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Review article

Controversial association between polycystic ovary syndrome and breast cancer

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ABSTRACT

Polycystic ovary syndrome (PCOS) risk factors overlap with breast cancer, and the hormonal profile may be implicated in breast cancer pathogenesis. This study aims to report a literature review considering epidemiological and molecular mechanisms that correlate PCOS and breast cancer, as well as the influence of PCOS treatment on the incidence of breast cancer.

Epidemiological studies failed to adjust potential variables that affect the risk and have thus provided inconclusive results. Molecular effects of androgenic pathways in breast cancer have been studied and androgens seem to have an inhibitory effect on mammary epithelial proliferation. However, increased bioavailable androgens were associated with recurrence of breast cancer due to conversion to oestrogens. Sex hormone-binding globulin has a role in hormone-dependent cancers and can be considered a marker for PCOS; a gene profile has already been linked to breast cancer risk in these patients. PCOS medical treatment is a promising tool for stratifying breast cancer risk due to the metabolic influence and hormonal environment.

Clinical reports are inconsistent, emphasizing the need for further studies with a prospective design. In the future, the role of pharmacological interventions in PCOS will increase knowledge and awareness of breast cancer pathogenesis and will help to refine breast cancer risk stratification.

Contents

Introduction

Polycystic ovary syndrome (PCOS) affects 5%–8% of women of reproductive age [1]. PCOS was thought to represent a reproductive dysfunction but is now recognized as part of a metabolic disorder, associated with type 2 diabetes mellitus, insulin resistance and metabolic syndrome, all recognized as risk factors for cardiovascular disease [2,3]. The metabolic and hormonal environment changes

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among these women and may increase the risk of some types of cancers [4].

The diagnostic criteria of PCOS rely on different clinical, biological and image-based characteristics, but there has been no consensus among experts over the years [5]. In 2003 the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM), defined the Rotterdam criteria, which included clinical and/or biochemical hyperandrogenism and oligo/amenorrhea anovulation, defined by National Institutes of Health (NIH) in 1990, and added polycystic ovarian morphology on ultrasound. For the diagnosis of PCOS, two out of three criteria were required [6]. In 2006 the Androgen Excess Society and PCOS Society (AES-PCOS) published the diagnostic criteria with an emphasis on hyperandrogenism, demanding its clinical or biochemical evidence for diagnosis [7]. The diagnostic criteria of PCOS, published after NIH Evidence-based Methodology Workshop Panel on Polycystic Ovary Syndrome in 2012, proposed two main changes, renaming the diagnosis and the inclusion of different sub-phenotypes [8]. All the diagnostic criteria published exclude anyone with an underlying pathological condition that could explain hyperandrogenism or menstrual dysfunction, such as congenital adrenal hyperplasia, androgen-secreting tumours, hyperprolactinaemia, thyroid dysfunction or drug-induced androgen excess. Most recently, the 2018 International Guidelines for PCOS made a few adjustments to the Rotterdam criteria: there is now no need for an ultrasound for diagnosis if hyperandrogenism and irregular menstrual cycles coexist, but it is still performed to characterize the phenotype. Also, ultrasound is not recommended in adolescents and if the two above-mentioned conditions are present, two years must have passed after menarche [9].

The absence of international agreement on diagnostic criteria for PCOS affects the prevalence of PCOS in terms of geographical location and racial or ethnic groups [10]. Some epidemiological data suggests that there is no racial or ethnic influence on PCOS prevalence, particularly due to the report from the United States, the United Kingdom, Spain, Greece, Australia, Asia, and Mexico using NIH criteria, ranging from 6% to 9% [10]. However, other studies report a wide range of prevalence influenced not only by the criteria, but also by the recruitment methods and study design. In US, prevalence varied from 10.3% to 47.5% according to the different regions of the country [11]. In Caucasians, the incidence of PCOS using NIH criteria represented 6.5% [12]. In Australia, the prevalence was 8.7%, 11.9% and 10.2% using NIH, Rotterdam and AES criteria, respectively [13]. Using Rotterdam criteria, the prevalence reported in China was 5.6% and in the Middle East 16.0%. In this region, this prevalence decreased to 12.6% using AES criteria. Considering NIH criteria in black women, the prevalence was 6.1% [14]. The existing data is not consistent enough to ensure significant differences according to geographic regions or racial and ethnic groups.

