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Association between Polycystic Ovary Syndrome and Breast Cancer: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author VJTA conceptualized and designed the study. Authors NAD and VJTA supervised and conducted critical revision of the manuscript. Authors KJN and DTSS contributed to the literature search, data analysis and writing of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: Polycystic ovary syndrome (PCOS) is a common endocrine disorder seen in women of reproductive age. The hormonal profile and comorbidities seen in women with PCOS like obesity and diabetes are some of the main risk factors of breast cancer. The aim of this review is to investigate the plausible association between PCOS and breast cancer. This review focuses on the epidemiological evidence, association of PCOS-related symptoms and PCOS medications on the incidence of breast cancer.

Methodology: A comprehensive literature search using Ovid MEDLINE, Google Scholar and PubMed was performed to identify epidemiologic studies that have been published in the last 10 years (from 2010 to 25th June 2020) that reported on the association between PCOS and breast cancer. The following keywords were used: polycystic ovary syndrome, breast cancer and breast neoplasms.

Results: Most of the epidemiological studies did not observe significant association between PCOS and breast cancer. However, evidence shows that elevated androgen levels and estrogen levels are associated with increased risk of estrogen receptor positive breast cancer. In addition, this review found increased breast cancer risk in women with obesity, hyperinsulinemia and low level of sex

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hormone binding globulin. Unlike metformin and clomiphene citrate, combined hormonal contraceptive, being the first line treatment for PCOS is linked with higher breast cancer risk.
Conclusion: Clinical findings from this review are inconsistent, hence a firm conclusion cannot be made regarding the association between PCOS and breast cancer, emphasizing the need for more prospective studies to be conducted in the future.

Keywords: Polycystic ovary syndrome; breast cancer; hormonal profile; medications.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders seen in women of reproductive age. It is a complex syndrome with different clinical manifestations owing to various genetic, metabolic and environmental factors. However, many aspects of its pathophysiological mechanisms remain obscure [1]. Women with PCOS often have menstrual irregularity, clinical and biochemical hyperandrogenism, anovulatory infertility and metabolic dysfunction.

There are 3 different guidelines for diagnosing PCOS as shown in Table 1. Rotterdam criteria is used by most expert groups to make a diagnosis of PCOS. However, according to the most recent 2018 International Guidelines for PCOS, some adjustments were made on the Rotterdam criteria. Ultrasound is not required in adults and not recommended in adolescents if oligo- or anovulation and hyperandrogenism coexist [2].

Hyperandrogenism is a significant factor in the development of PCOS as it causes anovulation as well as ovarian stromal hyperplasia. It is also linked with increased insulin resistance and obesity. Meanwhile, breast cancer is a hormone dependent cancer as it depends on estrogen and other hormones for growth [6]. The hormonal profile of PCOS such as high androgen level, high estrogen level and low sex hormone binding globulin level may be implicated in the pathogenesis of breast cancer which will be further discussed later. This review aims to investigate the association between PCOS and breast cancer considering the significant overlap between the hormonal profile, clinical manifestation of PCOS and the risk factors of breast cancer.

2. EPIDEMIOLOGIC EVIDENCE OF THE ASSOCIATION BETWEEN PCOS AND BREAST CANCER

Looking into the hormonal profile and comorbidities of women with PCOS provides us with an overview of the possible relationship between PCOS and breast cancer. Table 2 summarizes the epidemiological studies that looked into PCOS and breast cancer risk. 10 published articles were included: 1 systematic review, 2 meta-analyses, 5 cohort studies and 2 case-control studies.

The most recent meta-analysis which comprised 5 cohort studies and 3 case-control studies revealed no significant association between PCOS and risk of breast cancer (RR for cohort studies: 1.18, 95% CI: 0.93-1.43; OR for case-control studies: 0.87, 95% CI: 0.44-1.31) [7]. The other systematic review by Harris et al. [8] and meta-analysis by Barry et al. (OR: 0.95, 95% CI: 0.64-1.39) [9] demonstrated similar null association.

