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The effect of polycystic ovarian syndrome on fibrocystic breast changes in postmenopausal women

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ABSTRACT

Background: Fibrocystic breast changes (FCCs) are benign lesions thought to be caused by an increased estrogen-to-progesterone ratio. One of the most common endocrinopathies that increases this ratio is polycystic ovarian syndrome (PCOS). Although nonproliferative FCCs do not increase the risk of breast cancer, they can make mammographic detection of malignancy in postmenopausal women more difficult. The aim of this study was to investigate the effects of PCOS on the development of postmenopausal FCCs.

Methods: This retrospective cohort study used the TriNetX research network to identify two cohorts of postmenopausal women (Z78.0) older than 45, without a prior diagnosis of FCCs (N60.1) or hormone replacement therapy (Z79.890). One cohort included a diagnosis of PCOS (E28.2). The cohorts were balanced for age, race, ethnicity, and hormonally relevant comorbidities. The cohorts were then evaluated for the development of FCCs after menopause.

Results: Postmenopausal patients with PCOS were 52% more likely to develop FCCs than those without PCOS (2.2% vs. 1.4%, relative risk 1.52, 95% confidence interval 1.05, 2.22, $P = 0.03$).

Conclusion: Postmenopausal women with PCOS have a higher risk of developing FCCs. Further studies are needed to improve the differentiation of benign FCCs from malignant lesions on imaging for postmenopausal women with PCOS who develop FCCs.

KEYWORDS Breast cancer screening; breast radiology; fibrocystic breast changes; polycystic ovarian syndrome; postmenopausal

CME

Target audience: Radiologists, obstetricians/gynecologists, oncologists, endocrinologists.

Learning objectives: After completing the article, the learner should be able to

1. Understand the hormonal imbalances that contribute to the development of fibrocystic breast changes (FCCs)
2. Recognize the potential effect that polycystic ovarian syndrome (PCOS) has on the development of FCCs and how these changes can make it difficult to distinguish from malignancy, especially in early postmenopausal women
3. Reflect on the importance of improving breast cancer screenings for postmenopausal women with PCOS through careful evaluation and monitoring of new breast changes

Faculty credentials/disclosure: Brittany Dang and Madison Clewis are currently medical students at the University of Texas Medical Branch. Dr. Brittany Miles is a radiology resident at Baylor University Medical Center. Dr. Quan Nguyen is radiology faculty and associate professor for the breast imaging division of the Department of Radiology at Baylor College of Medicine with an MBA from the University of Houston C.T. Bauer College of Business in Healthcare Leadership, Leadership Development. The authors and planner for this educational activity have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Fibrocystic breast changes (FCCs) are common, benign breast lesions with an observed lifetime prevalence of up to 70% to 90% in women.[1,2] These changes are mostly found in women aged 20 to 50 years and in postmenopausal women who use hormone replacement therapy. They often present as tender breast nodules that cycle with menstruation and are characterized by stromal hyperplasia, fibrosis, adenosis, and cyst formation.[3] They can also present as complex cystic lesions or a solid mass, which can be concerning for malignancy and indicate the need for a biopsy.[4] Nonproliferative lesions do not pose an increased risk of breast cancer, proliferative lesions without atypia minimally increase the risk, and rare proliferative lesions with atypia can increase the risk by approximately fourfold.[5] FCCs are predominantly found in ovulating premenopausal women due to their higher estrogen levels compared to postmenopausal women and are believed to be associated with the transient increase in the estrogen-to-progesterone (E:P) ratio before their menstrual cycle. Postmenopausal women no longer experience the regular hormone fluctuations associated with menstrual cycles and display lower absolute levels of estrogen than premenopausal women, which makes the development of FCCs in postmenopausal women extremely rare when not on hormone replacement therapy. One study reported an incidence of 11.5 new FCCs per 1000 person-years in women 50 or older compared to 29.3 per 1000 person-years in women younger than 50.[6]

