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Investigation of the relationship between breast cancer and clinical symptoms of polycystic ovarian syndrome: a case-control study

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Abstract

Background Breast cancer is the most commonly diagnosed cancer among women worldwide, and it is associated with significant number of metabolic and reproductive risk factors. Despite the overlap between hormonal and metabolic factors involved in the development of PCOS and many known risk factors for breast cancer, the relationship between PCOS and breast cancer, the most common type of cancer among women, remains unknown. This study was conducted with the aim of determining the relationship between breast cancer and clinical symptoms of PCOS.

Methods This case-control study was conducted on 285 women with breast cancer and 285 healthy women referred to three centers in Tehran in 2023. Both the case and control groups were matched in terms of age and body mass index. The data collection tool in this study was a researcher-made data registration form, that was completed in person by qualified individuals. A history of PCOS was identified according to the Rotterdam criteria. Women aged 15–49 years who were able to read and write were included in the study. The case group had a history of breast cancer, while the control group did not. Participants who did not consent to having their data use in the analysis were excluded. Data was analyzed using an independent t-test, a chi-square test and a logistic regression model.

Results The mean age of the participants in the case group was 43.05 ± 4.92 years and that of the control group was 42.78 ± 5.06 years. The two groups showed a statistically significant difference in terms of PCOS history ($p < 0.001$). After adjusting for confounding variables, the logistic regression model showed that women with PCOS had a significantly higher chance of developing breast cancer (0R: 3.677, 95%CI: 1.529–8.840, $P = 0.004$). Among PCOS symptoms, women with a history of hirsutism had a higher chance of developing breast cancer (OR: 2.188, 95% CI: 1.014–4.720, $P = 0.046$).

Conclusion The findings of the present study suggest that PCOS is a risk factor for breast cancer. Well-designed further studies are highly recommended to determine the role of PCOS in predicting breast cancer.

Keywords Polycystic ovary syndrome, Breast cancer, Endocrine disease, Predisposing factors, Ovarian disease

