ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20230138

Association of polycystic ovary syndrome with mammographic density in Turkish women: a population-based case-control study

Ayşe Rabia Şenkaya[1*], Sabahattin Anıl Arı[1], İbrahim Karaca[1], Eyüp Kebapçı[2], Eren İsmailoğlu[3], Deniz Can Öztekin[1]

SUMMARY

OBJECTIVE: The objective of this study was to investigate the breast densities and Breast Imaging-Reporting and Data System scores of patients with polycystic ovary syndrome and normoovulatory women and to determine whether these patients constitute a high-risk population for breast cancer.

METHODS: This retrospective case-control study was conducted at our institution between January 2022 and December 2022, involving patients diagnosed with polycystic ovary syndrome. Menstrual periods, hyperandrogenemic findings, and ultrasound reports of the patients were retrieved from our hospital's database. Patients who met at least two of the Rotterdam criteria were included in the polycystic ovary syndrome group. A total of 70 premenopausal patients over the age of 40 years, diagnosed with polycystic ovary syndrome, and 70 normoovulatory women, matched for age and body mass index, were included in the study. The two groups were compared regarding age at menarche, menstrual pattern, gravida, parity, levels of follicle-stimulating hormone, luteinizing hormone, and estradiol, endometrial thickness, breast density category, and Breast Imaging-Reporting and Data System classifications.

RESULTS: Patients in the polycystic ovary syndrome group had a higher age at menarche (12.7 vs. 12.3, p=0.006). There was no difference between the gonadotropin levels in both groups. However, the estradiol level was higher in the polycystic ovary syndrome group (p<0.001). There was no statistically significant difference between the two groups in terms of breast density and Breast Imaging-Reporting and Data System scores (p=0.319 and p=0.650, respectively).

CONCLUSION: Although we can conclude that the risk of breast malignancy is not increased in patients with polycystic ovary syndrome, the impact of the complex hormonal status of polycystic ovary syndrome on breast cancer remains unclear in the literature.

KEYWORDS: Breast density. Breast neoplasms. Mammography. Menarche. Polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by hyperandrogenism, anovulation, and polycystic ovaries (PCOs), affecting approximately 5–10% of women of reproductive age[1]. The diagnosis of PCOS is based on the Rotterdam criteria, with oligo-anovulation defined as a menstrual cycle length of less than 35 days[2]. Although PCOS patients are categorized into different phenotypes, this classification remains a topic of debate[3].

PCOS patients often exhibit various metabolic changes, such as high body mass index (BMI), hyperandrogenism, and hyperinsulinemia[4].

Consequently, PCOS has been associated with an increased risk of several types of cancer[5].

The relationship between PCOS and breast cancer is intricate due to various factors that both elevate (e.g., first pregnancy at an advanced age) and reduce (e.g., late onset of menarche) the risk of breast cancer. Furthermore, obesity, which is common in PCOS, is also linked to cancer[6].

Several studies have examined the association between breast cancer and PCOS, but the results have been inconsistent[7,8].

Mammography is considered the gold standard screening method for early detection of breast cancer, significantly reducing breast cancer mortality. The current approach in mammography evaluation involves assessing the Breast Imaging-Reporting and Data System (BI-RADS) score within six categories and breast density within four categories, as outlined by the American College of Radiology (ACR) (Figures 1 and 2)[9].

[1]Bakırçay University, Faculty of Medicine, Gynecology and Obstetrics Clinic – İzmir, Turkey.
[2]Bakırçay University, Faculty of Medicine, General Surgery Clinic – İzmir, Turkey.
[3]Bakırçay University, Faculty of Medicine, Radiology Clinic – İzmir, Turkey.
*Corresponding author: dr.aysekanbak@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 08, 2023. Accepted on July 09, 2023.
Institution where the study was conducted: Bakırçay University Çiğli Training and Research Hospital, 8780/1 Street No:18 Yeni Mahalle Ata Sanayi/Çiğli/İzmir/35620/Turkey.

Mammographic density (MD) is a measurement used to describe the fibrous and glandular breast tissue, comprising epithelial tissue and stroma, observed on a mammogram[10].

