Evaluation of the association of endometriosis and mammographic breast density, a cross-sectional study

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Abstract

Background

Endometriosis is a common benign but painful gynecologic condition. Studies suggest that the risk of some types of malignancies such as breast cancer is higher in women with endometriosis. Mammographic breast density (MBD) is known as an important predictor for breast cancer. The present study aimed to investigate the potential relationship between endometriosis and MBD.

Methods

This cross-sectional study was conducted on 370 women over 40 years of age. Laparoscopic surgery was carried out for the diagnosis of endometriosis. MBD was classified into four categories according to the ACR BI-RADS classification. Statistical analysis was performed using SPSS software to evaluate the potential association between variables.

Results

The mean age of all participants was 47.2±6.4 years, and most participants (76.8 %) were premenopausal. Multivariate analysis of the potential predictors of MBD, including age, body mass index, oral contraceptive consumption, progesterone consumption, family history of breast cancer and endometriosis showed that age (P-value=0.002), history of progesterone consumption (P-value=0.004) and endometriosis (P-value=0.006) were the independent factors for MBD.

Conclusion

This study indicated that endometriosis had an inverse association with MBD. Age and history of progesterone use were also independent influential factors for MBD. This finding shows that the positive association between breast cancer and endometriosis is not mediated through MBD.

Introduction

Endometriosis is a painful gynecologic condition defined by the presence of endometrial-like tissue outside the uterus [1]. As one of the most prevalent benign disorders of the female genital system, endometriosis is a debilitating disease with detrimental effects on social, occupational and psychological functioning. There are some similarities between endometriosis and female malignancies: progressive and invasive growth, estrogen-dependency, recurrence and tendency to metastasize [2]. According to the different epidemiological studies around the world, endometriosis affects about 10% of women at reproductive age and 30 to 50% of those who are suffering from chronic pelvic pain or infertility, which are the two major clinical symptoms of endometriosis [3]. It is known that sex steroid hormones have a

key role in endometriosis development and progression [1]. Existing evidence suggests that the risk of some chronic diseases like cardiovascular disease, and some types of malignancies including ovarian and breast cancer might be higher in women with endometriosis [4]. Mammographic breast density (MBD), which indicates the fibro-glandular tissue content of the breast, is considered one of the important predictors for breast cancer among females in the general population. It has been shown that a high MBD (75% density) increases the risk of breast cancer by four-to-six folds in comparison to a low MBD (<5% density) [5]. It is assumed that exposure to sex-steroid hormones may have a role in MBD, particularly, menopausal hormone replacement therapy increases MBD, while menopausal status and tamoxifen decrease it [6].

As sex steroid exposure is associated with both endometriosis and MBD, and both are related with breast cancer, we aimed to investigate the potential relationship between endometriosis and MBD in women over 40 years of age.

Methods

This is a cross-sectional study carried out in Arash women's hospital, Tehran, Iran. The study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Approval ID: IR.TUMS.MEDICINE.REC.1398.130), and as a resident's thesis by the Institutional Research Board of the University (Proposal Code: 961129000). All the protocols involving humans was in accordance to the institutional guidelines of Ethical Research of Tehran University of Medical Sciences and to the Declaration of Helsinki. Written informed consent was obtained from all participants.

The study was conducted on women over 40 years of age. The estimated sample size was 180 for each group, calculated based on a prevalence of 40% for high MBD reported in the study of Alipour et al. [7], 95% confidence interval (CI), power of 80% and precision level of 5%. The final sample size was 360 plus 10 extra cases in the control group. Women who were diagnosed with endometriosis by laparoscopy were considered as cases, and controls were selected from women who had previously undergone laparoscopic surgery due to any reason (pelvic pain, dysmenorrhea, unknown infertility, etc.), and in whom the absence of endometriosis was confirmed during the surgery. Women who had undergone mammography less than one year sooner, those with a history of any type of cancer, positive genetic test for breast cancer (BRCA1, BRCA2), history of radiotherapy, and history of breast cancer in first degree relatives were excluded from the study. Data regarding demographic information and other risk factors including reproductive features were obtained through interview. Then, all eligible participants underwent mammography in our radiology center. MBD was classified into four categories and defined according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) by two expert radiologists [8]. Data was analyzed using SPSS software Version 26.

