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REVIEW ARTICLE

An overview of the risk, underlying factors, and mechanism of cancer progression in polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder among women of reproductive age. PCOS is characterized by ovulatory dysfunction, clinical or biochemical features of hyperandrogenism, and polycystic ovaries. The risk of cancer among PCOS patients has been a topic of discussion for decades due to the overlapping metabolic and endocrine abnormalities. This review article focuses on the association of PCOS with various types of reproductive (such as endometrial cancer, ovarian cancer, and breast cancer) and non-reproductive cancers, considering different aspects, such as the risk of cancer progression in PCOS patients, the underlying factors, and the mechanism through which PCOS might progress to cancer. The information provided in this article would help create awareness among PCOS patients about the need to take risk-reducing measures. This article might also aid in the effort of identifying novel therapeutic targets to counteract the progression of cancer in PCOS.

Keywords: Polycystic ovary syndrome; Cancer; Risk; Mechanism

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder among females of reproductive age in developed countries. According to reports, 6–20% of women of reproductive age suffer from PCOS[1]. This syndrome, which is heterogeneous, may be defined by a combination of signs and symptoms related to androgen excess and ovarian dysfunction in the absence of any specific diagnoses[1]. Women who are diagnosed with PCOS may complain of heavy or irregular menstrual bleeding, infertility, obesity, oily skin, seborrhea, cystic acne, or hirsutism. These symptoms may have a significant negative effect on a woman's quality of life and may cause psychological anguish that jeopardizes both her femininity and physical health. As a result, the illness may lead to issues at work, dysfunctional family dynamics, and changing perceptions of oneself[2].

The pathophysiology of PCOS is known to be affected by both genetic and environmental factors, but its exact cause is unclear[3]. Despite the fact that the molecular

mechanism behind PCOS pathogenesis is still largely unknown, there is a vast amount of evidence indicating that hyperandrogenism is crucial to the progression and consequences of PCOS[4]. Whether PCOS is a single clinical entity or a conglomerate of many diseases with a common clinical appearance is unclear as of yet. Researchers have reported heightened risks of insulin resistance, diabetic mellitus, cardiovascular disease, metabolic syndrome, endometrial dysfunction, and pregnancy complications in PCOS patients[5-7].

The risk of cancer among PCOS-affected women has been a topic of debate over the years[8]. Given the high incidence of PCOS, any link to cancer would be crucial from the standpoint of public health. Identifying the component that significantly increases the risk of developing cancer is extremely challenging due to the multifactorial nature of the syndrome, along with its heterogeneous presentation[9]. In more developed countries, endometrial cancer is one of the most common reproductive cancers, but it is ranked as the second most common in less developed countries[10]. Stein and Leventhal initially described PCOS in 1935, but the first study of PCOS and the risk of endometrial cancer was only published after 14 years later[11,12]. Although the direct association of PCOS with breast cancer and ovarian cancer has yet to be established, the incidence of these cancers in PCOS patients has been observed over the years in several studies[13-15]. Androgens are believed to be involved in the pathogenesis of ovarian cancer in PCOS patients, while the level of estrogen is related to the progression of endometrial cancer[16-18]. One of the key drugs used in PCOS management is oral contraceptives. Studies have suggested that oral contraceptives interfere with cancer-associated regulations and reduce the risk of developing cancer in PCOS women[19,20]. The association of breast cancer with PCOS is unclear, but incessant research efforts have been made to find a strong link between them. Although the effects of androgen on breast cancer development in PCOS have not been fully understood, studies have shown evidence of the role of estrogen in breast cancer development[21-23]. Several studies are also underway to identify the genes responsible for cancer pathogenesis in PCOS[24,25].

We reviewed the current state of knowledge in a comprehensive manner, specifically the overall potential of hazardous cancers that could occur in patients with PCOS, along with the underlying factors and mechanism. The information provided in this article would help create awareness among the younger generation, thus ameliorating these problems. Early detection and proper treatment can lessen the burden of clinical symptoms and concomitant psychological anguish, thus reducing the risk of developing cancer and the effect on PCOS patients' quality of life in terms of their health. This article might also aid in the efforts of identifying novel therapeutic targets to counteract shared dysregulation in PCOS and cancer.