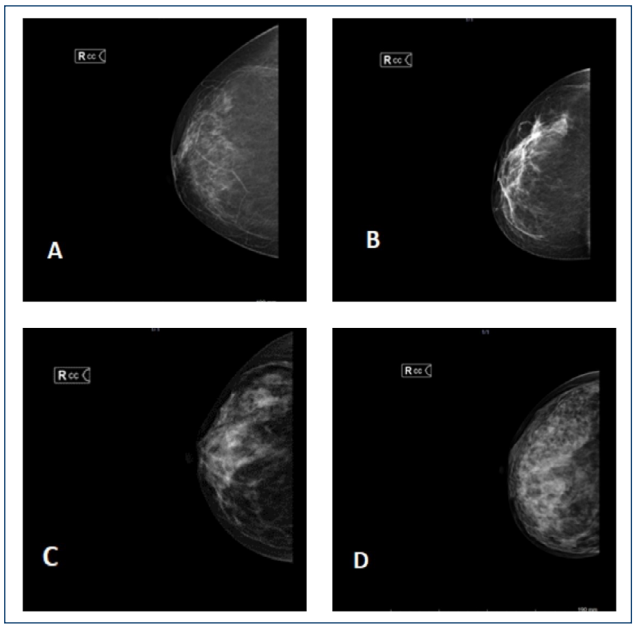

Figure 1. ACR BI-RADS classification for breast density.

Increasing MD serves as a valuable biomarker for breast cancer development. A meta-analysis demonstrated that women with an MD of at least 75% have a sixfold higher risk of developing breast cancer compared with those with an MD≤10%. A recent biological study conducted in 2018 revealed a higher transformation rate to malignant cells in dense breast tissue compared with non-dense tissue[11,12].

The objective of this study was to investigate the relationship between PCOS, high breast density, and an increased risk of breast cancer.

METHODS

This retrospective case-control study was conducted at our institution between January 2022 and December 2022, involving patients diagnosed with PCOS. PCOS was diagnosed according to the Rotterdam criteria: amenorrhea, clinical/biochemical hyperandrogenism, and PCOs on ultrasound and at least two of these criteria[5].

The database of our hospital was scanned, and the history of the patients, their menstrual status, hyperandrogenemic findings, and ultrasound reports were examined. Patients meeting at least two of these criteria were included in the PCOS group.

