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From hyperandrogenism to tumorigenesis; a mechanistic perspective on cancer development in PCOS-affected women

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Abstract

The mechanistic sequence from hyperandrogenism to tumorigenesis in women with polycystic ovary syndrome (PCOS) encompasses a constellation of structural and functional aberrations spanning the endocrine, metabolic, immunologic, and genetic domains. Chronic hyperandrogenism incites an interconnected cascade through chronic anovulation and unopposed estrogen action, insulin resistance with hyperinsulinemia, low-grade systemic inflammation, oxidative stress, and gut dysbiosis, each playing a synergistic role in promoting oncogenesis. It has been demonstrated that, this syndrome is most strongly associated with an increased risk of endometrial cancer, with a more modest and less consistent association with ovarian and breast cancers. Thyroid cancer risk may also be elevated, particularly in younger women. The underlying mechanisms involve hormonal imbalances, metabolic dysfunction, chronic inflammation, and genetic predisposition. Women with PCOS should be monitored for early signs of these cancers, and management should focus on mitigating risk factors such as obesity, insulin resistance, and chronic anovulation.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders affecting individuals of reproductive age, with an estimated global prevalence ranging from 6% to 20% depending on diagnostic criteria (1). This condition, characterized by a constellation of symptoms including oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology, PCOS is not merely a reproductive condition but a systemic metabolic and endocrine disorder with far-reaching implications (2). Among the most concerning long-term health consequences associated with PCOS is an elevated risk of certain malignancies, particularly endometrial cancer, but also potentially ovarian and breast cancers (3). The mechanistic underpinnings linking PCOS to tumorigenesis are complex and multifactorial, involving intertwined hormonal, metabolic, inflammatory, and genetic pathways. Central to this nexus is hyperandrogenism as the hallmark biochemical feature of PCOS, which appears to exert both direct and indirect oncogenic influences (4). The association of chronic hyperandrogenism with neoplastic transformation requires a detailed exploration of endocrine dysregulation, insulin resistance, chronic low-grade inflammation, alterations in the tumor microenvironment, and disruptions in key cellular signaling cascades (5). This review, therefore, sought to assess all interacting mechanisms of cancer enhancement in PCOS.

Search strategy

The literature search for this narrative review was conducted using a comprehensive,

Key point

The mechanistic pathway from hyperandrogenism to tumorigenesis in polycystic ovary syndrome (PCOS)-affected women is multifactorial and involves a complex interplay of hormonal, metabolic, inflammatory, and immune factors. Hyperandrogenism initiates a cascade of events that disrupt endocrine homeostasis, promote insulin resistance, and foster a pro-inflammatory environment. These changes, compounded by obesity and epigenetic alterations, create conditions conducive to cancer development, particularly in gynecological tissues.

multi-database strategy to ensure broad coverage of relevant scientific evidence. Searches were conducted across PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. A combination of controlled vocabulary and free-text terms was applied, incorporating key concepts such as hyperandrogenism, PCOS, cancer risk, tumorigenesis, hormonal dysregulation, metabolic dysfunction, and ovarian pathology. These keywords were used individually and in various Boolean combinations to maximize the retrieval of studies addressing the mechanistic links between PCOS-related endocrine and metabolic disturbances and cancer development. No restrictions were placed on publication year, and additional sources were identified through manual screening of reference lists.

The origin of hyperandrogenism in PCOS

Hyperandrogenism in PCOS arises from a combination of ovarian and adrenal overproduction of androgens, coupled with reduced sex hormone–binding globulin levels, which increases the bioavailability of free testosterone and dihydrotestosterone (6). While androgens are essential for normal physiological functions, their chronic elevation in the context of PCOS creates a hormonal milieu that can foster cellular proliferation, inhibit apoptosis, and promote genomic instability (7). In the endometrium, for example, unopposed estrogen stimulation, often secondary to chronic anovulation is traditionally cited as the primary driver of endometrial hyperplasia and subsequent carcinoma. However, emerging evidence suggests that androgens themselves may directly contribute to endometrial carcinogenesis (8). Androgen receptors (AR) are expressed in both normal and malignant endometrial tissues, and activation of these receptors by elevated androgens can modulate the expression of genes involved in cell cycle progression, such as cyclin D1, and suppress tumor suppressor pathways (9). Moreover, androgen signaling can cross-talk with estrogen receptor pathways, amplifying mitogenic signals even in the absence of high estradiol levels (7). This synergy between androgen and estrogen signaling may accelerate endometrial epithelial proliferation beyond the threshold of normal repair mechanisms, setting the stage for malignant transformation (7).