In 2001, D'Amelio et al found that 92% of their sample of women with PCOS had co-occurring FCCs.[7] A separate study in 2009 found a 3.17 times higher risk of FCCs in patients with PCOS.[8] Women with PCOS experience a chronic elevation in the E:P ratio, similar to the transient hormonal changes ovulating women have before their menstrual cycle. The prolonged nature of progesterone-unopposed estrogen exposure in this group increases their risk of developing FCCs compared to women without PCOS.[9] Despite the significant association between PCOS and benign breast disease, the unopposed estrogen stimulation induced by PCOS does not appear to be correlated with an increased risk of breast malignancy.[10]

PCOS is the most common endocrine disorder in women, affecting 8% to 13% of premenopausal women[11,12] and 6% to 9% of postmenopausal women.[13,14] The exact etiology of PCOS is not fully understood, but some proposed causative factors include hypothalamic-pituitary axis abnormalities, insulin resistance, and enzymatic defects of steroidogenesis in the ovaries and adrenal glands.[15] The diagnosis of PCOS requires the exclusion of other endocrine abnormalities and two of the following three criteria: chronic anovulation, clinical evidence of hyperandrogenism, and the appearance of ovarian cysts on ultrasound. Women are typically not diagnosed with PCOS after menopause as the clinical signs and symptoms that help with diagnosis, such as irregular menses and hyperandrogenism, have either ceased or present similarly to postmenopausal symptoms and make it difficult to distinguish between the two. Women are often told that the symptoms of PCOS, like FCCs, will resolve after menopause due to the drop in estrogen. However, PCOS still demonstrates hormonal impacts after menopause.[7,16]

Although most FCCs are considered benign and do not increase the risk of breast cancer, their presence makes the detection of breast cancer more challenging, particularly in postmenopausal women. FCCs can mimic the radiographic appearance of malignant breast tumors or obscure small malignant lesions. The uncertainty that can accompany FCCs often leads to unnecessary operation and an increased false-positive rate of breast cancer detection in postmenopausal women. Women with PCOS exhibit a hormone profile that contributes to the development of FCCs, but few studies have thoroughly investigated whether their risk of developing new FCCs remains elevated after menopause or is comparable to that of postmenopausal women without PCOS. Therefore, understanding the relationship between PCOS and FCCs in postmenopausal women may help reduce the number of avoidable operations and false-positive detections of breast cancer in this population. The aim of this study was to evaluate the risk of new FCCs in postmenopausal women with PCOS.

METHODS

The TriNetX research network was used for this study. TriNetX provides access to anonymized medical record information for more than 107 million patients in 75 large

Table 1. Baseline characteristics of cohorts after propensity score matching

Variable	No PCOS	PCOS	*P* value
Current age	59.5 ± 8.6	59.5 ± 8.6	0.90
Age at index	55.1 ± 8.3	55.1 ± 8.4	0.98
Caucasian	81.6%	81.7%	0.90
Black or African American	7.7%	7.6%	0.93
Asian	1.5%	1.4%	0.84
Unknown race	6.2%	6.1%	0.80
Hispanic or Latino	6.8%	7.0%	0.66
Not Hispanic or Latino	76.7%	76.3%	0.73
Unknown ethnicity	16.5%	16.6%	0.92
Body mass index (kg/m^2)	33.2 ± 9.1	35.0 ± 9.3	0.29
Type 2 diabetes mellitus (E11)*	34.4%	34.3%	0.90
Impaired fasting glucose (R73.01)	7.7%	8.0%	0.68
Hypothyroidism (E03.9)	28.0%	28.0%	0.96
Androgen excess (E28.1)	0.9%	1.1%	0.53

* International Classification of Disease-10 code.
PCOS indicates polycystic ovarian syndrome.

Table 2. Risk of fibrocystic breast changes in postmenopausal women with and without PCOS

Cohort	Patients	Events	Risk percent
PCOS	3053	67	2.2%
No PCOS	3125	45	1.4%

PCOS indicates polycystic ovarian syndrome.

healthcare organizations. The current study did not involve the collection, use, or distribution of identifiable patient information. Two patient cohorts were created by the identification of International Classification of Disease–10 (ICD-10) codes. Both consisted of postmenopausal women (Z78.0) older than 45 who were not treated with hormone replacement (Z79.890) and who did not have a prior diagnosis of fibrocystic changes of the breast (N60.1). One cohort contained a diagnosis of PCOS (E28.2) prior to menopause, while the other did not have a diagnosis of PCOS. The cohorts were balanced for age, race, ethnicity, type 2 diabetes mellitus (E11), impaired fasting glucose (R73.01), hypothyroidism (E03.9), androgen excess (E28.1), and body mass index.