A population-based cohort study carried out by Yin et al. in 2019 including 14,764 women with PCOS showed that PCOS was positively linked with an increase overall cancer risk (fully adjusted HR: 1.15, 95% CI: 1.00-1.33) but not

Table 1. Diagnostic criteria for PCOS

NIH Consensus Criteria 1990 [3] (2 out of 2 criteria required)	Rotterdam criteria 2003 [4] (2 out of 3 criteria required)	AE-PCOS Criteria 2006 [5] (2 out of 2 criteria required)
- Menstrual irregularity due to oligo- and/or anovulation - Clinical and/or biochemical signs of hyperandrogenism	- Oligo- and/or anovulation - Clinical and/or biochemical signs of hyperandrogenism - Polycystic ovaries on ultra sound	- Clinical and/or bioche mical signs of hyperandro genism - Ovarian dysfunction- oligo /anovulation or polycystic ovaries on ultrasound

** NIH: National Institutes of Health; AE-PCOS: Androgen Excess and PCOS Society*

Table 2. Epidemiologic evidence of the association between PCOS and breast cancer

Author	Year	Study design	Breast cancer cases (n)	Overall result RR/OR/HR (95% CI)	Conclusion
Yin et al. [7]	2019	Cohort study	48	0.85 (0.64-1.13)	No association
Ding et al. [8]	2018	Cohort study	102	0.98 (0.58-1.65)	No association
Harris et al. [5]	2016	Systematic review	14486	-	No association
Shobeiri et al. [4]	2016	Meta-analysis	-	Case-control studies: 0.87 (0.44 -1.31) Cohort studies: 1.18 (0.93 -1.43)	No association
Kim et al. [12]	2016	Case-control study	1508	2.74 (1.13-6.63)	Increased risk
Shen et al. [9]	2015	Cohort study	44	1.61 (0.91-2.84)	No association
Gottschau et al. [10]	2015	Cohort study	59	1.1 (0.8-1.4)	No association
Barry et al. [6]	2014	Meta-analysis	3618	0.95 (0.64-1.39)	No association
Brinton et al. [11]	2010	Cohort study	9	0.90 (0.4-1.7)	No association
Ghasemi et al. [13]	2010	Case control study	166	0.66 (0.299-1.48)	No association

the breast cancer risk (fully adjusted HR: 0.85, 95% CI: 0.64-1.13) [10]. The null association between PCOS and breast cancer was also demonstrated by the other 4 cohort studies [11-14].

Out of the 10 published articles, only 1 article by Kim et al. which examined the relationship between clinical symptoms or sequelae related to PCOS and risk of breast cancer by using cluster analysis showed a significant positive result. This population-based case control study included 1,508 women with newly diagnosed in situ or invasive breast cancer and 1,556 controls. The results showed nearly threefold increase in breast cancer risk in premenopausal women with PCOS (multivariable-adjusted OR: 2.74, 95% CI: 1.13-6.63) [15]. On the contrary, a case-control study conducted in Iran which compared the frequency of 166 patients with premenopausal breast cancer and 166 health controls did not find significant association between PCOS and breast cancer risk [16].

3. ASSOCIATION BETWEEN PCOS-RELATED SYMPTOMS AND BREAST CANCER

3.1 Biochemical Hyperandrogenism

Biochemical hyperandrogenism frequently seen in women with PCOS is characterized by raised serum testosterone and free testosterone. Besides, in 40-70% of women with PCOS, dehydroepiandrosterone sulfate (DHEAS), an adrenal androgen is also raised. Almost one third of women with PCOS also have raised androstenedione and dehydroepiandrosterone (DHEA) [17]. These circulating androgens may contribute to breast cancer carcinogenesis.