The influence of steroid hormones on breast cancer is better described for oestrogens and more recently progesterone but the influence of androgens is still a controversial issue. Steroid hormones are interrelated due to the intermediate metabolism of precursor steroids. The inhibition or stimulation of proliferation in hormone-dependent breast cancer depends on the precursor, its concentration and the hormone receptor profile [15]. The response of breast tissue to androgens is controversial, as some reports make it clear that androgens promote the risk of breast cancer, while others display that they have a protective role for hormone-dependent breast carcinomas [16].

The aim of this review is to describe the epidemiological and molecular findings considering PCOS and breast cancer risk and also to identify the influence of medical treatment of PCOS on breast cancer risk stratification.

Epidemiologic evidence of the link between polycystic ovary syndrome and breast cancer

The first reports of an association between PCOS and cancer were related to endometrial disease [2], as a result of chronic oestrogen exposure with no opposing progesterone caused by chronic oligo- or anovulation, one of the main clinical symptoms of PCOS [2,4]. Three recent meta-analyses documented an increased risk for endometrial cancer among women with PCOS [2,17,18].

Based on its reproductive and metabolic repercussions, PCOS is expected to affect the risk of endometrial cancer and other oestrogen-dependent gynaecological tumours, for example breast and ovarian cancer [19].

The plausible association between PCOS and breast cancer has been investigated in the last two decades due to overlap between clinical manifestations of PCOS and risk factors for breast cancer [2,20]. Examples of the mentioned previously are age at first pregnancy at older age and nulliparity. Also, obesity is a major risk factor for breast cancer not only in post-menopause but also in premenopause and is often linked with PCOS [1,3,21]. In addition, hyperandrogenaemia and hyperinsulinaemia are independent risk factors for breast cancer and may have the main mediators of the obesity-breast cancer relationship [22]. Recently, a large prospective study reported the positive association between circulating anti-müllerian hormone (AMH) and breast cancer risk, statistically significant for hormone-dependent breast cancer [23]. However, it is likely that this association results from the higher prevalence of PCOS in the group with high AMH levels.

Table 1
Summary of epidemiological studies of PCOS and breast cancer risk.

Author	Year	Study design	Breast Cancer cases (n)	Overall result RR or OR (95% CI)
Yin et al. [82]	2019	Cohort	–	0.87 (0.66–1.15)
Ding et al. [14]	2018	Cohort	102	0.98 (0.58–1.25)
Shobeiri et al. [1]	2016	Meta-analysis		0.9 (0.4–1.3)
Kim et al. [83]	2016	Case-control	1508	2.8 (1.1–6.6)*
Gottschau et al. [3]	2015	Registry cohort	59	1.1 (0.8–1.4)
Shen et al. [26]	2015	Registry cohort	44	1.6 (0.9–2.8)
Barry et al. [2]	2014	Meta-analysis	3618	1.0 (0.6–1.4)
Brinton et al. [39]	2010	Cohort	89	1.3 (1.1–1.6)
Chittenden et al. [18]	2009	Review systematic		0.9 (0.4–1.8)
Baron et al. [25]	2001	Case-control	5659	1.6 (0.8–3.2)
Anderson et al. [20]	1997	Cohort	883	1.2 (0.7–2.0)
Talamini et al. [24]	1997	Case-control	2569	0.9 (0.4–1.8)
Gammon et al. [84]	1991	Case-control	4730	0.47 (0.3–0.9)

* Premenopausal women.

Understanding how PCOS is related to breast cancer development is very important for further clarification of hormonal aetiology among both conditions. Also, regarding the high prevalence of PCOS, the recognition of this association can lead to the development of a screening program for patients with increased breast cancer risk and to the establishment of primary interventions in order to decrease their risk.