2. Pathophysiology of PCOS

PCOS is a multifaceted syndrome and its complex pathophysiology is yet to be fully understood. The two most notable phenotypes of PCOS are hyperandrogenism and ovarian dysfunction. Increased blood levels of free (unbound) testosterone, a crucial hormone involved in the pathogenesis of PCOS, are indicative of hyperandrogenism[26-28]. Figure 1 illustrates the pathophysiology of PCOS.

Androgens, including dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, dihydrotestosterone, and androstenedione, are found in serum in decreasing order of concentration[29,30]. The hypothalamic-pituitary-ovarian axis is thought to be imbalanced in PCOS as a result of neuroendocrine dysregulation. This leads to increased frequency of gonadotropin-releasing hormone pulses. The increase in frequency of GnRH pulses promotes luteinizing hormone (LH) rather than follicle-stimulating hormone (FSH) production, leading to an increase in LH: FSH ratio in PCOS, which causes hyperandrogenism[31,32]. The anti-Müllerian hormone (AMH) produced by ovarian granulosa cells is a regulatory factor of GnRH release. In PCOS patients, high AMH stimulates LH production through AMH receptor on the hypothalamus and pituitary, increasing the secretion of androgen by ovarian theca cells. At the same time, high AMH suppresses FSH receptor and aromatase production in granulosa cells; a low level of FSH prevents testosterone from being converted to estrogen, thus resulting in androgen excess. Elevated testosterone, in turn, promotes the direct and indirect release of AMH from granulosa cells[33,34].

In PCOS, there are disruptions in the interactions and coordination between LH, FSH, insulin-like growth factor 1 (IGF-1), AMH, androgen conversion enzymes, and additional variables, resulting in arrested ovarian follicular development. Ovarian hyperandrogenism, hyperinsulinemia from insulin resistance, and intra-ovarian paracrine signaling are all factors in PCOS that disrupt follicle growth. The reduced FSH level inhibits ovarian follicular development, which may cause amenorrhea, anovulation, and polycystic morphology[33,35-36].

Although insulin receptor gene alterations are uncommon, hyperinsulinemia, and insulin resistance are two prominent clinical conditions of PCOS in women. Insulin resistance, a disordered physiological state caused by impaired glucose transport and utilization, is a result of the biological effects of insulin being reduced when it is