The Endogenous Hormones and Breast Cancer Collaborative Group carried out pooled analyses of data from 7 prospective cohort studies. 767 women with breast cancer and 1699 controls were involved in the risk analyses. The results suggested that breast cancer risk was positively associated with doubling in concentrations of androstenedione (OR: 1.30, 95% CI: 1.10-1.55), DHEAS (OR: 1.17, 95% CI: 1.04-1.32) and testosterone (OR: 1.18, 95% CI: 1.03-1.35) in premenopausal women [18]. This result is consistent with other case-control studies which showed positive links between circulating androgens and breast cancer [19-21].

In addition, a few studies also looked into the influence of androgens on hormone receptor status of breast cancer. Higher testosterone level was associated with increased risk of estrogen receptor (ER) positive breast cancer. This is evident in a nested case-control study conducted within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) which enrolled 297 postmenopausal women with ER-positive and ER-negative breast cancer. The study reported that women with free testosterone level in the top quartile range had a 2.23-fold increased risk of getting ER-positive breast

cancer (95% CI: 1.23-4.1) [22]. Another nested case-control study by Zhang et al. showed similar result of significant twofold increase in both ER+/PR+ tumors with elevated testosterone (multivariable RR: 1.8, 95% CI 1.3-2.5) and free testosterone level (multivariable RR:2.6, 95% CI 1.8-3.8) in postmenopausal women [23].

3.2 High Estrogen Level

Women with PCOS have raised estrogen level which is one of the main hormones that drives cellular proliferation in breast epithelial tissue, leading to breast cancer. Many studies have been conducted to confirm the association between estrogen and breast cancer. The nested case-control study conducted in UKCTOCS reported ER-positive breast cancer was seen more in postmenopausal women with elevated serum estradiol (OR: 2.26, 95% CI: 1.28-4.05) and free estradiol (OR: 2.77, 95% CI: 1.5-5.21) [22]. This aligns with the findings of other studies which showed positive association between higher concentrations of estradiol, free estradiol and estrone with breast cancer risk [8-21,23].

3.3 Low Progesterone Level

A recent case-cohort study by Trabert et al. that looked into the association between circulating progesterone as well as its metabolites and the risk of breast cancer in postmenopausal women reported that postmenopausal women with elevated circulating progesterone levels had higher risk of breast cancer (HR: 1.16, 95% CI: 1.00-1.35) [24]. Besides, there is a hypothesis stating that breast cancer may be promoted by the change in concentration of progesterone metabolites namely 3a-dihydroprogesterone (3aHP) which has cancer-inhibiting properties and 5a-dihydroprogesterone (5aP) which has cancer-promoting properties [25]. However, in this study, no association was seen between these progesterone metabolites and breast cancer [24]. Nonetheless, another collaborative reanalysis and nested case-control study which evaluated sex hormones and risk of breast cancer showed contradicting results. No association was found between progesterone level and breast cancer risk in premenopausal women [18,19].

To date, epidemiological evidence regarding the role of endogenous progesterone in the etiology of either premenopausal or postmenopausal breast cancer is very limited. This is due to the variation of progesterone levels in menstrual phases of premenopausal women, low levels of circulating progesterone in postmenopausal women and inadequate assay sensitivity. There is only one study which found a positive association between endogenous progesterone and PCOS. The question remains whether low progesterone levels in women with PCOS due to anovulation protects against breast cancer. More studies need to be done to clarify the relationship between endogenous progesterone and breast cancer.

3.4 Low Sex Hormone Binding Globulin (SHBG) Level

Women who suffer from PCOS also have abnormally low levels of SHBG. Studies have shown inverse association between SHBG level and breast cancer risk. A recent Mendelian randomization study published in 2019 showed decreased risk of overall (OR: 0.94, 95% CI: 0.90-0.98) and ER-positive (OR: 0.92, 95% CI: 0.87-0.97) breast cancer per 25nmol/L increase in SHBG levels [26]. Besides, a meta-analysis of 26 prospective studies reported a similar result that higher concentration level of SHBG was linked with reduced breast cancer risk (OR: 0.64, 95% CI: 0.57-0.72) [27]. This is further supported by another case-control study that estimated an OR of 0.35 (95% CI: 0.19-0.64) associated with ER-positive breast cancer in postmenopausal women [22]. However, a collaborative reanalysis of individual participant data from 7 prospective studies found no association between SHBG and breast cancer in premenopausal women (OR: 1.07, 95% CI: 0.94-1.23) [18]. This may suggest that the role of SHBG in the pathogenesis of breast cancer is influenced by menopausal status.