However, inconsistent data has been reported regarding the association of PCOS and breast cancer, described in Table 1. The first systematic review [18], included three case-control studies [3,24,25], and demonstrated that women with PCOS did not appear to be at increased risk for breast cancer (OR 0.88, 95% CI 0.44–1.77). A meta-analysis including two case-control studies and one cohort study (USA) reported no overall increased breast cancer risk for PCOS women (OR 0.95, 95% CI 0.64–1.39), identical in premenopausal women with breast cancer (OR 0.78, 95% CI 0.46–1.32) [2]. Similarly, a recent registry-based cohort study comprising more than 12,000 women with PCOS showed no relation between PCOS and breast cancer risk in standardized incidence ratio of 1.1, 95% CI 0.8–3.2 [3]. Besides, a retrospective cohort study in Taiwan including 3566 PCOS patients and 14,264 control patients showed that the mean adjusted hazard ratio (HR) for the development of breast cancer was not higher compared to the control group (mean adjusted HR: 1.61, 95% CI: 0.91–2.84) [26]. The most recent meta-analysis included five cohort studies and three case-control studies. Based on related risk from the first and OR estimates from the latter, there was no significant association between these two conditions, RR: 1.18, 95% CI 0.93–1.43 and OR: 0.87, 95% CI 0.44–1.31, respectively [1]. More recently, Ding et al., in a population-based cohort study including 8155 patients with PCOS and 32,620 control patients, showed no association between PCOS and breast cancer (mean adjusted HR: 0.98, 95% CI: 0.58–1.65) [26]. This null association was also demonstrated in a cohort study by Yin et al. (fully adjusted HR: 0.85, 95% CI 0.64–1.13) [26].

However, other studies reported increased risk of breast cancer in PCOS patients. A large population-based case-control study investigated the relationship between breast cancer and clinical hyperandrogenism (acne, hirsutism and polycystic ovaries). A total of 5659 breast cancer patients between 50 and 75 years old and 5928 controls were interviewed and provided suitable data by telephone interview. Physicians diagnosed PCOS without specific diagnostic criteria. Baron et al. found that the disorders associated with androgen excess conferred an increased risk of breast cancer. A history of acne had an OR: 1.4, 95% CI 1.0–1.9, of hirsutism had an OR: 1.2, 95% CI 0.81–1.8, and of polycystic ovaries had an OR: 1.6, 95% CI 0.8–3.2 [25]. More recently, a population-based case-control study included 1508 women all ages and races with a personal history of breast cancer *in situ* or invasive and 1556 controls. Given the changes in the diagnosis criteria, Kim et al. used a cluster analysis to investigate the association between PCOS-related clinical symptoms/sequelae among all women and related breast cancer risk. The authors observed a strong positive association between PCOS and premenopausal breast cancer (multivariate-adjusted OR 2.74, 95% CI 1.13–6.63). Cluster analysis revealed that among all PCOS-related symptoms/sequelae, the cluster which included contraceptives users was most strongly associated with breast cancer. However, no risk change was founded in women with metabolic syndrome-related symptoms and sequelae or even those who had ovulatory dysfunction without oral contraceptive use [27]. These results were consistent with other reports, demonstrating an increased premenopausal breast cancer risk in progesterone deficient conditions [28].

Inconsistent results, including increased and null risk, may be due to the many study limitations. Most studies that explored the risk of breast cancer in women with PCOS are case-control studies. Critical issues in these case-control studies were different criteria and multiple bias, such as recall bias, interviewer bias and inaccuracy of recorded information about exposure. Therefore, the diagnosis of PCOS was self-reported in most studies [3]. Further, changes in the diagnostic criteria over time and the unclear aetiology of PCOS was well recognized causes for reported variations in morbidity associated with this syndrome [2,19] and give strength to the challenges in the conceptualization of the study design as well as the statistical analysis. Another limitation is that many studies failed to control the body mass index (BMI) [2]. High BMI is a common characteristic of PCOS and is a recognized risk factor for breast cancer. Thus, it is difficult to characterize a BMI-independent PCOS association, since BMI may be both a mediator and confounder for these two conditions. Also, it is plausible that associated factors, such as parity, age at first pregnancy and use of hormones, type 2 diabetes, insulin resistance and metabolic syndrome may potentially influence cancer risk. Few studies have adjusted these potential intermediate variables, which may underestimate the real association [26]. Certainly, the

Table 2
Summary of clinical data of the influence of endogenous androgen excess and breast cancer risk.