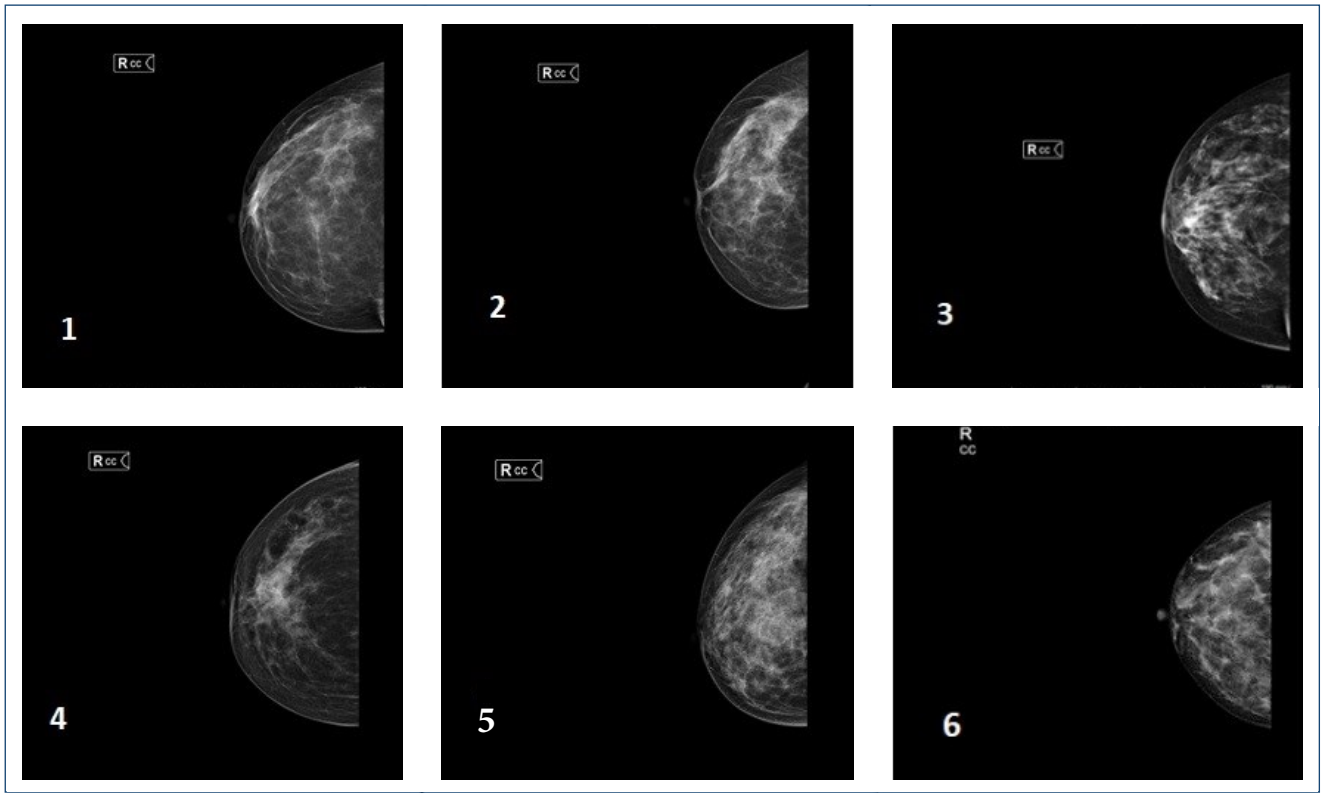

Figure 2. BI-RADS categorization.

A total of 70 PCOS and 70 normoovulatory women who had routine mammography in the premenopausal period and over the age of 40 years were included in the study. Mammograms are taken by the radiology technician in the hospital where the study is performed and interpreted by the radiologist. Two standard mediolateral-oblique and craniocaudal breast scans are routinely performed in our hospital with digital mammography for all patients aged 40 years and over. The study data were obtained from the hospital database by the researchers. Both groups were matched for age and BMI. Exclusion criteria were renal failure androgen-producing neoplasm, late-onset adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, breast surgery, and history of breast cancer.

All patients underwent mammography in the first half of the menstrual cycle, which was performed by radiology technicians with at least 10 years of experience. The BI-RADS is used to determine breast density. The final assessment includes the BI-RADS 0–6 categorization. A category assessment of BI-RADS 0 refers to an incomplete evaluation with further imaging, requiring additional mammographic views including spot compression or magnification and/or ultrasound. BI-RADS 1 refers to a negative examination, meaning that there are no masses, suspicious calcifications, or areas of architectural distortion. BI-RADS 2 is consistent with benign findings, including secretory calcifications, simple cysts, fat-containing lesions, calcified fibroadenomas, implants, and intramammary lymph nodes. BI-RADS 3 is probably benign and should have shortened interval follow-up to determine stability. Findings are a non-palpable, circumscribed mass on a baseline mammogram, a focal asymmetry, which becomes less dense on spot compression images, or a solitary group of punctate calcifications. BI-RADS 4 is a suspicious abnormality, representing the chance of being malignant (in percent). It is subdivided into a, b, and c. The subcategory of (a) has a low probability of malignancy with a 2–10% chance of malignancy. The subcategory of (b) has an intermediate change of malignancy ranging from 10 to 50%. The subcategory of (c) has a high probability of malignancy ranging from 50 to 95%. BI-RADS 5 is highly suggestive of malignancy more than 95%. The final category that was recently added is the BI-RADS 6, which is used for determining pathology-proven malignancy (Figure 2)[9].

The ACR BI-RADS is used for measuring breast density. ACR BI-RADS Atlas 2013 (version 5) is the updated version of the 2003 Atlas. It defines density as follows: (a) breasts are almost completely oily; (b) there are scattered areas of fibroglandular density; (c) heterogeneous density of breasts may hide small masses, and (d) excessive density of breasts reduces the sensitivity of mammography[9] (Figure 1).

Age, age at menarche, BMI, menstrual pattern, gravida, parity, estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels on the third day of menstruation, endometrial thickness measurements in the first 3 days of menstruation, BI-RADS classification scores and ACR breast density categories in mammography, and the presence of solid or cystic masses on breast ultrasound were scanned from computer-based hospital records (I.K). The data of the PCOS group and the normal group were compared.