3.5 Obesity

Obesity is commonly seen in women with PCOS. It is a well-known risk factor for breast cancer. A prospective cohort study conducted in Italy showed that obese women with body mass index (BMI) 30kg/m^2 or more had higher risk of postmenopausal breast cancer (RR: 1.32, 95% CI: 1.00-1.75) [28]. This finding is compatible with all previous studies. The studies reported significant association between overweight and obesity with breast cancer risk in postmenopausal women, especially ER-positive breast cancer [29-31]. Another meta-analysis

was conducted to evaluate the risk of premenopausal breast cancer in overweight and obese women from different ethnic groups. 29 studies were included; 18 were case-control studies and 11 were cohort studies. The result showed significant inverse relationship between increase in 5kg/m^2 of BMI and breast cancer risk in African (RR: 0.95, 95% CI: 0.91-0.98) and Caucasian women (RR: 0.93, 95% CI: 0.91-0.95). However, a significant positive association was reported among Asian women (RR: 1.05, 95% CI: 1.01-1.09). These results may suggest that in certain populations, using BMI to gauge body fat might not accurately quantify the association between adiposity and breast cancer [32].

3.6 Hyperinsulinemia, Diabetes Mellitus

Apart from being obese, women with PCOS often have insulin resistance leading to hyperinsulinemia and type 2 diabetes. Many studies had been conducted to identify the association between diabetes and breast cancer. A Mendelian randomization analysis reported positive association between genetically predicted fasting insulin (OR: 1.71, 95% CI: 1.26-2.31) and 2-h glucose level (OR: 1.80, 95% CI: 1.30-2.49) with risk of breast cancer [33]. This finding is consistent with the result of a meta-analysis conducted by Hardefeldt et al. which included 43 studies. Women with type 2 diabetes were 1.2 times more likely to have breast cancer (OR: 1.22, 95% CI: 1.07-1.40) [34]. Another cross-sectional study also showed similar result where both premenopausal and postmenopausal women with insulin resistance were at higher risk of getting breast cancer (OR: 1.98, 95% CI: 1.19-3.32; OR: 1.29, 95 CI: 1.01-1.63) [35]. A study which evaluated the relationship between diabetes and clinicopathological breast cancer subtypes reported that in premenopausal women with diabetes, a higher incidence of PR-negative (OR: 2.44, 95% CI: 1.07-5.55), HER2-negative (OR: 2.84, 95% CI: 1.11-7.22) and basal-like (OR: 3.14, 95% CI: 1.03-9.60) tumours were seen [36]. Nonetheless, a meta-epidemiological analysis which included 4 cohort studies in Korea, Taiwan, Japan and China did not observe higher breast cancer risk in Asian women with a history of diabetes. The author suggested that this may be associated with the earlier age of onset of breast cancer in this population [37].

4. ASSOCIATION BETWEEN PCOS MEDICATIONS AND BREAST CANCER

4.1 Combined Hormonal Contraceptives (CHC)

In women who do not desire pregnancy, combined hormonal contraceptives (CHC) are usually the first line treatment in managing symptoms of PCOS which includes the regulation of menstrual cycles and improvement of hyperandrogenism-mediated symptoms such as acne and hirsutism. However, various studies that investigated the relationship between breast cancer and CHC had shown inconclusive results.

A nationwide prospective study published in 2017 enrolled all women in Denmark aged between 15 and 49 years old. After an average follow-up of 10.9 years, 11,517 breast cancer cases arose. Among women who were current and recent (within 6 months) users of hormonal contraceptives, 20% higher risk of breast cancer was noted among this group as compared with those who had never taken them. A positive association was observed between combined oral contraceptives (COC) and breast cancer risk (RR: 1.19, 95% CI: 1.13-1.26). This risk increased from 1.03 (95% CI: 0.89-1.19) with less than 1 year of COC usage to 1.46 (95% CI: 1.32-1.61) with more than 10 years of COC usage [38].