Author	Year	Study design	Results Breast cancer risk: RR, HR, SIR or OR (95% CI)
Androgen excess increases the risk of breast cancer			
Micheli et al. [36]	2007	Cohort	Testosterone: HR 1.77 (1.06–2.96)
Tworoger et al. [37]	2006	Case-control	DHEA: RR1.60 (0.90–2.80) DHEA-Sulfate: RR 1.90 (1.1–3.3)
Eliassen et al. [38]	2006	Cohort	Testosterone: RR 2.0 (1.1–3.6)
Key et al. [35]	2002	9 Cohort studies	Androstenedione (quintile 5): RR 2.15 (1.44–3.21) Testosterone (quintile 5): 2.22 (1.59–3.10)
Brinton et al. [39]	2010	Retrospective cohort	Androgen excess: SIR 1.31 (1.05–1.62)
Rinaldi et al. [40]	2006	Case-control	Testosterone (adjusted to anthropometric measurements): RR 1.12 (1.01–1.23)
Kaaks et al. [41]	2005	Case-control	Testosterone: OR 1.73 (1.16–2.57) Androstenedione: OR 1.56 (1.05–2.35) DHEA sulfate: OR 1.48 (1.02–2.14)
No influence of androgens in breast cancer risk			
Page et al. [42]	2004	Prospective, observational	DHEA: OR 0.92 (0.59–1.43) DHEA sulfate: OR 1.08 (0.69–1.69)
Adly et al. [43]	2006	Observational	Testosterone: OR (1^{st} quartile) 1.5 (0.8–3.1), (4^{th} quartile) 1.3 (0.6–2.6) DHEA: OR (1^{st} quartile) 1.3 (0.7–2.5), (4^{th} quartile) 1.6 (0.8–3.2) Androstenedione: OR (1^{st} quartile) 0.9 (0.5–1.7), (4^{th} quartile) 1.2 (0.6–2.4)
Beattie et al. [44]	2006	Case-cohort	Testosterone: RR (1^{st} quartile) 0.41, (4^{th} quartile) 0.51
Rinaldi et al. [40]	2006	Case-control	All androgens (adjusted to anthropometric measurements): RR 1.09 (0.98–1.22)

RR: relative risk; HR: hazard risk, SIR: standardized incidence ratios; OR: Odds-ratio; dehydroepiandrosterone (DHEA).

epidemiological data considering the association between PCOS and breast cancer could have greater potential if prospective longitudinal cohort studies were available.

Androgen excess and breast cancer

Previous studies have proposed that steroid hormones have a role in the pathogenesis of breast cancer [29]. Androgen excess has been proposed in the carcinogenesis of breast cancer and not only oestrogen but also androgens have been associated with higher incidence and recurrence of breast cancer. High levels of serum testosterone at baseline were considered critical prognostic factors for contralateral breast cancer, loco-regional and distant recurrence and metastasis [30]. Circulating androgens may influence the carcinogenesis of breast cancer [21]. The bioavailable testosterone at baseline in post-menopausal women has been associated with recurrence of breast cancer [31]. The influence of androgens on hormonal receptors was also highlighted in post-menopausal women. The higher testosterone levels had a lower risk of oestrogen receptor (ER)-negative breast cancer, but the opposite was observed for ER-positive breast cancer. This association might be partially justified by oestrogen levels [32]. In fact, circulating sex-hormones were related to several risk factors for breast cancer, namely age, obesity, smoking and alcohol intake but not with age at menarche, parity, age at first pregnancy or family history [33]. The levels of circulating testosterone were also considered prognostic factors for contralateral breast cancer, local relapse and distant metastasis. The decrease in testosterone levels may be associated with a reduced risk of worst prognosis [30].

Clinical and animal studies have suggested that androgens inhibit the proliferation of mammary epithelium and that oestrogen therapy suppresses endogenous androgens [16]. Equilibrium of androgens and oestrogens seems crucial in breast cancer progression, particularly depending on the breast cancer stage [34]. The epidemiological data is controversial, as described in Table 2. The influence of excess of endogenous androgens has been associated with breast cancer risk [33,35–41] but other studies report no risk influence [40,42–44]. Some authors suggested that testosterone treatment can positively be related to breast cancer risk [45], but other authors found that androgens can act as protective factors [46,47].