The continuous variables are reported as means ± SD, and numbers and percentages are used for reporting categorical variables. Normality for continuous variables was determined by the Kolmogorov-Smirnov test, which revealed the normal distribution of continuous variables (P>0.05). The Independent T-

Test, Pearson's Chi-square and Fisher exact test were used for the comparison of differences between the variables in the study groups. Univariate and Multiple linear regression were applied to evaluate the possible association between endometriosis and potential risk factors. *P* values of <0.05 were accepted as significant.

Results

A total of 370 women were entered into the study. The mean age of all participants was 47.2 ±6.4; the youngest and oldest were 40 and 71 years old, respectively. Among all participants, 284 (76.8 %) were premenopausal and 86 (23.2 percent) women were postmenopausal.

According to the analysis of demographic and clinical characteristics of participants, most of the variables were significantly different between the two groups, except for age at menarche, age at first pregnancy, duration of progesterone usage, history of infertility treatment, abortion, abdominal surgery and breast disease, which were not different between the two groups. The result are shown in Table 1.

Univariate and multivariate analysis were carried out to understand the relative importance of potential predictors of MBD. Variables including age, body mass index (BMI), oral contraceptive (OCP) use, progesterone use, family history of breast cancer and endometriosis were included as independent predictors for MBD. Univariate analysis revealed that endometriosis (P-value=0.001), as well as age (P-value=0.001) were associate with MBD. Consequently, the potential factors were included in multivariate analysis, and the results showed that endometriosis (P-value=0.006), age (P-value=0.002), and history of progesterone consumption (P-value=0.004) were independent factors for MBD (Table 2).

Table1. Demographic and clinical characteristics in the two study groups

Characteristic	Cases (N = 180)	Controls (N = 190)	P-value
Age	44.51 ± 4.40	49.85 ± 6.99	0.001
Parity	1.61 ± 1.22	2.47 ± 1.37	<0.001
Gravidity	1.95 ± 1.40	2.8 ± 1.49	<0.001
BMI	27 ± 4.27	28.7 ±4.36	0.001
Age at menarche	13.41 ± 1.5	13.33 ± 1.20	0.57
Age at first pregnancy	22.45 ± 4.94	21.44 ±5.12	0.07
Menopause age	46.15 ± 4	49.34 ± 4.82	0.002
OCP usage duration (Year)	1.85 ± 2.43	3.51 ± 4.87	0.002
Progesterone usage duration (Year)	1.41 ± 2.46	1.50 ± 2.45	0.86
Lactation duration	42(23.3%)	13(6.8%)	0.001
Never	3(1.7%)	3(1.6%)	
Less than 6 months	0(0%)	9(4.7%)	
7-12 month	63(35%)	73(38.4%)	
13-24 month	72(40%)	92(48.4%)	
More than 24 month			
Menopausal status	28(15.4%)	58(30.5%)	0.001
Infertility	49(27.2%)	17(8.9%)	0.001
Infertility treatment (n=66)	33(67%)	9(52.9%)	0.28
History of miscarriage	50(27.8%)	59(31.1%)	0.49
History of curettage	20(11.1%)	31(16.3%)	0.14
OCP usage	114(63.3%)	101(53.2%)	0.047
Progesterone usage	93(51.7%)	34(17.9%)	0.001
Adenomyosis	27(15%)	14(7.4%)	0.01
Abdominal surgery	116(64%)	108(56.8%)	0.13
Dysmenorrhea	121(67.2%)	92(48.4%)	0.001
Dyspareunia	78(43.3%)	49(25.8%)	0.001
Pelvic pain	111(61.7%)	60(31.6%)	0.001

Characteristic	Cases (N = 180)	Controls (N = 190)	P-value
Breast disease	49(27.2%)	74(38.9%)	0.01
Type of breast disease	1(2.1%)	4(5.8%)	0.32
Fibro adenoma (n=48)	47(97.9%)	65(94.2%)	
Fibrocystic disease (n=69)			
Fist degree family history of breast cancer	16(8.9%)	33(17.4%)	0.01
Oophorectomy	4(2.2%)	1(0.5%)	0.01
Unilateral	10(5.6%)	0(0%)	
Bilateral			
Hysterectomy	16(8.9)	4(2.1)	0.004
Breast density	113(62.8%)	77(40.5%)	0.001
Grade1	56(31.1%)	96(50.5%)	
Grade2	11(6.1%)	13(6.8%)	
Grade3	0(0%)	4(2.1%)	
Grade4			