Focus on insulin resistance in PCOS

The role of insulin resistance as a near-universal feature in both lean and obese women with PCOS, further compounds the oncogenic risk. Insulin resistance leads to compensatory hyperinsulinemia, which not only exacerbates hyperandrogenism by stimulating ovarian theca cell androgen production and suppressing hepatic sex hormone–binding globulin synthesis but also activates insulin-like growth factor 1 (IGF-1) signaling (10). The insulin/IGF-1 axis is a well-established driver of tumorigenesis across multiple cancer types. Hyperinsulinemia increases bioavailable IGF-1 by reducing IGF-binding proteins, thereby enhancing IGF-1 receptor (IGF-1R) activation (11). Previous studies found that, IGF-1R signaling promotes cell proliferation, inhibits apoptosis, and stimulates angiogenesis through downstream effectors such as the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways, both of which are frequently dysregulated in cancers. In the endometrium, this signaling cascade can lead to unchecked epithelial growth (12). Similarly, in ovarian surface epithelium or breast tissue, chronic activation of these pathways may lower the threshold for oncogenic mutations and support the survival of pre-malignant clones (12). Notably, mTOR activation also contributes to metabolic reprogramming as a hallmark of cancer by enhancing glycolysis and lipid synthesis, thereby fueling tumor cell energetics and biosynthesis (13).

Impact of low-grade inflammation on PCOS

Chronic low-grade inflammation is another critical mediator linking PCOS to cancer development. Women with PCOS consistently exhibit elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein, even after adjusting for body mass index (14). Adipose tissue dysfunction, particularly in visceral fat depots, plays a central role in this inflammatory state (15). Hypertrophic adipocytes in insulin-resistant states secrete excess free fatty acids and adipokines, recruiting macrophages and other immune cells that perpetuate inflammation (16). This inflammatory microenvironment fosters DNA damage through the generation of reactive oxygen species and reactive nitrogen species, which can induce mutations in oncogenes and tumor suppressor genes (17). Furthermore, inflammatory cytokines activate transcription factors like nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3, both of which regulate genes involved in cell survival, proliferation, and immune evasion. In endometrial tissue, persistent NF-κB activation has been linked to the transition from hyperplasia to carcinoma (18). In ovarian and breast tissues, chronic inflammation may similarly create a permissive niche for tumor initiation and progression. The interplay between hyperandrogenism and inflammation is bidirectional (19). Androgens can

modulate immune cell function and cytokine production; for instance, testosterone has been shown to enhance pro-inflammatory responses in macrophages under certain conditions (20). Conversely, inflammatory cytokines such as TNF-α can upregulate enzymes involved in androgen biosynthesis, including 17α-hydroxylase/17,20-lyase thereby, which amplifying androgen production in the ovaries and adipose tissue. This positive feedback loop between androgen excess and inflammation creates a self-sustaining pathological state that may accelerate oncogenic processes over time (10).

Role of genetic and epigenetic factors

Genetic and epigenetic factors further modulate individual susceptibility to cancer in the context of PCOS. Genome-wide association studies have identified several susceptibility loci for PCOS that overlap with genes implicated in cancer pathways, including those involved in cell cycle regulation (like DENND1A, YAP1) and insulin signaling (e.g., HMGA2, TOX3) (21). Recent studies detected that, DENND1A is involved in clathrin-mediated endocytosis and has been linked to altered androgen biosynthesis; its overexpression in PCOS theca cells may contribute to both hyperandrogenism and dysregulated growth factor signaling (22). Epigenetic modifications, such as DNA methylation, histone acetylation, and non-coding RNA expression are also increasingly recognized as mediators of long-term disease risk (23). In women with PCOS, global and gene-specific DNA methylation patterns differ from those in controls, particularly in genes related to metabolism and inflammation. These epigenetic changes, potentially established early in life or even in utero due to maternal androgen exposure, may predispose tissues to malignant transformation later in adulthood by silencing tumor suppressors or activating oncogenes (24).