Molecular mechanisms of PCOS and breast cancer

The main factor for mammary cell regulation, either in normal and in cancer tissues, is the balance of oestrogens stimulation and androgens inhibition [16]. The influence of androgens in breast cancer is the subject of debate, namely because the role of androgen receptors (AR) is controversial [16,48].The AR, ER and progesterone receptors (PR) are located in epithelial cells but are not detected in mammary stroma or myoepithelial layers [49]. The contribution of androgens to breast cancer risk can be attributed mainly to their substrate for oestrogens production. The conversion of dehydroepiandrosterone to oestrogens, mainly oestradiol, is necessary for the mitogenic response of breast tissue [50]. Some clinical reports describe an influence of AR- and ER-positive tumours [34,51]. The majority of ER-positive tumours express AR, but in the ER negative group, AR is observed mainly in HER2 and in a few triple-negative breast cancers, with apocrine differentiation [52]. The development of ER-negative/AR-positive tumours can be activated using AR or ERBB2 overexpression. In fact, it seems that in growing tumours, androgens can have an inhibitory or stimulatory effect and can be influenced by different steps of cancer biology, as described in Fig. 1.

In vitro studies using breast cancer cell lines demonstrate the stimulation of androgens. 5-androstene-3β,17β-diol stimulated

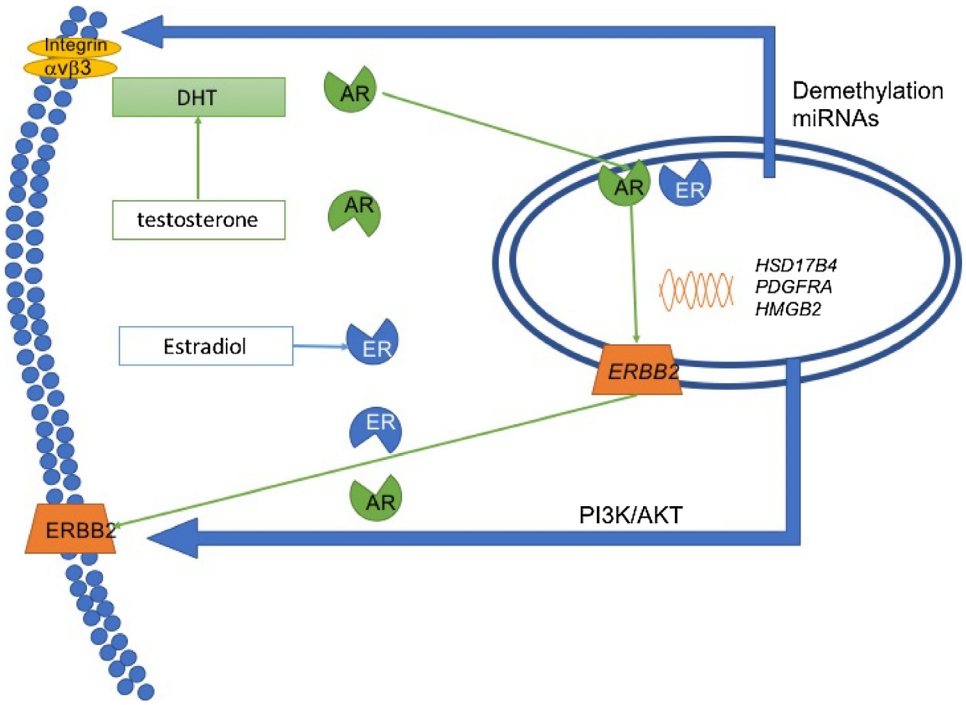

Fig. 1. Illustration of the influence of androgens in the different tumour biology and mechanisms highlighted in PCOS. RE positive tumours express AR, ER negative/AR positive use activation pathways via AR or ERBB2 receptor and were PI3K pathway plays a central role in tyrosine kinase receptor activation. AR can have an inhibitory or stimulate proliferation according with disease stage and tumour biology. Epithelial-to-mesenchymal transition has been associated to DHT via integrin αvβ3 and influence by gene demethylation of lysine-specific demethylase 1A.Three genes were described in PCOS and breast cancer development: hydroxysteroid (17-beta) dehydrogenase 4 (*HSD17B4*), platelet-derived growth factor receptor (*PDGFRA*), alpha polypeptide/PDGFRA and high-mobility group box 2 (*HMGB2*). DHT: dihydrotestosterone, AR: androgen receptor, ER: oestrogen receptor.