Statistical analysis

According to a previous study, the number was calculated as 70 for each group with 80% power and 0.05 alpha error to detect the 25% difference between the two groups in breast density by using the Epi Info website (www.cdc.gov/epiinfo/)[13].

Frequency tables for categorical variables and descriptive statistics for continuous variables were calculated. The Shapiro-Wilk test of normality was used to examine whether the continuous data were normally distributed.

As the data were not normally distributed, continuous data in two independent groups (normoovulatory/PCOS) were compared with the Mann-Whitney U test. Categorical data were analyzed with the Pearson chi-square test for the presence/absence of PCOS. The significance was taken as 0.05 in all hypothesis tests. For statistical analysis, the IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp., Released 2017) program was used.

Statement of ethics

The ethics committee approval was obtained. The approval date is 29.12.2021, and the ethics committee decision number is 466. Due to the retrospective design of the study, it was not possible to obtain informed consent from the patients.

RESULTS

No significant difference was found between the group with PCOS (Group 1) and the group with normoovulatory women (Group 2), in terms of age, BMI, gravida, and parity. The mean menarche age of Group 1 was 12.7 years, while the mean menarche age of Group 2 was 12.3 years, which was statistically significant (p=0.006). Table 1 shows the demographic data.

When the endometrial thickness, FSH, and LH levels were compared, no statistically significant difference was found. The mean of E2 was found to be significantly higher in the PCOS group compared with the other group (p<0.001). There was no statistically significant difference between the two groups in terms of the presence of fibroadenoma and cystic mass in the

breast. When the ACR breast density category and BI-RADS score were compared, no statistically significant difference was found between the two groups (p=0.319 and 0.650, respectively). A comparison of study data by PCOS status is shown in Table 2.

DISCUSSION

Both epidemiological and experimental data suggest that the cumulative exposure of the mammary epithelium to estrogen unopposed by progesterone plays a role in breast cancer

Table 1. Demographic data.

	PCOS group/group 1 (n=70) (Mean±SD)	Normoovulatory group/group 2 (n=70) (Mean±SD)	P
Age (year)	42.6±3.7	42.2±3.2	0.230[a]
BMI (kg/m^2)	24.2±3.80	24.4±3.80	0.706[a]
Gravidity	2.6±1	2.5±0.9	0.358[b]
Parity	2.2±1.1	2.1±0.9	0.784[a]
Age of menarche (years)			
<12 years	7 (10%)	4 (5.7%)	0.006[b]
12–14 years	58 (82.8%)	59 (84.3%)	
≥14 years	5 (7.2%)	7 (10%)	

[a]Mann-Whitney U test, and [b]chi-square test; BMI: body mass index.

Table 2. Comparison of study data by polycystic ovary syndrome status.

	PCOS group/group 1 (n=70) (Mean±SD)	Normoovulatory group/group 2 (n=70) (Mean±SD)	p
Endometrial thickness (mm)	6.5±2.8	7±2.6	0.128[b]
FSH (mIU/mL)	12.4±11.05	13.1±11.6	0.687[b]
LH (mIU/mL)	16.1±12.03	13.5±12.4	0.802[b]
Estradiol (pg/mL)			
0–40 pg/mL	(7) 10%	(41) 58.6%	**<0.001[c]**
40–80 pg/mL	(11) 15.7%	(18) 25.7%	
≥80 pg/mL	(52) 74.3%	(11) 15.7%	
ACR breast density (n %)			
A	(3) 4%	(9) 12%	0.319[b]
B	(21) 30%	(18) 26%	
C	(39) 56%	(35) 50%	
D	(7) 10%	(8) 12%	
BIRADS (median)	1	2	0.650[b]
BIRADS 1 (n%)	(16) 22.9%	(21) 30%	
BIRADS 2 (n%)	(32) 45.7%	(26) 37.1%	
BIRADS 3 (n%)	(20) 28.6%	(19) 27.2%	
BIRADS 4 (n%)	(1) 1.4%	(1) 1.4%	
BIRADS 5 (n%)	(1) 1.4%	(1) 1.4%	
BIRADS 6 (n%)	0	(2) 2.9%	
Presence of cystic mass in the breast[a]	50%	64.3%	0.088[c]
Cyst size in the breast (mm)	8.8±6.6	7.9±6.1	0.665[b]
Presence of fibroadenoma in the breast[a]	8.60%	18.60%	0.084[c]
Fibroadenoma size (mm)	9.2±3.6	9.4±5.1	0.691[b]

[a]n (%), [b]Mann-Whitney U test, and [c]chi-square test; BMI: body mass index. Bold indicates statistically significant p-value.

development[14]. While planning our study, we set out with the idea of whether this unopposed estrogen status, which is mostly seen in PCOS, affects breast density and BI-RADS scores and therefore breast cancer risk.