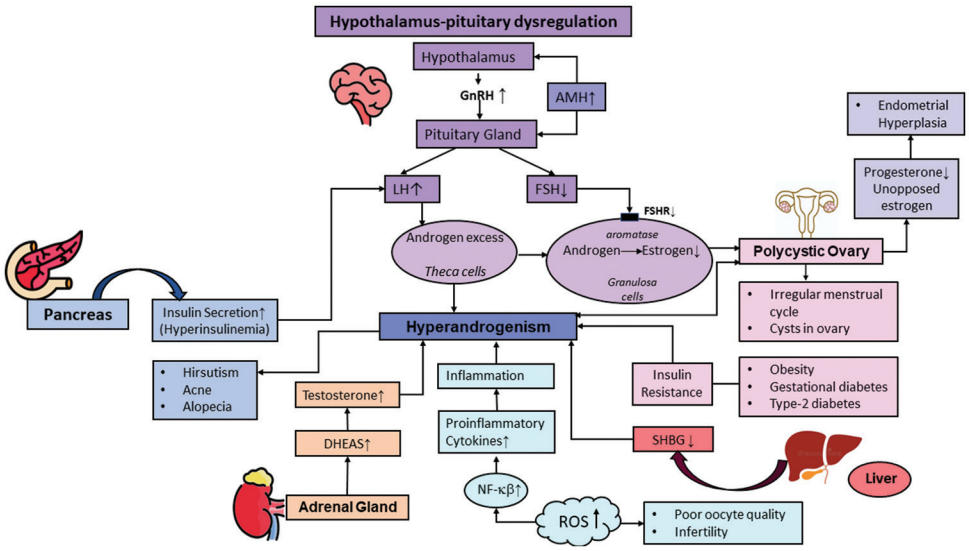

Figure 1. Pathophysiology of PCOS. Hyperandrogenism and ovarian dysfunction are the main phenotypes of PCOS. Neuroendocrine dysregulation disrupts the balance of the hypothalamic-pituitary-ovarian axis, resulting in an increase in frequency of GnRH release. The increased GnRH pulse frequency causes an elevated LH: FSH ratio, leading to hyperandrogenism. Several factors such as elevated AMH level, insulin resistance, hyperinsulinemia, low SHBG level, and increased ROS generation contribute to hyperandrogenism in PCOS. Clinical features of hyperandrogenism include hirsutism, acne, and androgenic alopecia, while decreased FSH level causes amenorrhea, anovulation, and polycystic morphology. Low progesterone, along with unopposed estrogen, leads to endometrial hyperplasia.

AMH: Anti-Müllerian hormone; DHEAS: Dehydroepiandrosterone sulfate; FSHR: Follicle-stimulating hormone receptor; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; NF-κB: Nuclear factor kappa B; PCOS: Polycystic ovary syndrome; ROS: Reactive oxygen species; SHBG: Sex hormone-binding globulin.

present at high amounts[35,37]. Insulin resistance is higher in peripheral tissues, particularly in skeletal muscles. Burghen *et al.*, who noted that hyperinsulinemia is related to insulin resistance, made the initial argument that insulin plays a role in ovarian function in women with hyperandrogenemia[38,39]. In particular, it has been shown that insulin secreted from pancreatic beta cells acts directly through its own receptor at physiological concentrations on cultivated polycystic ovary theca cells and stimulates androgen production, which is noticeably higher than in ovarian theca cells from normal women. Importantly, insulin can work in synergy with LH to boost androgen biosynthesis, while increasing androstenedione production on its own[38,40,41].

Hirsutism, acne, and androgenic alopecia are clinical signs and symptoms of hyperandrogenism caused by hyperinsulinemia[42]. The majority of women with PCOS, in fact, have insulin resistance and compensatory hyperinsulinemia, which is partially attributed to an innate insulin resistance mechanism, especially in those who are overweight or obese, or have diabetes[8,43,44]. In PCOS women, the hypersecretion of adrenocorticotropic hormone causes the overproduction of androgens from the adrenal glands[45].

Hyperandrogenism is mainly manifested by free or unbound testosterone in the blood. Only 1–2% of the testosterone in the blood is unbound, while the remaining 98% is predominantly bound to sex hormone-binding globulin (SHBG). Growing levels of testosterone are considered a characteristic of puberty in teenage females. PCOS may develop if this condition worsens and there is an overproduction of testosterone[46,47]. In addition to directly increasing ovarian androgen production, hyperinsulinemia also increases the fraction of free testosterone in PCOS by lowering the synthesis of liver SHBG[48]. Hence, low serum SHBG level in PCOS patients leads to hyperandrogenism.

The production of a large amount of ROS can be considered a contributing factor in the pathophysiology of PCOS. The imbalance between free radicals and antioxidants in the body occurs from the overproduction of ROS, leading to oxidative stress[45]. Oxidative stress is more frequent in obese PCOS patients who develop early insulin resistance[49]. The vast amount of ROS causes increased production of pro-inflammatory cytokines[50]. The pro-inflammatory cytokines that are produced inside the endometrium can easily hinder the mechanism of action of insulin in PCOS, resulting in insulin resistance and eventually causing hyperandrogenism[51,52].

The detailed mechanism of the entire process of oxidative stress causing inflammation and eventually leading to hyperandrogenism is still under investigation, with several pathways and factors considered to be potential

areas of study[49,53]. Among the factors, nuclear factor-κB (NF-κB) is a potential effector of inflammation induced by hyperandrogenism. The expression of NF-κB is enhanced through increased level of phosphorylation that induces ROS production and inflammatory responses[36,49,54].