growth of hormone-dependent breast cancer cell lines at physiological levels, using ER mediated mechanisms. The pathway provides an insight into the response of aromatase inhibitors. In the long term, 5-androstene-3β,17β-diol and 5α-dehydrotestosterone inhibit proliferation influenced by 17β- oestradiol in hormone-dependent breast cancer [15].

Another author reported that dehydrotestosterone, a non-aromatizable androgen, stimulates both ER positive and ER negative cell lines. Different mechanisms underlying the influence of androgens seem to be present. On one hand, the proliferation induced by dehydrotestosterone was blocked by an inhibitor of ER in MCF-7 cell line (ER and AR positive). On the other hand, the AR inhibitor flutamide did not affect cell proliferation with dehydrotestosterone. This is consistent with the influence of androgens in ER in hormone-dependent breast cancer. In the absence of ER, dehydrotestosterone interacts with plasma membrane integrin αvβ3 in order to stimulate cell growth [53]. Recently it has been highlighted in basic research that dehydrotestosterone induces epithelial-to-mesenchymal transition, a process implicated in cancer invasion and metastasis. In fact AR seem to play an important role besides genetic influence via demethylation activity of lysine-specific demethylase 1A [54].

Sex hormone-binding globulin (SHBG) binds sex steroids and thus influences the levels of free hormones that are bioavailable, which may influence the risk of hormone-related disorders. In a recent meta-analysis, lower levels of SHBG were associated with the risk of PCOS and it may be considered a diagnostic and therapeutic marker [55]. Increased levels of SHBG were associated with decreased risk of breast cancer probably due to low oestrogen levels [56]. Levels of SHBG may be increased or its clearance decreased according to gene polymorphisms in women with Asn allele (Asp/Asn + Asn/Asn). The change of aspartic acid (Asp) to asparagine (Asn) in codon 356 (rs6259) at exon 8 is responsible for lower free oestradiol and decreased breast cancer risk [17].

Androgen excess has been associated with the development of ER-negative breast cancer, involving tyrosine kinase receptors, and these pathways may be responsible for the development of this type of tumour [34]. Also, androgens seem to trigger triple-negative breast cancer and recently has been described a regulatory mechanism via Src complex, which regulates PI3-K [57].

To summarize, clinical and molecular data have tried to establish a correlation between androgen excess and the pathogenesis of PCOS and breast cancer but it is still controversial. An overlap between regulatory genes of these diseases was recently reported. Three genes, hydroxysteroid (17-beta) dehydrogenase 4 (HSD17B4), platelet-derived growth factor receptor (PDGFRA), alpha polypeptide/PDGFRA and high-mobility group box 2 (HMGB2) seem to have a role in PCOS and breast cancer. These genes are involved in the development of male sexual characteristics. AR signalling can be modulated by AR cofactors as HMGAB2 [58]. HSD17B4 controls the last step in androgen synthesis and degradation of androstenediol to testosterone, downregulated in PCOS. PDGFRA, a tyrosine kinase receptor, influences mesenchymal cell proliferation and is upregulated in PCOS [59].

The increased risk of breast cancer in PCOS patients was already associated with proteomic biomarkers and epigenetic regulation. Fascin (singed-like protein), which organizes filamentous actin into bundles, was detected in ovarian biopsies in PCOS. This protein identifies and mediates breast cancer metastasis to the lungs [60]. Other proteomic markers should be studied in order to identify an overlapped phenotype as well as a prognostic factor in breast cancer patients. Several studies have identified some influence of miRNAs and AR expression in breast cancer, but the evidence is still limited to clarify this interaction [61].