Although there are studies in the literature on whether PCOS increases the risk of breast cancer or not, a common conclusion has not been reached[15-20].

In our study, we used the evaluation of ACR breast density and BI-RADS in mammography, which is accepted as one of the best detection methods of breast cancer risk. However, the most important thing is to raise awareness of women on this issue and to facilitate access to health services for women with symptoms[21].

The normoovulatory women group and the group with PCOS have no significant difference in terms of age distribution, BMI, gravida, and parity, and the two groups were homogeneous in terms of these data. There are results in the literature that obesity increases the risk of especially estrogen receptor (ER)-positive breast cancer[22,23]. In our study, the homogeneity of the BMI index between the two groups excluded the obesity factor.

Although there are studies showing that hormonal factors affect the endometrium in PCOS patients[24], we did not find a significant difference in endometrial thickness between the two groups as a result of our study. There is no difference between the two groups in terms of FSH and LH levels. When E2 levels were compared, E2 levels of Group 1 patients were found to be significantly higher, as expected in the PCOS clinic.

In the literature, very different results have been suggested regarding breast density and breast cancer risk in PCOS patients, which is the main starting point of our study. In the literature, Mendelian randomized studies have shown that the risk of ER-positive breast cancer is increased in PCOS in particular[15,20].

A retrospective cohort study showed that the most common cause of death in PCOS patients was breast cancer, but there was no evidence that PCOS patients have a higher risk of breast cancer[18].

In one study, unopposed estrogen has been shown to increase the level of IGF-1[25]. However, in another study, no relationship was found between the IGF-1 level and the risk of developing breast cancer[26].

Contrary to these studies, there are also results in various meta-analyses. Barry et al. suggested that patients with PCOS do not have an increased risk for breast cancer[16].

In other meta-analyses in the literature, they stated that the relationship between breast cancer risk and PCOS is complex and a clear conclusion could not be reached[17,19].

Eslami et al. compared the BIRADS scores reflecting breast densities of the normal group with those of the PCOS group and found no significant difference in breast density between the two groups[27].

When the ACR breast density category and BI-RADS score were compared, no statistically significant difference was found between the two groups (p=0.319 and 0.650, respectively). Contrary to the hypothesis we thought at the beginning of the study, we did not detect a significant difference in BI-RADS scores and breast density in PCOS patients compared with normoovulatory women. As in many studies in the literature, it can be said that the reason why this relationship has not been clarified is that PCOS has an environment of both unopposed estrogen and hyperandrogenemia. D'Amelio et al. showed a significant association between PCOS and benign breast pathologies[28]. In another study, they suggested that there was no significant association between benign breast pathologies and PCOS[29].

In our study, we did not find a significant difference between the two groups in terms of benign breast pathologies detected on ultrasound.

PCOS is divided into phenotypes. The clinical picture of hyperandrogenism varies in different PCOS phenotypes[30]. Metabolic disorder is also seen in PCOS patients, and it may affect the breast tissue[31]. However, as laboratory hyperandrogenism and metabolic status were not evaluated in our study and PCOS patients were not examined according to phenotypes, no comment could be made on metabolic status in PCOS, PCOS phenotypes, and breast density.

The limitation of our study is that this is a retrospective study. The advantageous aspect of our study is that age, BMI, gravida, and parity numbers were homogeneous for both groups.

Our study aimed to investigate the relationship between PCOS and breast density as well as breast cancer risk. Despite the existing epidemiological and experimental data suggesting a potential link between unopposed estrogen exposure and breast cancer development, there is no consensus in the literature regarding the association between PCOS and breast cancer risk. Our study utilized ACR breast density evaluation and BI-RADS scoring in mammography, which are considered reliable methods for assessing breast cancer risk. We found no significant difference in breast density and BI-RADS scores between the group of women with PCOS and the normoovulatory group. It is worth noting that the complex hormonal milieu of PCOS, characterized by both unopposed estrogen and hyperandrogenemia, may contribute to the lack of clarity in this relationship. Furthermore, our study did not reveal a significant difference in the incidence of benign breast pathologies between the two groups.