Another reported results from the Royal College of General Practitioners' Oral Contraception Study showed an elevated risk of breast cancer among women who were current and recent (less than 5 years) CHC users (RR: 1.48, 95% CI: 1.10-1.97). However, after 5 to 15 years of discontinuation, the risk of breast cancer was similar to the women who had not previously used CHC [39].

Furthermore, a meta-analysis of 44 studies which consisted of 29 case-control studies, 14 cohort studies and 1 pooled analysis demonstrated a slight but significant increase in breast cancer incidence among women who consumed oral contraceptives (OR: 1.08, 95% CI: 1.00-1.17). Results also showed a time-dependent relationship in which higher breast cancer risk was associated with more recent use of oral contraceptives (0-5 years since last use OR: 1.21, 95% CI: 1.04-1.41) [40].

A prospective population-based cohort study- The Norwegian Women and Cancer study (NOWAC) collected information regarding oral contraceptives use from 74862 premenopausal women. It aimed to investigate the effect of COC on the hormone receptor status of breast cancer risk. The study showed that the use of COC was associated with ER-negative (HR: 1.50, 95% CI: 1.06-2.13) and both ER-/PR-negative breast cancer (HR:1.60, 95% CI: 1.07-2.38). Besides, usage of COC for five years or more was also associated with higher risk of ER-negative (HR: 1.73, 95% CI: 1.17-2.56) and ER-/PR-negative breast cancer (HR: 1.79, 95% CI: 1.14-2.80) [41].

4.1.1 Menopausal hormonal therapy

Although hormone replacement therapy is not indicated in women with PCOS, 2 articles that assessed the effect of menopausal hormonal therapy (MHT) were included in this review to evaluate the role of estrogen and progestogen in breast cancer.

The Women's Health Initiative (WHI) hormone therapy trials which enrolled 27,247 postmenopausal women investigated the effect of conjugated equine estrogens (CEE) with medroxyprogesterone acetate (MPA) and CEE alone on incidence of invasive breast cancer. During the intervention phase, the HR for breast cancer in CEE+MPA trial was 1.24 (95% CI: 1.01-1.53). On the other hand, the HR in CEE alone trial was 0.79 (95% CI: 0.61-1.02). During the post-intervention phase, breast cancer risk in CEE+MPA trial remained statistically significantly raised (HR: 1.32, 95% CI: 1.08-1.61) [42].

The most recent meta-analysis published in 2019 by the Collaborative Group on Hormonal Factors in Breast Cancer with 58 studies included, had gathered the worldwide evidence on MHT and the incidence of breast cancer. 143,887 postmenopausal women with breast cancer and 424,972 controls were involved. In general, breast cancer risk was higher in postmenopausal women who had taken MHT before than never users (RR: 1.26, 95% CI: 1.24-1.28). As compared with estrogen-only preparation, estrogen-progestogen preparation of HRT had higher breast cancer risk, especially when progestogen was given daily rather than cyclically. There was a remarkable excess risk between the 2 preparations even during year 1 to 4 of current use: for estrogen-progestogen, the RR was 1.60 (95% CI: 1.52-1.69) and for estrogen alone, the RR was 1.17 (95%: 1.10-1.26). Moreover, this risk increased steadily with longer duration of use, from 1.20 when used less than 1 year (95% CI: 1.01-1.43) to 2.51 when used for 15 years or more (95% CI: 2.35-2.68) [43].

The findings from these 2 studies suggest that exogenous progestogen may have a significant role in the carcinogenesis of breast cancer.