Influence of PCOS medical treatment on breast cancer risk

Combined hormonal contraceptives

Combined hormonal contraceptives (CHC) are the first-line PCOS treatment when pregnancy is unintended. CHC are indicated for menstrual irregularities, dermatologic symptoms of hyperandrogenism and provide a protective effect against endometrial and ovarian cancer [21]. They significantly reduce endometrial and ovarian cancer incidence and mortality among CHC users and these benefits persist for decades after CHC discontinuation [62,63]. The mechanisms responsible for this protective effect are a reduced exposure to unopposed oestrogen, limiting endometrial cell proliferation as a promotion factor and a reduction in lifetime ovulations for ovarian cancer [21].

The association between breast cancer and hormonal contraception has been controversial for decades, with inconclusive and unclear results. The recent Danish nationwide prospective cohort enrolled women aged 15–49 years and included 11,517 breast cancers. The relative risk (RR) of breast cancer considering current and recent (within 6 months) users was 1.2, 95% CI: 1.14–1.26, with increased risk among women with at least 10 years of use. The specific use of combined oral contraceptives was associated with a RR of 1.19. The risk was higher among ever users for at least 5 years, compared with never users, besides discontinuation. However, the absolute increased risk was small, one additional breast cancer diagnosed per 7690 users over one year [64].

In a US case-control study that included 4575 women aged 35–64 years with breast cancer diagnosis, there was no association between current or recent CHC use and breast cancer risk. However, in younger people there was a small increase in breast cancer risk, compatible with the Danish study [65].

The recently reported results from the Royal College of Practitioners cohort study, which started in 1968 and recruited 23,000 CHC users and 23,000 non-users, showed a significant decrease in long-term cancer risk in ovarian, endometrial, colorectal and lymphatic/hematopoietic cancers among CHC users. There was an increased risk of breast cancer among current and recent CHC users (within 5 years), but this risk was similar to those who had not used CHC after 5–15 years of discontinuation [66].

These results reveal a relatively small and temporary increase in breast cancer risk among current and recent CHC users. The absolute risk of breast cancer is small among young women, representing few additional cases. Considering contraceptive effectiveness, providing a drastic reduction in unwanted pregnancies, the protective effect against other types of cancer and the effective management of various gynaecological conditions, including PCOS, the risk-benefit analysis should be individualized and based on the WHO eligibility criteria for the use of contraceptives.

Metformin

Metformin is a biguanide used for the treatment of type 2 diabetes. Among patients with PCOS it is used for prevention and treatment of type 2 diabetes, by improving insulin resistance, and may be helpful in regulation of the menstrual cycle and induction of ovulation [21,67]. It acts by increasing insulin sensitivity, reducing insulin levels, inhibiting liver gluconeogenesis and improving glycaemic control [67].

Impairment of metabolic and hormonal environment in type 2 diabetes, metabolic syndrome and PCOS may increase the risk of some types of cancer [21,68]. High insulin levels promote mitogenic effect by activation of insulin-like growth factor receptor and insulin receptor A, increasing the risk of cancer both in diabetic and non-diabetic patients [67,69–71]. Several studies

suggested that metformin acts as an anticancer agent in patients with diabetes, reducing cancer risk in this population [69,71,72]. Several mechanisms have been described, namely activation of adenosine 5'-monophosphate-activated protein kinase, (AMPK) which mimics the effect of calorie restriction, reducing all energy-consuming processes in the cells, including protein synthesis and cell proliferation [69]. In addition, the inhibition of the mammalian target of rapamycin (mTOR), the inhibition of mitochondrial complex I in the electron transport chain, the reduction of endogenous reactive oxygen species and the consequent DNA damage [68] as well as the improvement of insulin sensitivity, lead to a reduction in insulin levels [69,71]. The association between the antineoplastic activity of metformin and breast cancer has been the most studied [21], whereby other putative mechanisms provided by metformin in breast cancer were reported, as modifications in adipose tissue and breast epithelium that leads to tumour progression [73].

A recent meta-analysis showed that the use of metformin in women with diabetes decreased the incidence of invasive breast cancer, but not with other treatments for diabetes, OR 0.83, 95% CI 0.71-0.97. A stronger effect was found, related to longer duration of metformin therapy, suggesting that metformin may reduce the risk of breast cancer in women with impaired glucose homeostasis [74].

Another meta-analysis of 47 independent studies in diabetic patients showed that metformin may reduce overall cancer incidence and mortality in these patients, even after adjustment for BMI or time-related biases. The analysis recognized an established risk factor for breast cancer of 0.8, 95% CI 0.7–1.0, after BMI adjustment, which is a risk factor for breast cancer [68].