CONCLUSION

Our study did not provide evidence supporting an association between PCOS, breast density, and breast cancer risk as assessed by ACR breast density and BI-RADS scoring. Further research, including prospective studies with larger sample sizes and longer follow-up periods, is needed to elucidate the complex relationship between PCOS and breast cancer risk.

AUTHORS' CONTRIBUTIONS

ARŞ: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. **SAA:** Data curation, Investigation. **Eİ:** Data curation, Methodology. **İK:** Formal Analysis, Methodology, Writing – review & editing. **EK:** Formal Analysis, Validation. **DCÖ:** Project administration, Resources, Supervision, Visualization.

REFERENCES

1. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Polycystic ovary syndrome. Nat Rev Dis Primers. 2016;2:16057. https://doi.org/10.1038/nrdp.2016.57
2. Yildiz BO. Diagnosis of hyperandrogenism: clinical criteria. Best Pract Res Clin Endocrinol Metab. 2006;20(2):167-76. https://doi.org/10.1016/j.beem.2006.02.004
3. Baracat EC, Baracat MCP, José M SJ. Are there new insights for the definition of PCOS?. Gynecol Endocrinol. 2022;38(9):703-4. https://doi.org/10.1080/09513590.2022.2121387
4. Christ JP, Gunning MN, Fauser BCJM. Implications of the 2014 Androgen Excess and Polycystic Ovary Syndrome Society guidelines on polycystic ovarian morphology for polycystic ovary syndrome diagnosis. Reprod Biomed Online. 2017;35(4):480-3. https://doi.org/10.1016/j.rbmo.2017.06.020
5. Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. Hum Fertil (Camb). 2000;3(2):101-5. https://doi.org/10.1080/1464727002000198781
6. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97(1):28-38.e25. https://doi.org/10.1016/j.fertnstert.2011.09.024
7. Gottschau M, Kjaer SK, Jensen A, Munk C, Mellemkjaer L. Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study. Gynecol Oncol. 2015;136(1):99-103. https://doi.org/10.1016/j.ygyno.2014.11.012
8. Shen CC, Yang AC, Hung JH, Hu LY, Tsai SJ. A nationwide population-based retrospective cohort study of the risk of uterine, ovarian and breast cancer in women with polycystic ovary syndrome. Oncologist. 2015;20(1):45-9. https://doi.org/10.1634/theoncologist.2014-0311
9. Magny SJ, Shikhman R, Keppke AL. Breast ımaging reporting and data system. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
10. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med. 2003;138(3):168-75. https://doi.org/10.7326/0003-4819-138-3-200302040-00008
11. Boyd N, Berman H, Zhu J, Martin LJ, Yaffe MJ, Chavez S, et al. The origins of breast cancer associated with mammographic density: a testable biological hypothesis. Breast Cancer Res. 2018;20(1):17. https://doi.org/10.1186/s13058-018-0941-y
12. El-Bastawissi AY, White E, Mandelson MT, Taplin SH. Reproductive and hormonal factors associated with mammographic breast density by age (United States). Cancer Causes Control. 2000;11(10):955-63. https://doi.org/10.1023/a:1026514032085
13. Alipour S, Bayani L, Saberi A, Alikhassi A, Hosseini L, Eslami B. Imperfect correlation of mammographic and clinical breast tissue density. Asian Pac J Cancer Prev. 2013;14(6):3685-8. https://doi.org/10.7314/apjcp.2013.14.6.3685
14. Key TJ, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol. 1988;24(1):29-43. https://doi.org/10.1016/0277-5379(88)90173-3
15. Wen Y, Wu X, Peng H, Li C, Jiang Y, Su Z, et al. Breast cancer risk in patients with polycystic ovary syndrome: a Mendelian randomization analysis. Breast Cancer Res Treat. 2021;185(3):799-806. https://doi.org/10.1007/s10549-020-05973-z
16. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014;20(5):748-58. https://doi.org/10.1093/humupd/dmu012
17. Carvalho MJ, Subtil S, Rodrigues Â, Oliveira J, Figueiredo-Dias M. Controversial association between polycystic ovary syndrome and breast cancer. Eur J Obstet Gynecol Reprod Biol. 2019;243:125-32. https://doi.org/10.1016/j.ejogrb.2019.10.011
18. Ding DC, Chen W, Wang JH, Lin SZ. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: a population-based cohort study in Taiwan. Medicine (Baltimore). 2018;97(39):e12608. https://doi.org/10.1097/MD.0000000000012608
19. Shobeiri F, Jenabi E. The association between polycystic ovary syndrome and breast cancer: a meta-analysis. Obstet Gynecol Sci. 2016;59(5):367-72. https://doi.org/10.5468/ogs.2016.59.5.367
20. Zhu T, Cui J, Goodarzi MO. Polycystic ovary syndrome and breast cancer subtypes: a Mendelian randomization study. Am J Obstet Gynecol. 2021;225(1):99-101. https://doi.org/10.1016/j.ajog.2021.03.020
21. Gonçalves R, Soares-Jr JM, Baracat EC, Filassi JR. Ethical issues surrounding breast cancer screening in Brazil. Clinics (Sao Paulo). 2019;74:e1573. https://doi.org/10.6061/clinics/2019/e1573
22. Gravena AAF, Romeiro Lopes TC, Demitto MO, Borghesan DHP, Dell' Agnolo CM, Brischiliari SCR, et al. The obesity and the risk of breast cancer among pre and postmenopausal women. Asian Pac J Cancer Prev. 2018;19(9):2429-36. https://doi.org/10.22034/APJCP.2018.19.9.2429
23. Bhardwaj P, Au CC, Benito-Martin A, Ladumor H, Oshchepkova S, Moges R, et al. Estrogens and breast cancer: mechanisms involved in obesity-related development, growth and progression. J Steroid Biochem Mol Biol. 2019;189:161-70. https://doi.org/10.1016/j.jsbmb.2019.03.002
24. Baracat MCP, Baracat EC, Simões RS, Simões MJ, Maciel GAR, Azziz R, et al. Hormonal and metabolic factors ınfluence the action of progesterone on the endometrium of women with polycystic ovary syndrome. Diagnostics (Basel). 2023;13(3):382. https://doi.org/10.3390/diagnostics13030382
25. Marshman E, Streuli CH. Insulin-like growth factors and insulin-like growth factor binding proteins in mammary gland function. Breast Cancer Res. 2002;4(6):231-9. https://doi.org/10.1186/bcr535

