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Increased risk of ovarian and breast malignancies in women with polycystic ovary syndrome: a review article

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the common abnormalities in 5 to 8% of reproductive-age women, which is associated with high levels of androgens and polycystic ovaries. A clear connection between the level of sex hormones and some women's cancers and infertility abnormalities has been identified. Investigating common mutations in ovarian and breast cancer in people with PCOS can help to better understand the risk and their relationship. Epidemiological data suggest that the induction and biology of breast and ovarian cancer are related to estrogen levels. According to molecular findings, there are common mutations in BRCA genes in ovarian and breast cancer and PCOS patients. The BRCA1 gene produces proteins that prevent malignant tumor formation in the body. Despite common cancer mutations, there is a risk of ovarian and breast cancer in polycystic patients, and these mutations can confirm the risk of ovarian and breast cancer in PCOS patients. Of course, long-term laboratory studies are needed to confirm this relationship. In addition, the presence of genetic mutations can be considered a predisposing marker in connection with ovarian and breast cancer onset, and this awareness can be effective in preventing them from developing in the future.

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Introduction

PCOS is one of the most common abnormalities in 5-8% of reproductive-age women, which is associated with ovulation abnormalities, high levels of androgens, and polycystic ovaries. Several conditions and factors such as glucose intolerance, diabetes, high blood pressure, obesity, metabolic syndrome and cardiovascular diseases can cause PCOS (1-4). The high prevalence of endometrial hyperplasia and carcinoma due to chronic anovulation, along with long-term exposure to estrogen, are the most common causes of PCOS. Meanwhile, factors such as obesity, diabetes, and high blood pressure are also among the factors affecting endometrial carcinoma (5,6). Women with PCOS suffer more pregnancy complications compared to women with normal ovaries, and these complications include an increased risk of miscarriage, gestational diabetes, and preeclampsia (7).

Research has shown a clear connection between the level of sex hormones and some women's cancers and infertility abnormalities. Female sex hormones cause the development and maintenance of female sexual characteristics and also play a role in menstrual cycle and pregnancy. According to endometrial, ovarian and breast cancer studies, these diseases are related to chronic hormonal changes, and continuous increase in estrogen level is related to hormone-sensitive breast tumor development. Therefore, sex hormones play a decisive role in women, and changes in hormone levels and lack of ovulation can be considered as an important risk factor in women with PCOS (8).

Another important issue that has been recently paid attention to is the relationship between PCOS and breast cancer in women. There are conflicting results regarding the relationship between PCOS and breast cancer. Some studies have reported an association, but others have not (9,10). The actual risk remains unclear; Because their results are often contradictory and the risk of developing these cancers in women with PCOS is still debated (11,12).

Evidence suggesting a hormonal role in breast cancer development began with the initial observation that bilateral oophorectomy significantly reduced the risk of breast cancer and that risk was reduced if ovaries were removed as soon as possible. In addition, some risk factors, including early menstruation onset, late menopause, being nulliparous, or having children late in life, are associated with developing breast cancer. Most breast tumors are ER positive (ER+) and are actually sensitive to estrogen, so it is important to know what estrogen levels are and that changes in this hormone increase the risk of breast cancer (13-15).

Epidemiological data suggest that induction and biology of ovarian cancer are also related to estrogen expo-

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sure and its metabolism. Ovarian cancer cells, like breast cancer, are very similar in terms of estrogen-regulated pathways, and hormonal changes pathways can be similar in these cancers (16,17). Estrogen causes tumorigenesis in two ways: receptor-dependent and independent. In the receptor-dependent pathway, estrogen binding to estrogen receptor leads to the activation of estrogen-responsive genes, which results in the creation of a cell division and differentiation signal. The estrogen receptor causes genes activation such as c-fos, c-myc and HER2/neu, cell cycle regulating cyclins, growth factors, etc. (18). On the other hand, the binding of estrogen to estrogen receptor with membrane-bound G protein results in excessive cell proliferation (19). In another pathway (independent of the receptor), the mutation in the receptor causes an increase in DNA mutation active metabolites formation. The accumulation of mutations in different genes in fallopian tube cells and ovaries leads to carcinogenesis (20,21).