4.2 Progestin Only Contraceptives (POC)

Progestin-only pill is an effective alternative for women who are unable to take combined hormonal contraceptives due to certain contraindications like hypertension and migraine. To date, there are very limited studies on the effect of progestin-only contraceptives on breast cancer risk. The biological mechanism that can possibly link progestin to breast cancer development has been the subject of controversy [24].

A systematic review included 6 studies published between 2000 and 2015; 3 case-control studies and 3 cohort studies. 5 out of the 6 studies showed that progestin-only formulations were not associated with risk of breast cancer. The progestin-only formulations included oral progestin, depot medroxyprogesterone acetate (DMPA) and levonorgestrel-releasing intrauterine system. However, the number of studies and sample size of each studies was relatively small [44].

Nonetheless, a more recent prospective population-based cohort study- NOWAC conducted by Busund et al. showed that POC use of 5 years or more was significantly associated with hormone receptor positive premenopausal breast cancer, consisting of both ER-positive (HR: 1.59, 95% CI: 1.09-2.32) and ER+/PR+ (HR: 1.63, 95% CI: 1.07-2.48) breast cancers [43]. Another prospective cohort study in Denmark showed positive association between current or recent use of levonorgestrel progestin-only pill (RR: 1.93, 95% CI: 1.18-3.16) and levonorgestrel-releasing intrauterine system (RR: 1.21, 95% CI: 1.11-1.33). However, limitations of this study include the lack of information about participants' usage of hormonal contraceptives before study entry [38].

Since results are inconsistent, more studies need to be conducted to identify the relationship between POC and breast cancer.

4.3 Clomiphene Citrate

Clomiphene citrate is the first line treatment for women with anovulatory infertility. It induces ovulation and increases estradiol levels, which is one of the crucial mechanisms of causing breast cancer development.

A recent case-control study by Taheripanah et al. included 928 women with breast cancer along with 928 controls. The results suggested no significant association between ovulation induction drugs and breast cancer risk (OR: 1.13, 95% CI: 0.7-1.85). Focusing on clomiphene citrate, it was also not associated with increased breast cancer risk (OR: 0.8, 95% CI: 0.45-1.5) [45]. This result is consistent with a prospective cohort study of over 30 years of follow up (standardized incidence ratios, SIR= 1.21, 95% CI: 0.91-1.58) [46]. Another cohort study by Brinton et al. that observed 749 breast cancer cases among infertile women also showed null association between clomiphene and breast cancer risk (HR: 1.05, 95% CI: 0.90-1.22). However, there was a non-significant increased risk for those who received 12 or more cycles of clomiphene (HR: 1.37, 95% CI: 0.97-1.92) [47].

However, a registry-based cohort study which obtained data from the Norwegian Prescription Database observed 20,128 breast cancer cases from all women born in Norway between 1960 and 1996 showed contradictory results. There was a 26% increase in breast cancer risk in parous women who had taken clomiphene citrate before (HR: 1.26, 95% CI: 1.03-1.54). Unlike the study result reported by Brinton et al., no relation was seen between the number of clomiphene cycles and breast cancer risk [48].

A meta-analysis published in 2015 made a conclusion that hormonal infertility treatment was weakly associated with breast cancer risk. However, it emphasized that clomiphene citrate should not be used extensively due to the worrying and inconsistent findings regarding breast cancer risk [49].

4.4 Metformin

Metformin belongs to the biguanide class of antidiabetic medication. Patients with PCOS are often prescribed with metformin to prevent or treat their type II diabetes. Not only it improves insulin resistance, it also helps in regulating the menstrual cycle and inducing ovulation.

The most recent systematic review and meta-analysis published in 2018 evaluated the effect of metformin on the incidence of breast cancer in patients with type II diabetes. 12 observational studies were included for analysis. Results showed no significant association between metformin and breast cancer incidence (OR: 0.93, 95% CI: 0.85-1.03). In fact, metformin may improve overall survival in patients with type II diabetes and breast cancer as there was a 45% risk reduction for all-cause mortality (HR: 0.55, 95% CI: 0.44-0.70) [50].