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Introduction

Breast cancer is the most common type of cancer and the leading cause of cancer-related deaths in women [1]. With more than 2.3 million new cases per year, breast cancer has followed lung cancer as the most commonly diagnosed cancer in the world. It also accounts for 46.8% of all cancers in women, 11.6% of all cancer cases and 6.9% of annual deaths [2]. It is predicted that by 2040, the number of newly diagnosed cases of breast cancer will reach 3 million per year and the number of deaths from breast cancer will also reach 1 million per year [3]. The potential connection between polycystic ovary syndrome (PCOS) and breast cancer has been investigated due to the significant overlap between the hormonal and metabolic manifestations of PCOS and the risk factors for breast cancer [4, 5]. PCOS is associated with hyperandrogenism, oligomenorrhea, amenorrhea, acne, hirsutism, insulin resistance, obesity and infertility [6]. In addition to increasing the risk of breast cancer, it can also increase the risk of other cancers such as endometrial and ovarian cancer [7]. PCOS is one of the most common and complex endocrine and metabolic disorders [8, 9] defined as a multisystem disorder in women of reproductive age. The prevalence of PCOS varies based on different diagnostic criteria [10], and is reported in the range of 4–21% [11]. It appears that abnormal metabolic and hormonal conditions in women with PCOS, such as high levels of androgens and estrogens and low levels of sex hormone-binding globulin (SHBG) in particular, may play a role in the development of breast cancer [12]. In other words, hyperandrogenism, which is the main feature of this syndrome [13], can play an important role in the development of breast cancer. This is done by inducing a lack of ovulation and ovarian stroma hyperplasia, as well as increasing insulin resistance and obesity [14]. On the other hand, being exposed to estrogen without progesterone due to the decrease or chronic lack of ovulation caused by PCOS can increase the risk of estrogen-dependent cancers such as breast cancer [15]. Another point to note in PCOS patients is the low levels of SHBG in these women [16]. Studies have shown an inverse and significant relationship between serum SHBG levels and breast cancer risk [17]. Obesity diagnosed in association with high levels of androgens, elevated levels of insulin, and insulin-like growth factor-1 (IGF-1) in women with PCOS may accelerate the development of breast cancer [18, 19]. Hyperandrogenemia and hyperinsulinemia, which are independent risk factors for breast cancer, can also serve as the primary mediators of the relationship between breast cancer and obesity [15]. Additionally, the use of oral contraceptives is a common clinical consequence of PCOS. They are typically prescribed as the initial treatment for PCOS symptoms, which include regulating menstrual cycles and improving common symptoms of hyperandrogenism like acne and hirsutism [20]. However, prolonged use of hormonal contraceptives has been significantly linked to an elevated risk of breast cancer [21]. Previous studies investigating the potential association between PCOS and breast cancer have yielded conflicting [16] and null results [22, 23]. The discrepancies in findings may be attributed to the varying prevalence of PCOS in different population, as well as the diversity in individual symptoms. PCOS is typically diagnosed based on symptoms, each of which may independently contribute to an increased risk of breast cancer risk. Hyperandrogenemia, which can contribute to high estrogen production in women with PCOS, can stimulate the proliferation of mammary epithelial cells. Anti-Mullerian hormone (AMH) and hyperinsulinemia, due to insulin resistance, are also involved in the pathophysiology of PCOS and the development of breast cancer [4]. Additionally, a high body mass index (BMI), commonly seen in individuals with PCOS, is recognized as a significant risk factor of breast cancer. As a result, high BMI may both mediate and complicate the relationship between PCOS and breast cancer. With this in mind, we took a novel approach by matching two groups based on age and BMI to better understand the impact of genetics on cancer development and its potential association with PCOS. Recognizing breast cancer as a leading cause of death in women globally, this study aimed to investigate the relationship between breast cancer and the clinical symptoms of PCOS.

Methods

Study design and setting

This case-control study was conducted between May 2023 and August 2023. The research design adhered to the guidelines and regulations of the Declaration of Helsinki ethical principles for medical research. It was approved by the Research Ethics Committee of Iran university of Medical Sciences, with ethics code IR.IUMS.REC.1402.080. Artificial intelligence has been used to edit the English grammar in this manuscript.

Study population

This study was conducted on 570 women (285 with breast cancer and 285 healthy women) who were visited at the breast clinics of Rasoul Akram Hospital, Firouzgar Hospital and the Breast Cancer Research Center at Motamed Cancer Institute in Tehran in 2023. Sampling was conducted continuously and proportionally for three months among eligible women who visited these centers. Women in the case group had a history of definitively diagnosed breast cancer, while those in the control group were women without diagnosed breast cancer who were referred to the centers for routine breast examinations, with normal results. The inclusion criteria for

this study were Iranian nationality, ability to read and write, age between 15 and 49 years, a confirmed diagnosis of breast cancer in the present or past based on the patient's medical records for the case group, and no history of breast cancer based on routine breast examinations and self-report for the control group. Additionally, participants could not have a history of other cancers or definite menopause. Participants were recruited continuously based on the number of referrals to the designated centers. Eligible women with breast cancer, whose disease was confirmed by pathology tests and expert confirmation in their files were included in the case group, and eligible women without breast cancer were included in the control group. Both the case and control groups were matched for age and body mass index using the minimization method. Participants in both groups were provided with an information registration form during their visits to the centers. Identification of women with a history of PCOS in this study was based on the Rotterdam criteria. In both groups, the history of PCOS symptoms (menstrual irregularities, alopecia, hirsutism, acne and polycystic ovary ultrasound appearance) for at least 5 years was examined. Participants who did not consent to having their data use in the analysis were excluded. To calculate the necessary sample size at a significance level of $P<0.05$, with a test power of 80% based on the study of Jalilian et al. [24], and assuming that the frequency of breast cancer in women is 10% higher than in the general population, we determined that 285 women per group would be needed based on the relevant formula. All women who participated in the study signed a written informed consent form after fully understanding the aims and methods of the study.