3. Polycystic ovary syndrome and cancer

PCOS is an intrinsic endocrine and metabolic condition that seriously affects menstrual and reproductive functions, causing detrimental effects on a woman's health throughout her lifetime. Although PCOS has been linked to hyperandrogenism, genetic, and epigenetic factors, the exact cause of PCOS remains unknown[55,56]. Between 6% and 20% of premenopausal women have PCOS, possibly making it the most prevalent endocrine and metabolic condition among women of reproductive age[57-59]. The risk of cancer among PCOS-affected women has been a debatable topic over the years[8]. There remains, however, absence of adequate conclusive research linking PCOS to the risk of various cancers due to uncertainties in its etiopathology, dubious diagnostic standards, and the complex endocrine and metabolic dysfunctions[60]. PCOS is conjectured to be linked to various types of reproductive cancers, including endometrial cancer, ovarian cancer, breast cancer, uterine cancer, and others. One of the primary clinical signs of PCOS, chronic oligo- or anovulation, induced by continuous estrogen exposure without counteracting progesterone, was linked to endometrial cancer in initial reports of the relationship between PCOS and cancer[61,62].

3.1. Risk and underlying factors of developing reproductive cancer in polycystic ovary syndrome

3.1.1. Endometrial cancer

Endometrial cancer predominantly affects 2–3% of postmenopausal women and is the most prevalent female genital tract malignancy worldwide[63,64]. According to studies, women with PCOS may have a higher chance of developing endometrial cancer than those without the condition[65]. Women with PCOS have multiple endometrial cancer risk factors and their risk for developing endometrial cancer may be higher[66]. Prolonged and unchallenged exposure of estrogen to the endometrium of PCOS patients, low progesterone, obesity, hyperinsulinemia, insulin resistance, IGF, diabetes, nulliparity, cyclin D1, and glutathione S-transferase constitute the clinical, metabolic, and molecular risk factors for endometrial cancer development[66-68].

Six studies have looked into the link between PCOS and endometrial cancer without taking body mass index (BMI) into consideration (Table 1). In a registry-based cohort study of 12,070 women with PCOS, Gottschau *et al.* observed that these patients had 4 times increased risk of endometrial cancer, with a standardized incidence ratio (SIR) of 3.9 (95% confidence index [CI] = 2.2 – 6.3) [69]. Nearly one-third of these women were between the ages of 15 and 24 at the time of their first admission or visit for PCOS, and about 50% were between the ages of 25 and 34[69]. In another population-based, retrospective, and cohort study, a higher mean adjusted hazard ratio (HR) of uterine cancer was found in PCOS patients[70]. A report by Haoula *et al.* concluded that endometrial cancer is 3 times more likely to develop in patients with PCOS in comparison with women without it[71]. A meta-analysis has reported increased risk of endometrial cancer in PCOS patients, with an odds ratio (OR) of 2.79 at CI = 1.31 – 5.95 ($P < 0.008$)[61]. The risk estimate increased when women aged <54 were excluded from the study[61]. A case–control study by Fearnley *et al.* showed a link between PCOS and an increased risk of endometrial cancer in women under the age of 50[72]. Pillay *et al.* also observed a higher prevalence of PCOS in endometrial cancer patients aged below 50[67].

3.1.2. Ovarian cancer

Ovarian cancer is the seventh most common type of neoplasm in women worldwide[73]. Around 239,000 new cases and 152,000 fatalities worldwide are reported each year, with Eastern and Central Europe having the highest incidence[60]. It has been proposed that PCOS increases the risk of ovarian cancer by increasing androgen exposure[74].

Cancer risk and infertility have been linked, albeit the debatable association with ovarian cancer. The most common reasons of infertility in female are hormonal conditions that interfere with ovulation, including PCOS. Ovarian cancer has been linked to a number of endocrine and reproductive changes. As a result, nulliparity, early menarche, and a later onset of menopause have all been linked to an increased risk of ovarian cancer[75-78]. Four studies have explicitly looked at the relationship between PCOS and ovarian cancer[61,69,70,79]. However, most these studies have presented mainly negative results although one recent meta-analysis of three studies did imply an elevated risk (OR = 1.4; 95% CI = 0.9 – 2.2)[61]. According to a Danish registry-based study, women with PCOS had a non-significantly higher risk of developing ovarian cancer than the general Danish female population (SIR = 1.8; 95% CI = 0.8 – 3.2); however, the study was constrained by its small sample size (10 ovarian cases)[69]. No correlation was found between PCOS and ovarian cancer in a recent Taiwanese investigation with only 11 occurrences of the disease (HR = 1.0; 95% CI = 0.2 – 4.6)[70]. Following a retrospective cohort study of women with PCOS, Brinton *et al.* found that patients with secondary infertility had a higher risk of developing ovarian cancer than those with