A short look at the ovarian microenvironment in PCOS

The ovarian microenvironment in PCOS also presents unique features that may influence cancer risk. Although the association between PCOS and ovarian cancer remains controversial, some epidemiological studies suggest a modest increase in risk, particularly for endometrioid and clear cell subtypes (25). The chronic anovulatory state in PCOS leads to repeated follicular arrest and cyst formation, resulting in prolonged exposure of the ovarian surface epithelium to local inflammatory mediators and growth factors (26). Additionally, theca and granulosa cell dysfunction may alter the balance of local hormones and cytokines, creating a pro-proliferative milieu. Androgen receptors are expressed in ovarian epithelial cells, and experimental models show that androgen exposure can increase ovarian epithelial cell proliferation and reduce apoptosis (7). Moreover, hyperinsulinemia may directly stimulate ovarian stromal cells, further contributing to a dysregulated microenvironment conducive to neoplastic change (10).

Impact of obesity in PCOS

Obesity, frequently associated with PCOS, amplifies these risks. Adipose tissue acts as an endocrine organ, secreting adipokines and inflammatory cytokines that contribute to a chronic low-grade inflammatory state. This inflammation is a recognized driver of tumorigenesis, as it promotes DNA damage, angiogenesis, and cellular proliferation (27). Additionally, adipose tissue is a site of peripheral estrogen synthesis via aromatization of androgens, further contributing to estrogen dominance in PCOS women (28). The interplay between hyperandrogenism, insulin resistance, and obesity creates a vicious cycle that perpetuates hormonal and metabolic disturbances, fostering a milieu conducive to cancer development (29) (Figure 1).

Gut microbiome in PCOS

The gut microbiome represents an emerging frontier in understanding the PCOS–cancer link. Women with PCOS exhibit distinct gut microbial compositions compared to healthy controls, characterized by reduced microbial diversity and altered ratios of Firmicutes to Bacteroidetes (30). Dysbiosis can contribute to increased intestinal permeability known as the leaky gut, allowing bacterial endotoxins like lipopolysaccharide to enter

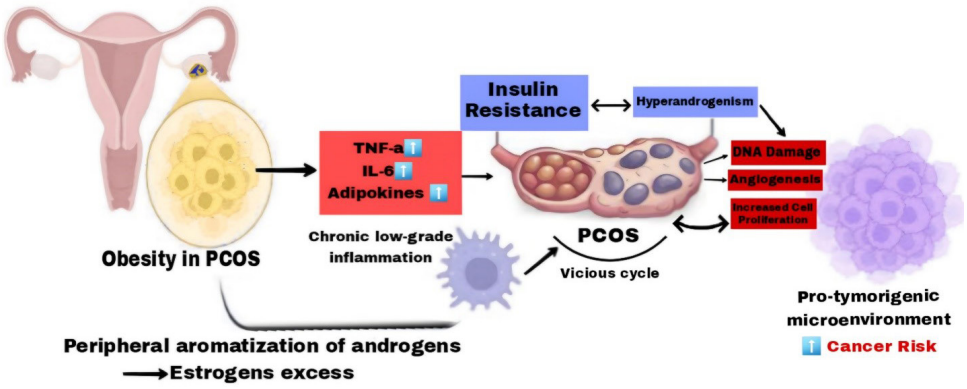

Figure 1. Obesity-driven endocrine and inflammatory mechanisms linking PCOS to cancer risk.

systemic circulation and trigger inflammation (31). Lipopolysaccharide activates toll-like receptor 4 signaling, which in turn stimulates NF-κB and promotes the release of pro-inflammatory cytokines (32). Then, this systemic inflammation may exacerbate insulin resistance and androgen production, creating another reinforcing loop that supports tumorigenesis (33). Moreover, certain gut bacteria possess enzymatic activity (e.g., β-glucuronidase) that deconjugates estrogens in the gut, allowing their reabsorption and contributing to estrogen recirculation, as a process known as the enterohepatic circulation of estrogens (34). In anovulatory women with PCOS, this may further elevate estrogenic tone in endometrial tissue, compounding the risk of hyperplasia and cancer (35).