Data collection method

The data collection tool used in this research was an information registration form that included the following sections:

1. Personal characteristics of the participants, such as age, height, weight, education, employment status and marital status.
2. Fertility records of the participants, included information such as the number of pregnancies, age at first pregnancy, number of abortions, breastfeeding history, number of times breastfed, average duration of breastfeeding, age at first breastfeeding, infertility history, type of infertility, history of infertility treatment, and contraceptive method. All the requested information pertained to the period before starting breast cancer treatment.
3. Menstrual records of the participants including age at first menstruation, number of menstrual days, interval between two menstruation period, regularity of menstruation, and amount of bleeding during menstruation. All the requested information pertained to the period before starting breast cancer treatment.
4. Status of breast cancer, including age at breast cancer diagnosis, and family history of breast cancer.
5. History of hirsutism using the Freeman-Galloway scoring system, alopecia using the Ludwig criteria, acne using the GAGS scale, and history of polycystic ovary diagnosis in ultrasound.

Validity and reliability

In the present study, face and content validity methods were utilized to validate the data collection tool. Initially, the data collection tool was selected by reviewing relevant and recent articles. Subsequently, it was reviewed by three members of the faculty of nursing and midwifery of Iran University of Medical Sciences to gather feedback for necessary corrections. Final adjustments were made to ensure the reliability of the data collection tool. To assess reliability, a test-retest method was employed on a sample of 15 individuals who not involved in the main study. Statistical analysis revealed a Kappa coefficient of 1 for the alopecia and acne, and a Kappa coefficient of 0.834 for the hirsutism.

Data analysis

Data was analyzed using SPSS version 22 (IBM Corp., Armonk, N.Y., USA). A chi-square test was used to compare qualitative variables, and an independent t-test for quantitative variables with a normal distribution. Logistic regression models were applied to adjust for possible confounding variables such as number of pregnancies, lactation, and history of infertility treatments. A significance level of less than 0.05 was considered in all tests.

Results

In the present study, 570 women were studied (285 cases and 285 controls). The mean age of women in the case group was 43.05±4.92 years and in the control group, it was 42.78±5.06 years. The body mass index (BMI) of women in the case group was 27.21±4.66 and in the control group, it was 27.47±4.56 kg/m2. There were no statistically significant differences in the mentioned variables between the groups. The mean age of breast cancer diagnosis in the case group was 40.73±5.37 years. The two groups showed a statistically significant differences in the number of pregnancies ($p=0.011$), breastfeeding ($p=0.001$) and history of infertility treatment ($p=0.031$). Among the participants in the two study groups, 36 (12.6%) in the case group and 12 (4.2%) in the control group reported a history of PCOS ($p<0.001$). Participants with breast cancer were more likely to have