Table 1. Prevalence of reproductive cancer in polycystic ovary syndrome patients

Type of study	Location	Total participants	Cancer type (reproductive)	Number of cancer patients	Adjusted HR/RR/SIR/OR (95% CI value)	References
Cohort	Denmark	12,070	Endometrium	16	3.9 (2.2 – 6.3)	[69]
			Ovarian	10	1.8 (0.8 – 3.2)	
			Breast	59	1.1 (0.8 – 1.4)	
			Cervix uteri	14	0.8 (0.5 – 1.4)	
Registry-based cohort	Taiwan	3,566	Ovarian	2	0.997 (0.214 – 4.636)	[70]
			Breast	14	1.976 (1.035 – 3.722)	
			Uterine	15	8.420 (1.615 – 43.888)	
Meta-analysis	USA Japan Australia Europe	919	Endometrium	5	2.79 (1.31 – 5.95)	[61]
			Ovarian	3	1.41 (0.93 – 2.15)	
			Breast	3	0.95 (0.64 – 1.39)	
Meta-analysis	United Kingdom	938 (cancer patients)	Endometrium	938	2.9 (1.5 – 5.5)	[71]
Retrospective cohort	USA	2,560	Uterine corpus	5	1.28 (0.49 – 3.35)	[79]
			Ovarian	2	0.42 (0.10 – 1.75)	
			Breast	23	0.81 (0.53 – 1.25)	
Case-control	Australia	1,399	Endometrium	156	3.64 (1.76 – 7.52)	[72]
Cross-sectional	United Kingdom	128	Endometrium	11	1.0 (0.4 – 2.7)	[67]
Cohort	USA	116,671	Breast	2267	0.8 (0.6 – 1.0)	[83]

HR: Hazard ratio; OR: Odds ratio; RR: Relative risk; SIR: Standardized incidence ratio

primary infertility (RR = 0.42; 95% CI = 0.10 – 1.75)[79]. In-depth research is required to ascertain if PCOS is related to ovarian cancer.

3.1.3. Breast cancer

Data from several organizations have shown that breast cancer is the most common cancer in women[80]. According to statistics from 2018, 627,000 women died from breast cancer, accounting for 15% of all cancer fatalities in women. Although breast cancer rates are greater in more developed areas, they are rising practically in every area of the world[61]. There is a theory that the dysregulated genes observed in PCOS patients and the genes linked to breast cancer overlap. Three such potential genes, discovered by Xu *et al.*, include alpha polypeptide, platelet-derived growth factor receptor, and hydroxysteroid (17-beta) dehydrogenase[81].

However, there have been studies done that did not find any connection between PCOS patients and a higher risk of breast cancer[82]. With 59 breast cancer cases observed and 56 expected, a recent Danish registry-based study has found no association between PCOS and breast cancer risk, with an SIR of 1.1 (95% CI = 0.8 – 1.4)[69]. Similarly, a retrospective and cohort study in Taiwan has also found no association between PCOS and breast cancer risk (HR = 1.6, 95% CI = 0.9 – 2.8)[70]. According to a meta-analysis, no increased risk was seen in women with PCOS (OR = 1.0; 95% CI = 0.6 – 1.4)[61]. When compared to women who had not been treated for infertility, women with ovulatory problems had a considerably lower risk of breast cancer (RR = 0.8; 95% CI = 0.6 – 1.0)[83]. In a study conducted by Brinton *et al.*, the patients with PCOS did not appear to have an increased risk of breast cancer (RR = 0.81; 95% CI = 0.53 – 1.25)[79].

