mentioning, however, that these investigations were conducted in postmenopausal breast cancer patients,¹⁴ and the selection of endometriosis cases was based on self-reported data,¹²⁻¹⁴ whereas, endometriosis was confirmed by laparoscopic surgery in our study. Evidence has revealed that the etiology of endometriosis differs considering menopausal status of women, and women diagnosed with endometriosis before age 40 have reduced risk of developing breast cancer in the future. This may be attributable to cumulative exogenous estrogen levels throughout women's life or the effect of antiestrogens in younger patients with endometriosis.¹⁰ Therefore, it seems that the differences in results could be due to the following factors: sample size, study design, diagnosis of patients (by the physician or self-reported), categorization of patients by the age of diagnosis or menopausal status, and different follow-up periods. One of the most important risk factor for breast cancer is the family history of breast cancer. One study reported the proportion of women with a positive family history of breast cancer in first- and second-degree relatives was significantly higher in woman with endometriosis compared with the controls.¹⁵ However, in the present study, the family history of breast cancer was similar in the case and the control group.

Cancer is a multifactorial disease influenced by strong genetic and lifestyle components, and



environmental factors and place of residency are important factors in the development of disease. Therefore, scientists should accept some differences between the results of causal studies due to the effect of environmental variables.

Consequently, it is necessary to establish a connection between world-wide cancer registration systems in order to draw a valid and reliable conclusion about the risks associated with endometriosis considering all risk factors.

This study had some advantages. Firstly, the study groups were selected according to laparoscopic results, and not based on self-reported data. Therefore, the method of selection (case and control) was more valid. Secondly, this was the first study on this subject in our population. Since the prevalence of cancer risk factors in Iran is high, and the trend is growing up,¹⁶ and breast cancer patients with advanced stages of disease are relatively younger (about 10 years) than their western counterparts,¹⁷ this type of study was needed to prevent the disease by setting up new screening programs in high-risk populations.

The limitation of this study was the study design. It would be better to conduct a retrospective cohort study in breast cancer patients and evaluate the history of endometriosis compared with the normal population, or carry out a prospective cohort study in endometriotic patients and follow them for a long time and evaluate them for the manifestation of any cancer in this population. The other limitation was the lack of knowledge about the stage of endometriosis and the origin of the disease.

In conclusion, we found some of the risk factors for breast cancer to have the same effect on endometriosis as they have on breast cancer. However, data on the association between endometriosis and breast cancer should be interpreted with caution because of the lack of consistency. Further study is needed to confirm the association between endometriosis and breast cancer.

For women with endometriosis, especially those with a history of OCP or hormone use and higher age at first pregnancy, counseling and screening for breast cancer are highly recommended.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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