5. DISCUSSION

Fig. 1. summarizes the association between PCOS-related symptoms and breast cancer with all the evidence included in this review. A positive association with breast cancer was seen with the hormonal profile of PCOS: biochemical hyperandrogenism, high estrogen level and low SHBG level as well as with the comorbidities of PCOS: obesity and diabetes. Hence, it is necessary to understand the biological mechanism that leads to breast cancer. Firstly, androgen excess plays a crucial role in the development of breast cancer. Evidence suggests that breast epithelial growth is controlled by testosterone. Its active metabolites have a balanced interaction where estradiol promotes cell proliferation while dihydrotestosterone inhibits it. However, in chronic overproduction of testosterone, estrogen synthesis rises leading to overstimulated cell proliferation and upregulation of estrogen receptor synthesis which could not be counter balanced by dihydrotestosterone. This androgen/estrogen imbalance is believed to play a role in the development of ER-positive breast cancer. In addition, androgens also stimulate the apocrine cells in the mammary gland. Subsequently, those cells make epidermal growth factor (EGF) which activates the ErbB family receptors, leading to cell proliferation. This contributes to formation of apocrine and apocrine-like tumour, a very rare type of breast cancer which is characterized by ER-negative and PR-negative but androgen receptor (AR)-positive [6].

Insulin resistance leading to hyperinsulinemia is an important pathophysiological mechanism associated with type 2 diabetes and obesity. Both hyperinsulinemia and obesity are linked with increased breast cancer risk. The relationship between adiposity and breast cancer

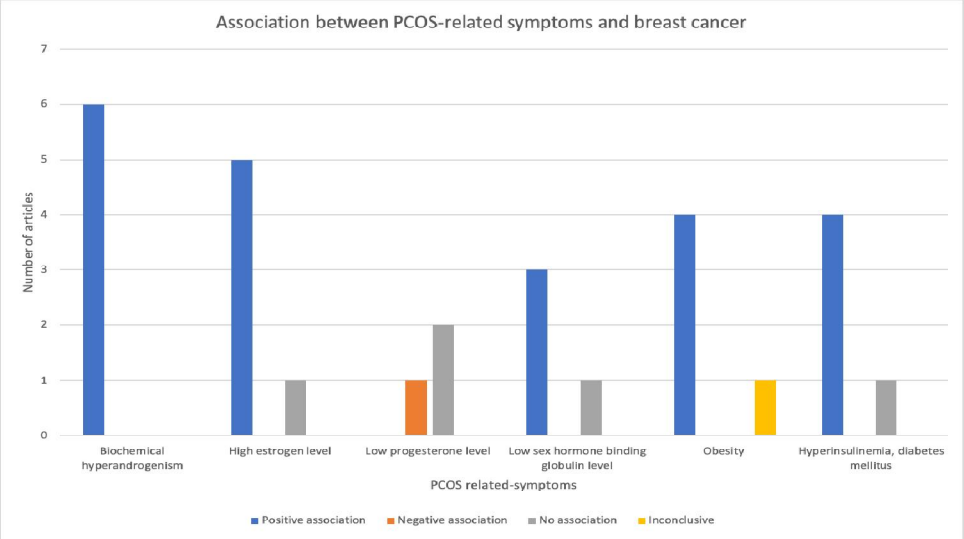

Fig. 1. Association between PCOS-related symptoms and breast cancer

can be explained by 3 proposed hormonal mechanisms. First, obese women with excess adiposity have higher estradiol level due to higher conversion rate from the androgenic precursors in the peripheral adipose tissue. Second, hyperinsulinemia which is closely related with obesity also contributes to breast cancer development. Increase in insulin and insulin-like growth factor 1 (IGF1) activates the insulin receptor and IGF1 receptor, leading to mitogenesis, anti-apoptosis and angiogenesis which promotes tumour development. Besides, high insulin level will reduce the SHBG, a transport carrier that binds to androgens and estrogen. It is responsible for regulating the biological activities of those hormones. Women with PCOS have abnormally low levels of SHBG, leading to elevated levels of bioavailable androgens and estrogen. Thirdly, increased BMI is associated with high leptin and low adiponectin levels. Leptin has mitogenic, anti-apoptotic and pro-angiogenic effects that promote cancer development. Contrarily, adiponectin influences carcinogenesis negatively by reducing cellular proliferation as well as increasing cell cycle arrest and apoptosis [51,52].