Table 1 Descriptive characteristics of the participants

Variable		Cases	Controls	*P*-value
		***N* (%)**	***N* (%)**	
Education	Elementary	33 (11.6)	40 (14.0)	0.310*
	Middle school	42 (14.7)	54 (18.9)	
	Diploma	112 (39.3)	95 (33.3)	
	University	98 (34.4)	96 (33.7)	
Employment status	Employed	53 (18.6)	57 (20.0)	0.880*
	Not employed	232 (81.4)	228 (80.0)	
Marital status	Married	230 (80.7)	240 (84.2)	0.413*
	Single	37 (13.0)	26 (9.1)	
	Widow or divorced	18 (5.4)	19 (6.7)	
Gravida	0	13 (5.2)	18 (6.9)	0.011*
	1	52 (21.0)	35 (13.5)	
	2	93 (37.5)	90 (34.7)	
	3≤	90 (36.3)	116 (44.8)	
Number of abortions	0	165 (66.5)	170 (65.6)	0.854*
	1	59 (23.8)	60 (23.2)	
	2≤	24 (9.7)	29 (11.2)	
History of breastfeeding	Yes	223 (78.2)	229 (80.4)	0.535*
	No	62 (21.8)	56 (19.6)	
Number of times breastfeed	1	79 (35.4)	52 (22.7)	0.001*
	2	108 (48.4)	109 (47.6)	
	3	29 (13.0)	57 (24.9)	
	4≤	7 (3.1)	11(4.8)	
History of infertility	Yes	26 (9.1)	15 (5.3)	0.750*
	No	259 (90.9)	270 (94.7)	
History of infertility treatment	Yes	26 (9.1)	13 (4.6)	0.031*
	No	259 (90.9)	272 (95.4)	
Contraception method	Hormonal	62 (21.8)	59 (20.7)	0.390*
	Withdrawal	105 (36.8)	122 (42.8)	
	Non-hormonal	54 (19.0)	57 (20.0)	
	No method	64 (22.5)	47 (16.5)	
Family history of breast cancer	Yes	63 (22. 1)	54 (18.9)	0.351*
	No	222 (77.9)	231 (81.1)	
History of PCOS	Yes	36 (12.6)	12 (4.2)	< 0.001*
	No	249 (87.4)	273 (95.8)	
		Mean ± SD	Mean ± SD	
Age of the menarche (years)		13.09 ± 1.47	13.33 ± 1.52	0.058**
Age at the first pregnancy (years)		23.53 ± 5.37	22.99 ± 4.77	0.247**
Age at the first breastfeeding (years)		23. 93 ± 5.49	23.34 ± 4.72	0.216**
Total duration of breastfeeding (months)		36.60 ± 20.56	39.93 ± 19.71	0.079**
Total duration of infertility (years)		8.88 ± 7.30	10.26 ± 7.63	0.569**

*. Comparisons were tested using the chi-square test

**. Comparisons were tested using the independent t-test

Table 2 Frequency distribution and percentage of symptoms of PCOS in participants

Variable		Cases	Controls	P-value
		N (%)	N (%)	
Alopecia	No	217 (76.1)	243 (85.3)	0.007*
	Grade1	67 (23.5)	39 (13.7)	
	Grade2	1 (0.4)	3 (1.1)	
Acne	No	210 (73.7)	214 (75.1)	0.082*
	Mild	62 (21.8)	67 (23.5)	
	Moderate	13 (4.6)	4 (1.4)	
Hirsutism	No	253 (88.8)	266 (93.3)	0.056*
	Yes	32 (11.2)	19 (6.7)	
Oligomenorrhea and Amenorrhea	No	232 (81.4)	260 (91.3)	< 0/001*
	Yes	35 (12.3)	8 (2.7)	
	Variable	18 (6.3)	17 (6.0)	
Regularity of the menstrual cycle	No	56 (19.6)	31 (10.9)	0.004*
	Yes	229 (80.4)	254 (89.1)	
Polycystic ovary in ultrasound	No	258 (90.5)	273 (95.8)	0.013*
	Yes	27 (9.5)	12 (4.2)	