26. Trinconi AF, Filassi JR, Soares JM, Baracat EC. Evaluation of the insulin-like growth factors (IGF) IGF-I and IGF binding protein 3 in patients at high risk for breast cancer. Fertil Steril. 2011;95(8):2753-5. https://doi.org/10.1016/j.fertnstert.2011.02.014
27. Eslami B, Alipour S, Hosseini R, Fattah B, Moini A. Breast density in polycystic ovarian syndrome patients: a case-control study. Int J Reprod Biomed. 2019;17(8):577-84. https://doi.org/10.18502/ijrm.v17i8.4823
28. D'Amelio R, Farris M, Grande S, Feraudo E, Iuliano A, Zichella L. Association between polycystic ovary and fibrocystic breast disease. Gynecol Obstet Invest. 2001;51(2):134-7. https://doi.org/10.1159/000052909
29. Kunicki M, Smolarczyk R. Polycystic ovary syndrome and fibrocystic breast disease: an updated review. Horm Metab Res. 2021;53(4):219-24. https://doi.org/10.1055/a-1392-0938
30. Baracat EC, Baracat MCP, José M SJ. Are there new insights for the definition of PCOS?. Gynecol Endocrinol. 2022;38(9):703-04. https://doi.org/10.1080/09513590.2022.2121387
31. Baracat MCP, Baracat EC, Simões RS, Simões MJ, Maciel GAR, Azziz R, et al. Hormonal and metabolic factors ınfluence the action of progesterone on the endometrium of women with polycystic ovary syndrome. Diagnostics (Basel). 2023;13(3):382. https://doi.org/10.3390/diagnostics13030382