3.2. Risk and underlying factors of developing non-reproductive cancer in polycystic ovary syndrome

PCOS patients have direct and indirect risks of developing cancers in their later life. If left untreated, the risk of developing atypical endometrial hyperplasia and carcinoma is high due to irregular menstruation with protracted exposure to unobstructed estrogen[84]. These risks are significantly higher among women with obesity or who are overweight. Only a few studies on the association of PCOS with non-reproductive cancers are available (Table 2). A registry-based cohort study by Gottschau *et al.* reported elevated risk of colon, kidney, and brain cancers, with SIR of 2.1, 3.9, and 2.2, respectively (95% CI = 1.1 – 3.8, 1.4 – 8.4, and 1.3 – 3.5, respectively), among PCOS patients but no significant risk of other types of cancers, such as lung cancer, melanoma, and other types of skin cancers[69].

4. Mechanism of cancer progression in polycystic ovary syndrome

Many reports exploring PCOS and the risk of cancer have been published. Hyperinsulinemia, high estrogen level, and chronic inflammation are some of the factors associated with normal PCOS progression[35,37], and there is an evidence that these chronic conditions may be contributing factors to oncogenesis and cancer progression in PCOS[85,86]. Hyperinsulinemia directly initiates and regulates the initiation of cancer development, while inflammation affects various pro-tumorigenic pathways that ultimately lead to angiogenesis and carcinogenesis, thus promoting cancer cell development in certain sites[87,88]. Recent evidence has suggested that the effect of sympathetic hyperactivity is also a risk factor for cancer progression in PCOS women. Sympathetic hyperactivity leads to the secretion of norepinephrine, in which increased norepinephrine acts as a biochemical switch for tumor angiogenesis[85,89-91]. Besides that, low progesterone level is directly associated with the development of endometrial cancer, and many studies have supported that low progesterone level is an indication of hyperandrogenism, thus providing a link between the two[92,93] (Figure 2).

A recent study has identified several PCOS-related genes (PRGs), based on literature review and genomics analysis, that showed significant genomic alterations in endometrial, ovarian, and breast cancers[94]. Interestingly, these PRGs included several cancer driver genes, such as *PTEN*, *ESR1*, and *TP53* in case of endometrial cancer, *PTEN* and *TP53* for ovarian cancer, and *ERBB2*, *NCOR1*, *ESR1*, *TP53*, *PTEN*, and *AKR1C3* for breast cancer[94]. Among these identified genes, the tumor suppressor gene *PTEN* showed the highest number of mutations in endometrial cancer[94]. Therefore, it is presumable that mutations in the cancer driver genes that are included in PRGs might drive PCOS patients toward cancer progression (Figure 2).

Based on clinical behavior and morphological feature, endometrial cancer can be generically divided into two distinct categories: Type I endometrial carcinoma, which is an estrogen-related malignancy with a favorable prognosis; and Type II endometrial carcinoma, which is not related to estrogen and carries a poor prognosis[95]. Studies have found increased endometrial expression of insulin signaling-related genes, such as *IGF1*, *IGFBP1*, and *PTEN*, both in PCOS and endometrial cancer patients[86,94]. *PTEN*, *KRAS*, *CTNNB1*, and *PIK3CA* mutations are

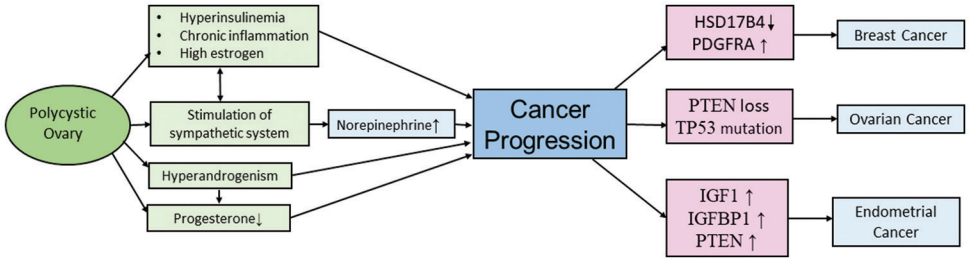

Figure 2. Proposed mechanism of cancer progression in polycystic ovary syndrome (PCOS). Chronic conditions such as hyperinsulinemia, high estrogen level, sympathetic hyperactivity, low progesterone level, hyperandrogenism, and chronic inflammation in PCOS might be the contributing factors to cancer progression. The chronic condition in PCOS might cause significant genomic alterations in the cancer driver genes that are included in PCOS-related genes, such as *PTEN*, *TP53*, *IGF1*, *IGFBP1*, *HSD17B4*, *PDGFRA*, and more, thus raising the possibility of developing cancer.