*. Comparisons were tested using the chi-square test

received treatment for infertility ($p=0.031$). In contrast, distributions of education, employment status, marital status, number of abortions, history of breast feeding or infertility, contraception method, and family history of breast cancer were not substantially different from women without breast cancer. More information about the demographic and fertility characteristics of the subjects is presented in Table 1. The results of the comparison of the frequency of PCOS in women participating in the two study groups are presented in Table 2. The table indicates significant differences between the two groups in terms of the alopecia history ($p=0.007$), menstrual cycle regularity ($p=0.004$), oligomenorrhea and amenorrhea ($p<0.001$), and polycystic ovary diagnosis by ultrasound ($p=0.013$). However, no statistically significant difference was found in terms of acne and hirsutism history. After adjusting for possible confounding variables such as number of pregnancies, number of times breastfeeding, and history of infertility treatment, the results of the logistic regression model indicated that the history of sonographic diagnosis of polycystic ovary and menstrual disorders were not significant. Among the clinical symptoms of hyperandrogenism, only hirsutism was found to be significant ($p=0.046$). Women with a history of hirsutism had a significantly higher chance of developing breast cancer compared to those without a history of hirsutism (OR: 2.188, 95%CI: 1.014–4.720, $p=0.046$). Furthermore, the results of the logistic regression model revealed that women with a history of PCOS had a significantly higher chance of developing breast cancer than women without a history of PCOS (OR: 3.677, 95%CI: 1.529–8.840, $p=0.004$) (see Table 3).

Discussion

The results of studies investigating the association between PCOS and breast cancer are controversial. However, it is important for individuals with PCOS to be aware of the possible risk of developing breast cancer, and to discuss appropriate and timely screening and prevention strategies with their health care provider. Early

Table 3 Results of logistic regression analysis on symptoms and history of PCOS in the participants

Predictor variables	B	*P*-value	OR	95% CI for Exp (B)	
				Lower	Upper
Alopecia	0.482	0.066	1.619	0.969	2.707
Hirsutism	0.783	0.046	2.188	1.014	4.720
Acne	-0.160	0.496	0.852	0.538	1.350
Regularity of the menstrual cycle	0.737	0.139	2.090	0.787	5.548
Oligomenorrhea and Amenorrhea	-0.342	0.439	0.710	0.298	1.690
Polycystic ovary in ultrasound	-0.730	0.103	0.482	0.200	1.158
History of PCOS	1.302	0.004	3.677	1.529	8.840

detection and intervention can greatly improve outcomes for the women at risk for developing breast cancer. The present study showed a significant increase of almost 3.7 times in the likelihood of developing breast cancer for individuals with a history of PCOS. Other researchers have also estimated a higher risk of breast cancer in women with PCOS compared to that of the general population [25, 26]. While our results are provocative, they must be interpreted with care, because previous research has reported an increased, unchanged, or decreased risk of breast cancer in relation to a history of PCOS [4, 15, 25]. Differences in the analytical approach, study population, and adjustment of variables that are likely mediators of the relationship between breast cancer and PCOS may play an important role in the inconsistency of results across different studies. However, there are possible mechanisms for how PCOS can lead to development of breast cancer. Since PCOS is characterized by chronic anovulation, it leads to prolonged estrogen secretion in the absence of progesterone [1]. On the other hand, breast cancer is primarily considered a hormone-dependent cancer [27]. Estrogen contributes to tumor growth by enhancing cell proliferation with existing mutations or by increasing the risk of mutation [28]. It has also been hypothesized that androgens increase breast cancer risk by promoting cellular growth and metabolic pathways, or through their conversion to estrogen [29, 30]. In a 2021 study, Wen et al., suggested that PCOS may be a causal factor in the development of estrogen receptor-positive breast cancer. This finding could lead to a better understanding of breast cancer etiology and improved methods for prevention [31]. However, the potential links between PCOS and breast cancer are too complex to fully understand. It requires consideration of PCOS diagnostic criteria, breast cancer characteristics, confounding and mediating factors, co-morbid conditions, as well as PCOS treatment methods that may interfere with cancer risk. Large well-designed studies, or pooled analyses, may help clarify this complex association [32].