Propensity score matching through TriNetX was performed using logistic regression analysis and the greedy nearest neighbor algorithm. Patients who had the outcome of fibrocystic changes of the breast before menopause were excluded from this study. The cohorts were then evaluated for the eventual development of fibrocystic changes. The risk ratio of developing fibrocystic changes of the breast after menopause was calculated with a 95% confidence interval. The statistical significance of the risk ratio was determined using a *P* value threshold of 0.05. Identification of the specific diagnostic modalities used to detect FCCs in patients was not possible with the use of ICD-10 codes, which remains a limitation of this study.

RESULTS

After propensity score matching, 3125 patients without PCOS and 3053 patients with PCOS were included in the final analysis. The average age of menopause for each group was 55.1 years old. There was no significant difference in race, ethnicity, body mass index, or comorbidities between the groups (*Table 1*).

Postmenopausal women with PCOS were 52% more likely to develop FCCs compared to postmenopausal women without PCOS (2.2% vs 1.4%, risk ratio 1.52, 95% confidence interval 1.05–2.22, $P = 0.03$) (*Table 2*).

DISCUSSION

In the current study of 6178 postmenopausal women, those with a diagnosis of PCOS had a 52% higher risk of developing new FCCs after menopause compared to women without PCOS. There were no observed differences in age at menopause, race, ethnicity, body mass index, or comorbidities between the cohorts, suggesting that our findings are not likely due to variations in these parameters. The significant increase in the risk of developing FCCs after menopause observed in this study is consistent with other studies evaluating this association.[7,8] This suggests that despite their change in hormone profile after menopause, women with PCOS have an increased risk of FCCs that persists into the postmenopausal period. Due to the lack of articles directly evaluating the association of FCCs exclusively in postmenopausal women with PCOS, further discussion is derived and extended from the available investigations that examined the hormonal changes of women with and without PCOS transitioning through menopause or in the early postmenopausal period.

Several factors related to hormonal imbalances in PCOS may contribute to the observed findings, and these imbalances may be aggravated by the changes that occur in the menopausal transition and early postmenopausal period. The relative estrogen dominance that occurs in PCOS has been implicated in the development of FCCs.[8] In PCOS, ovulation does not occur, which prevents the formation of the progesterone-secreting corpus luteum. Without the negative feedback of progesterone, luteinizing hormone (LH) continues to be secreted by LH-secreting cells. The resulting imbalance in the ratio of LH to follicle-stimulating hormone hinders the maturation of follicles for ovulation. Additionally, LH increases production of androgens by thecal cells, and this hyperandrogenism can exert further inhibitory effects on progesterone.

Normal breast growth and function are regulated by a delicate balance between estrogen and progesterone, with breast proliferation being largely estrogen dependent. Therefore, in the chronically progesterone-suppressed and estrogen-dominant state that PCOS creates, there is a greater likelihood of inappropriate stimulation of ductal and stromal proliferation of the breasts.

During menopause, ovarian function declines, resulting in a significant decrease in both estrogen and progesterone. However, the decrease in progesterone is more pronounced than the decrease in estrogen, causing an elevated E:P ratio.[17] This elevation has been shown to be significantly higher in women transitioning through menopause than in premenopausal women and is exaggerated in the setting of prolonged intermenstrual intervals.[17] Consequently, it is possible that women with PCOS, who already experience prolonged intermenstrual intervals and unopposed estrogen, may experience larger derangements in their E:P ratios compared to women without PCOS as they transition through menopause and enter the early postmenopausal period.