Table2. Univariate and multivariate analysis for mammographic breast density

	Univariate linear regression			Multivariate linear regression		
Variable	Mean	SD	P-value	Mean	SD	P-value
Age	0.02	0.005	0.001	0.01	0.006	0.002
BMI	0.008	0.008	0.28	-0.001	0.008	0.88
OCP	-0.11	0.07	0.10	-0.06	0.06	0.35
(No, Yes)						
Progesterone	0.027	0.07	0.71	0.15	0.07	0.04
(No, Yes)						
Family history of breast cancer	0.13	0.10	0.17	0.10	0.1	0.31
Endometriosis	-0.27	0.06	0.001	-0.21	0.07	0.006
SD= Standard deviation						

Discussion

In this study we evaluated the association between endometriosis and MBD, and the risk factors of endometriosis in the case and control groups. We found that women with endometriosis had a lower MBD than those without endometriosis. Age and progesterone usage were the other predictors of MBD.

According to the studies around the world, the rate of diagnosing endometriosis is rising due to the increased awareness of women about the disease, changing social patterns like late marriage, and the widespread use of laparoscopy [9].

On the other hand, MBD is a potential risk factor for breast cancer. There are several studies that confirm the association between this cancer and MBD [10–13]. The risk of breast cancer according to MBD category varies by studies, a study reported that women with high MBD have two times a higher risk for this cancer [10]. Another study reported a four-to-six fold risk of breast cancer in women with high MBD [14]. What stands out from these reports is that MBD has a major impact on breast malignancy. Thus, investigating the influential factors on MBD can play a major role in prevention and control of breast cancer, also evaluation of a possible association between endometriosis and MBD may pave the way to revealing the pathway from endometriosis to breast cancer.

To evaluate the role of endometriosis on MBD, we conducted Univariate and Multivariate linear regression analysis. In addition to endometriosis, age, BMI, OCP, progesterone use, and family history of breast cancer were expected to impact MBD based on previous knowledge; and were considered in the analysis. The result of Univariate analysis revealed that age and endometriosis were independently associated with MBD. Consequently, these factors were included in the multivariate analysis, and result showed that age, progesterone use and endometriosis were independently associated with MBD.

According to the findings, endometriosis is a significant predictor for MBD; however in contrast with our expectation, MBD was lower in women with endometriosis. The mechanism for this reverse association is not clear to us, but this shows that the association of endometriosis and breast cancer is not through MBD. It also infers that sex hormones alone are not implicated in female cancers after endometriosis. To the best of our knowledge, the only study which evaluated the relationship between endometriosis and MBD was that of Farland et al [15]. According to this study, endometriosis was not found to be associated with mammographic density, which was in contrast with our finding. However, our sample size was higher, and Farland et al did not consider the use of steroid hormones as a confounding factor.

Age and progesterone use were the other variables that showed significant relationship with MBD. We found that a history of progesterone consumption was associated with a higher MBD. There are studies that are in agreement with our finding about the role of progesterone in MBD [16–19]. Those studies also reported that higher levels of progesterone were associated with greater MBD. This finding is not unexpected, as progesterone has a key role in regulation of tissue development and maturation in the young breast, and atrophy and involution of the lobules and ducts during and after menopause [20].

Among variables that were evaluated as influential factors for MBD, BMI and OCP usage were not significantly associated with MBD. These variables have been reported as associated with MBD in some

studies. For instance, in a study conducted by Yang et al, BMI was negatively correlated with MBD [21]. In a study conducted on Chinese women, Shang et al identified BMI as an independent influential factor on MBD [22].

In conclusion, our study showed that endometriosis was inversely associated with BMD. Considering the increased risk of breast cancer in women with higher BMD, our findings show that were there a positive association between endometriosis and breast cancer, this is not mediated via MBD. Further studies are warranted to define the complex relations among endometriosis, MBD and breast cancer.

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Approval ID: IR.TUMS.MEDICINE.REC.1398.130). All the protocols involving humans was in accordance to the institutional guidelines of Ethical Research of Tehran University of Medical Sciences and to the Declaration of Helsinki. Written informed consent was obtained from all participants.

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