The insulin excess stimulates androgen production from theca cells and decreases SHBG production, increasing serum free testosterone levels [73]. In accordance with this, in a randomized phase II study from Campagnoli et al., a significant reduction of insulin and testosterone levels, as well as free androgen index, namely through increase of SHBG levels, was observed in a group of 43 postmenopausal women with breast cancer and without diabetes, who received 1500 mg/day of metformin for 5 months [67]. These results might lead to a new approach in breast cancer management, since high serum levels of insulin and testosterone may affect both breast cancer incidence and prognosis.

Recently, however, in a large retrospective database study that enrolled 8263 women with diabetes was not found an association between metformin users and breast cancer incidence comparing with sulfonylurea and insulin treatment, HR: 1.0; 95% CI 0.8–1.3 and HR: 1.1; 95% CI 0.7–1.7, respectively [75].

Ovulation-induction medications

Ovulation-induction drugs are used in PCOS for anovulatory infertility [21], increasing oestradiol levels, which is a mechanism associated with breast cancer risk. However, their effect on breast cancer remains uncertain [39]. Clomiphene citrate can reduce oestrogen receptor activity in some tissues [21]. A direct pro-apoptotic effect was described in breast cancer cell lines, suggesting a potential anticancer effect [76]. This may explain why some studies demonstrated a reduction in breast cancer in women who had taken clomiphene [77,78]. A cohort study that enrolled 12,193 women with infertility proved that clomiphene does not influence breast cancer risk. However, the authors found a non-significant increased risk in women treated with more than 12 cycles [39].

Letrozole is an aromatase inhibitor, used in PCOS anovulatory infertility. It is well tolerated, being associated with fewer side effects compared to clomiphene. In hormone-receptor-positive postmenopausal breast cancer women, letrozole is used as an adjuvant treatment, so a reduced hormonal-dependent cancer risk can be hypothesized [21].

In some cases, controlled ovarian hyperstimulation may be needed for *in vitro* fertilization (IVF), leading to temporarily elevated oestradiol levels that might affect breast cancer risk. Several studies observed conflicting results, mainly due to short follow-up periods. In a recent historical cohort study that included 19,158 women submitted to IVF treatments between 1983 and 1995, the long-term risk of breast cancer, with a median follow up of 21 years, was found not to be significantly different from that in the general population, standardized incidence ratios: 1.01 95% CI 0.93–1.09 and from the risk of a comparison group of 5950 women that started non-IVF treatments between 1980 and 1995, hazard ratios (HR): 1.01 95% CI 0.86–1.19 [79]. Considering that hyper-oestrogenism has been shown to affect breast cancer risk in BRCA 1/2 mutation carriers, a national study evaluated the risk among 2514 BRCA 1/2 germline carriers who underwent controlled ovarian hyperstimulation of IVF. This study showed no evidence of an increased breast cancer risk even among this high-risk population with ovarian stimulation, HR: 0.79 95% CI 0.46–1.36 [80]. Also, controlled ovarian hyperstimulation with letrozole co-administration is a safe fertility preservation option for women with breast cancer [81].

Conclusions

This review focused on PCOS controversial association with breast cancer risk in several aspects, from epidemiological to molecular mechanisms and the influence of PCOS therapeutic approaches in breast cancer incidence. A clinical association between PCOS and breast cancer risk was reported in several studies which had several limitations and consequently did not stablished a clear association. Androgen influence in breast tissue seems to be mainly due to conversion to oestrogens, but the molecular mechanisms involving AR and PCOS need to be clarified. Up to this point, basic research suggests an influence of androgens in hormone-receptor-positive breast cancer. However, clinical research considering PCOS has already emphasized an overlapping gene with breast cancer. Finally, the influence of medical treatment of PCOS in breast cancer risk and incidence appears to be a promising tool for basic and clinical research, considering the inconsistent study results, particularly concerning the role of metformin. Further research on this area should involve large prospective studies focusing on the epidemiological risk and intervention protocols allowing conclusions about the influence of PCOS medical treatment on breast cancer pathogenesis.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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