Interestingly, in our study, after adjusting for other confounding variables such as number of pregnancies, number of times breastfeeding, and history of infertility treatment, only women with a history of hirsutism had a 2.188 times higher chance of developing breast cancer compared to women without a history of hirsutism. However, there was no significant change in risk for women with other symptoms studied in relation to PCOS. A study by Baron et, al (2001) also showed that women with hirsutism have a 1.2 times higher risk of developing breast cancer [33]. Hyperandrogenism and insulin resistance likely play key roles in this relationship [34, 35]. High levels of serum testosterone were considered critical prognostic factors for breast cancer, distant recurrence, and metastasis. The influence of androgens on breast tissue seems to be primarily due to their conversion to estrogens [15, 36]. The molecular pathways involved in androgen synthesis and activity in breast cancer show great promise, but our understanding of this is still in the early stages [33]. However, more research is required to fully understand the relationship between androgen excess and its manifestations such as hirsutism, and the development of breast cancer.

Additional results from the present study revealed significant differences in the number of pregnancies and the frequency of breastfeeding between the two study groups. According to previous research, women who have given birth and breastfed, have a lower risk of developing breast cancer later in life. This protective effect is believed to be due to hormonal changes that occur during pregnancy. Stordal (2023) reported that with each birth, the risk of breast cancer decreases by 7%. Additionally, having two children and breastfeeding for 12 months with each one may decrease the risk of breast cancer by 8.6%. It seems that pregnancy may interfere with RNA processing and cellular differentiation and maintenance in stem cells of breast cancer, potentially leading to its own effects [37]. It is important for women to be aware of this potential benefit of pregnancy and breastfeeding when considering their overall risk of developing breast cancer. Our study also revealed a significant difference between two groups in relation to a history of infertility treatment. Infertility treatment was more frequent among women with breast cancer. Several studies have focused on the relationship between infertility treatment and breast cancer [38–40]. It is too early to determine if there is a relationship between infertility treatment and cancer risk. Momenimovahed et al. (2019) suggested that while the relationship between infertility drugs and cancer is theoretically plausible, the intricate mechanisms and numerous factors involved in cancer formation make it challenging to definitively confirm this relationship. They did not find any conclusive evidence linking infertility drug use to an increase in cancer incidence [41].

However, a recent study has confirmed that infertility plays a role in increasing the risk of developing cancer [42]. However, the relationship between infertility treatments and breast cancer remains unclear. More studies are required to better understand the influence of infertility treatment on the incidence of cancer [41].

To the best of our knowledge, our study is the first case-control study with two matched study groups for age and BMI. High BMI, a common feature of PCOS, and age are important risk factors for breast cancer [43]. We applied matching for these confounders to ensure the validity and plausibility of our findings. Although case-control studies can provide valuable insights into potential associations, they cannot definitively prove causal effects [44]. Further clarification of the relationship between diseases ultimately requires cohort studies, which provide precise information on the diseases. Certain limitations must be considered when generalizing our findings. Firstly, the sample size was relatively small, indicating a need for further studies with a larger sample size. Secondly, due to the retrospective nature of the study, we were unable to assess the history of biochemical hyperandrogenism, which is one of the Rotterdam diagnostic criteria for PCOS. Additionally, we did not evaluate the potential effects of confounding variables such as breast cancer subtypes, hormone replacement therapy, hormonal treatments for breast cancer, and menopausal status, which could impact our results. Therefore, the results of this study must be interpreted with caution.

Conclusion

Our findings indicate that PCOS is likely to increase the risk of developing breast cancer by more than 3.6 times. It seems that paying attention to PCOS symptoms and providing necessary information to women with PCOS can play a crucial role in preventing or early diagnosis of breast cancer, especially in high-risk women. To confirm the findings of this study, future research involving a larger sample size is highly recommended.

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Author contributions
A.H.: Study conception and design, data collection, draft manuscript preparation; L.A.: Study conception, supervision, and design, critical revision and article editing, corresponding author; E.A.H.: Conceptualization, data collection; SH.H.: Analysis and interpretation of Results.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was the result of a research project with the ethics code IR.IUMS.REC.1402.080 approved by the Research Ethics Committee of Iran university of medical sciences. All participants signed a written informed consent form.

Consent for publication
Not applicable.

Conflict of interest
The authors declare that they have no conflicts of interest.

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