Focus on oxidative stress

Oxidative stress is another downstream consequence of hyperandrogenism and insulin resistance in PCOS. Excess androgens upregulate NADPH oxidase activity, promoting reactive oxygen species generation and lipid peroxidation (36). Oxidative stress causes DNA damage, impairs repair mechanisms, and increases mutational rates—all hallmarks of the early steps in tumorigenesis. The mitochondria in PCOS cells exhibit impaired respiratory function and reduced ATP production, contributing further to metabolic imbalance and cellular vulnerability (37).

Strengthened risks of cancers in PCOS

Endometrial cancer is the most strongly linked malignancy in women with PCOS. The risk is elevated due to chronic anovulation, which leads to unopposed estrogen exposure in the endometrium (35). Normally, progesterone counteracts estrogen's proliferative effects, but in PCOS, the lack of regular ovulation means insufficient progesterone production, resulting in persistent estrogen stimulation. This can cause endometrial hyperplasia, a precursor to endometrial cancer (38). More recent studies have shown that women with PCOS have a higher risk of developing endometrial cancer compared to those without PCOS (39). The risk is further amplified by comorbidities such as obesity, insulin resistance, and type 2 diabetes, which are common in PCOS and independently increase endometrial cancer risk (40). Ovarian cancer is also associated with PCOS, though the evidence is less consistent than for endometrial cancer (3). Some large cohort studies have found a modest increase in ovarian cancer risk among women with PCOS too (41). The underlying mechanisms may involve chronic inflammation, hormonal imbalances, and metabolic dysfunction, all of which are features of PCOS. However, the absolute risk remains relatively low, and further research is needed to clarify the strength and nature of this association (14). Breast cancer risk in PCOS is controversial. Some studies suggest a possible link due to elevated androgen and estrogen levels, as well as insulin resistance, which can promote tumor growth (42). However, meta-analyses have not consistently demonstrated a significant increase in breast cancer risk among women with PCOS, and the available evidence is considered inconclusive. The risk may be influenced by factors such as age, BMI, and the presence of other metabolic (43).

Treatment options in PCOS to modulate cancer risk

Therapeutic interventions for PCOS may modulate cancer risk, offering indirect evidence for the mechanistic links described (44). Combined oral contraceptives, commonly used to regulate cycles and suppress androgen levels, have been shown to reduce the risk of endometrial cancer by providing progestin opposition to unopposed estrogen (45). Metformin, an insulin-sensitizing agent, not only improves metabolic parameters but also exhibits direct anti-tumor effects by inhibiting mTOR signaling and reducing systemic inflammation (46). Observational studies suggest that metformin use in women with PCOS is associated with a lower incidence of endometrial hyperplasia and cancer (47). Lifestyle interventions—particularly weight loss through diet and exercise—can ameliorate hyperandrogenism, insulin resistance, and inflammation, thereby potentially interrupting multiple oncogenic pathways simultaneously. These clinical observations reinforce the notion that the drivers of tumorigenesis in PCOS are modifiable and rooted in the core pathophysiological features of the syndrome (48).

Conclusion

In summary, the mechanistic perspective on cancer development in women with PCOS reveals a complex web of interconnected pathways centered on hyperandrogenism but extending far beyond it. The syndrome serves as a natural model of chronic endocrine and metabolic disruption, offering insights not only into gynecologic oncology but also into the broader principles of hormone-driven carcinogenesis.

Authors' contribution

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Writing–original draft: All authors.
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Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors

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