On the other hand, Fig. 2. shows that among all the medications taken by women with PCOS, combined hormonal contraceptives are positively associated with increased breast cancer risk as opposed to metformin and clomiphene citrate. However, inconsistent results were seen in the association between progestin only contraceptives and breast cancer. Estrogen plus progesterone therapy are shown in animal models to stimulate the expansion of the number of mammary stem and progenitor cells, generating a more complex and denser mammary epithelium. During the usage of combined hormonal contraceptives, estrogen and progesterone exposure is likely to upregulate these cellular and mitogenic mechanisms, hence increasing the risk of breast cancer [53].

Most of the epidemiological studies except the study done by Kim et al. showed that the overall incidence of breast cancer in women with PCOS appeared to resemble women in the normal population as shown in Table 2. Nevertheless, a firm conclusion cannot be made as there were several limitations in the studies. First, most of the studies did not address the confounding factors that can potentially affect the risk of breast cancer such as BMI, use of hormonal therapy, family history of breast cancer, age of first childbirth and menopausal status. Second, the usage of various diagnostic criteria for PCOS affected the prevalence of PCOS in different geographical locations and ethnic groups. As shown in Table 3, the clinical presentation of PCOS is heterogenous. Some women may have the classical phenotype with the presence of hyperandrogenism and ovulatory dysfunction with or without the polycystic ovarian morphology (phenotype A and B). However, women with non-classical PCOS (phenotype C and D) may be asymptomatic and might have been allocated to the control group in the studies based on different diagnostic criteria [54].

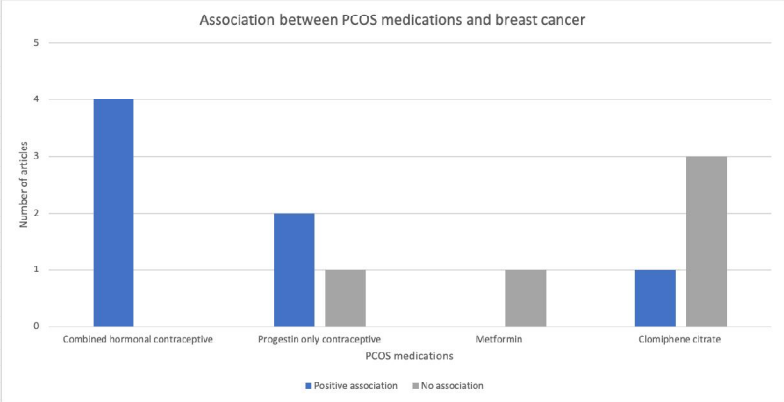

Fig. 2. Association between PCOS medications and breast cancer

Table 3. Phenotypes of PCOS

	Phenotype A	Phenotype B	Phenotype C	Phenotype C
Hyperandrogenism, hirsutism	Present	Present	Present	Absent
Ovulatory dysfunction	Present	Present	Absent	Present
Polycystic ovarian morphology	Present	Absent	Present	Present

6. CONCLUSION

This review focused on various aspects of the association of PCOS with breast cancer risk, such as the epidemiological evidence, the influence of PCOS-related symptoms and PCOS medications. Elevated androgen and estrogen levels, decreased SHBG level, obesity, insulin resistance and use of CHC are all linked to higher risk of breast cancer. Hence, a strong correlation between PCOS and breast cancer would be anticipated yet current epidemiologic evidence included in this review does not validate this association. Further research about this topic should be carried out. In view of the high prevalence of PCOS, it is important that we recognize the plausible association with breast cancer so that a screening program can be developed for patients with higher breast cancer risk.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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