While an elevated E:P ratio is known to increase the risk of FCCs, PCOS is also associated with other contributory endocrine abnormalities, including relative hyperandrogenism. Although the current study did not show a difference in the number of women diagnosed with androgen excess (*Table 1*), discussion of relative hyperandrogenism as a potential contributor to our findings is warranted because formal diagnoses may not be documented for use by TriNetX if the androgen excess is not absolute or if the individual symptoms of hyperandrogenism are reported separately instead. One study found that in older and younger women with PCOS, testosterone levels were increased compared to age-matched controls.[16] The relative increase in androgen levels also appears to fluctuate with age. Several studies suggest that although ovarian production of androgens decreases with age in women with and without PCOS, ovarian and adrenal secretion of androgens remains elevated in women with PCOS during menopausal transition and likely the early postmenopausal period for a more extended amount of time than in women without PCOS.[18,19] The increased volume of adipose tissue associated with PCOS and the postmenopausal period also allows for more peripheral conversion of androgens to estrogens.[20] Therefore, the extended hyperandrogenic state of postmenopausal women with PCOS may promote persistent aromatization of androgens to estrogen, which could contribute to a further enhanced E:P ratio and the formation of FCCs. As postmenopausal women with PCOS age, their estrogen and androgen levels fall to levels similar to those in women without PCOS, with statistically significant differences disappearing at a mean age of 62.[21] This suggests that the risk of postmenopausal women with PCOS developing conditions like FCCs may be highest in the early postmenopausal period, gradually decreasing as androgen and estrogen levels return to normal limits.

Mammography is the standard screening method for breast cancer in postmenopausal women. However, FCCs can make it challenging to differentiate between benign and malignant lesions on mammography due to increased breast density caused by extensive fibrosis and adenosis. Magnetic resonance imaging (MRI) is becoming more popular as a supplemental screening method after mammography in high-risk women, especially those with dense breasts. However, studies have shown that focal FCCs can mimic certain malignancies, leading to a higher rate of false positives and more unnecessary procedures.[22,23] Ultrasound can provide additional help in confirming benign breast findings in lesions that cannot be fully assessed on mammograms, particularly in women with dense or fibrocystic breasts.[24,25] Therefore, a multimodal screening approach with mammogram and ultrasound may be particularly beneficial for postmenopausal women with PCOS, who are at an increased risk of developing FCCs that are prone to misdiagnosis. For all lesions with an uncertain diagnosis or concerning features on either imaging modality, core-needle biopsy is still indicated, given that postmenopausal women are at an increased risk of developing breast cancer.

The current multi-institutional study provides valuable insights into the association between PCOS and FCCs in postmenopausal women. The study has several strengths, including the span of the population, propensity score matching for demographic and hormonally significant parameters, and exclusion criteria. To our knowledge, this is the first study to investigate the risk of developing FCCs exclusively in postmenopausal women with a diagnosis of PCOS. However, there are some limitations regarding the use of ICD-10 codes in this study that warrant consideration. This study relied heavily on diagnostic codes, and because TriNetX does not account for differences in diagnostic algorithms or testing across institutions, there is the possibility of documentation variability. Additionally, it is possible that women who received their diagnoses of PCOS or FCCs at separate institutions were excluded from the TriNetX analysis if their deidentified medical records from participating healthcare organizations did not include previous diagnoses from other nonparticipating healthcare organizations. Many women also go undiagnosed for these conditions for several years if they do not seek medical care or are lost to follow-up. Therefore, it is important to consider that the current dataset may underrepresent the number of postmenopausal women with PCOS who develop FCCs. Despite these limitations, this research is a crucial addition to understanding the relationship between PCOS and FCCs in an understudied population that would help improve breast cancer screening and management.

In conclusion, women with PCOS may experience lasting estrogen dominance and relative hyperandrogenism in the early postmenopausal period that can contribute to the development of rare FCCs. Although FCCs are mostly benign, they can make it challenging to distinguish between benign

and malignant changes on regular breast cancer screening mammograms. Therefore, it is important for clinicians to be aware that the new breast changes in postmenopausal women with a diagnosis of PCOS may be benign FCCs. However, for postmenopausal women with new suspected FCCs on screening mammograms, further evaluation with ultrasound could help confirm benign changes and exclude breast cancer. In ultrasound cases that are indeterminate, a core-needle breast biopsy may be performed for a definite diagnosis.

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