Table 2. Prevalence of non-reproductive cancer in polycystic ovary syndrome patients

Type of study	Location	Total participant	Cancer type (non-reproductive)	Number of cancer patients	Adjusted HR/RR/SIR/OR (95% CI value)	References
Cohort	Denmark	12,070	Lung	9	1.1 (0.5 – 2.0)	[69]
			Colon	11	2.1 (1.1 – 3.8)	
			Thyroid	8	1.5 (0.7 – 3.0)	
			Kidney	6	3.9 (1.4 – 8.4)	
			Brain	18	2.2 (1.3 – 3.5)	
			Melanoma	22	0.9 (0.5 – 1.3)	
Retrospective cohort	USA	2,560	Melanoma	5	1.17 (0.45 – 3.02)	[79]
			Thyroid	5	2.68 (1.24 – 10.63)	
			Lymphatic	5	1.99 (0.64 – 4.64)	

HR: Hazard ratio; OR: Odds ratio; RR: Relative risk; SIR: Standardized incidence ratio

some of the common genetic mutations associated with Type I endometrial carcinoma[96]. These observations are indicative of how patients with PCOS might be more prone to developing endometrial cancer.

Elevated androgen level is positively correlated with the development of both PCOS and breast cancer[81]. Xu *et al*. identified 53 potent key genes that contribute to the onset of PCOS[81]. Among these genes, *HMGB2*, *PDGFRA*, and *HSD17B4* are involved in the development of male sexual characteristics. Xu *et al*. suggested that PCOS patients with downregulated HSD17B4 and upregulated PDGFRA may have more risk of developing breast cancer[81].

Ovarian cancer and PCOS are strongly associated; however, the underlying molecular mechanism remains largely unknown[97]. Ovarian cancer can be divided into two separate categories based on clinical behavior and molecular genetic abnormalities[98]. Low-grade endometriosis, borderline serous tumors, low-grade serous carcinomas, mucinous, and clear cell carcinomas are examples of Type I tumors, while examples of Type II ovarian cancer include undifferentiated tumors, carcinosarcomas, and high-grade serous carcinomas. High levels of genomic instability are present in Type II tumors. *TP53* is a PCOS-related gene that is highly mutated in high-grade serous carcinoma[94]. However, ovarian cancer, as observed in a mouse model, was not triggered by *TP53* mutation alone but, rather, was cooperatively associated with *PTEN* loss[99].

5. Conclusion

PCOS is becoming a growing public health concern globally because of its high incidence. Although there is a growing body of evidence indicating the inclination of PCOS patients to develop cancer due to shared metabolic and endocrine abnormalities, the overall association remains dubious. In our review, we extensively explored the association of PCOS with various types of cancers, along with the potential risk factors and molecular mechanism. We found that PCOS patients are more susceptible to developing endometrial cancer than other reproductive cancers, but there is contradictory evidence linking PCOS to either ovarian cancer or breast cancer. Due to the lack of studies, it is difficult to draw a strong link between PCOS and non-reproductive cancers. Disrupted hormonal balance, hyperinsulinemia, unchallenged high estrogen level, chronic inflammation, sympathetic hyperactivity, hyperandrogenism, and low progesterone level are all associated with normal PCOS progression and can also contribute to oncogenesis and cancer progression in PCOS. PRGs have shown significant genomic alterations in endometrial cancer, ovarian cancer, and breast cancer. These PRGs include several cancer driver genes, thereby indicating that mutations in the cancer driver genes that are included in the PRGs might drive PCOS patients toward cancer progression. Ethnically diverse and larger clinical trials along with molecular and bioinformatics approaches in an integrated manner are required to fully understand the association of PCOS with cancer.

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Conflict of interest

The authors declare that they have no competing interests.

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