In women with PCOS, chronic estrogen stimulation can often cause endometrial hyperplasia. Endometrial carcinoma is the most common female malignancy, and an increasing number of clinical trial studies have focused on the association between PCOS and endometrial cancer. However, cancer-related biological mechanisms shared between these two conditions have not been extensively studied and most studies are based on the assumption that chronic anovulation is the main factor in both conditions, leading to high levels of estrogen, which naturally affects endometrium. Park et al. (22) reported that thick endometrium is a risk factor for the development of endometrial hyperplasia and cancer in patients with PCOS. Furthermore, polycystic ovarian morphology has been shown to be significantly more common in younger patients (less than 40 years) with endometrial carcinoma (23).

In recent years, things like the treatment of cancers and infertility issues have been among the interest areas for research and study by researchers around the world. Despite extensive research in the field of risk factors affecting the occurrence of ovarian and breast cancer, research is still ongoing to confirm the existence of a significant relationship between PCOS and the increased likelihood of breast and ovarian malignancy, and so far, little data has been obtained to confirm this relationship. Therefore, investigating the relationship between abnormality and cancer has attracted a lot of attention in the last two decades. With the evidence that shows estrogens have a causal role in cause of breast and ovarian cancer, in this review, we will investigate the increased risk of ovarian and breast malignancies in women with polycystic ovary syndrome.

The cause of the polycystic syndrome and the prevalence of the polycystic syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-age women and is the most common cause of infertility due to lack of ovulation. Several factors, including genetic predisposition, nutrition and living conditions are effective in PCOS. A person may have a genetic predisposition and its symptoms may be aggravated by environmental and lifestyle factors. The main complications of this disease in adolescence are amenorrhea, oligomenorrhea, hypertension, obesity and acne. In reproductive age, irregular ovulation and infertility are complications of this disease. In age before and after menopause, this syndrome can increase the risk of high blood pressure, type 2 diabetes, dyslipidemia, cardiovascular diseases, and even endometrial and possibly breast cancer (24-27).

Polycystic ovary syndrome is associated with hormonal abnormalities, so the LH/FSH ratio is considered a criterion for diagnosing the disease. This disease may start with dysfunction of the adrenal, hypothalamus or central nervous system or only the ovary. The prevalence of PCOS is higher in women under 35 years of age and in different studies, the prevalence of this syndrome has been reported among different populations (28,29). Among the factors that may play a role in this disease are (30):

1. Insulin resistance. The hormone insulin allows cells to use sugar, body's primary energy source. If cells become resistant to insulin action, blood sugar levels can rise. This can cause more insulin production and lower blood sugar levels. Too much insulin causes the production of a large amount of male hormone androgen (30).
2. low degree of inflammation. White blood cells initiate a low-grade inflammatory response in response to infection or injury. Research shows that people with polycystic ovary syndrome have a long-term, low-grade inflammation that causes androgen production in polycystic ovaries (30).
3. Heredity. Research suggests that certain genes may be associated with PCOS. Having a family history may play a role in the development of this disease (31).
4. High androgen. If PCOS is present, the ovaries may produce high levels of androgens. Having too much androgen interferes with ovulation. This means that the eggs do not develop regularly and are not released from the follicles in which they grow. Excess androgens can also lead to acne (30,31).

Risk of ovarian and breast cancer in PCOS

Many diseases related to glands are caused by changes in gene expression or mutations of them. Gene defects or mutations can change pathways of differentiation and proliferation. Non-differentiation and non-stop proliferation are the main characteristics of cancer cells. Some studies have considered the risk of ovarian and breast cancer in PCOS patients to be considerable, and some have not observed a significant relationship (11,32). Other studies have shown that the risk of uterine and breast cancer was higher in people with PCOS (10-12). In several systematic reviews, it was found that endometriosis is related to PCOS. Of course, the relationship between breast cancer and PCOS was not significant (33,34). In a study, the incidence of ovarian and breast cancer was higher in PCOS patients, but the difference was not statistically significant (33). Investigating common gene mutations in ovarian and breast cancer in people with PCOS can help to better understand the risk and their relationship.

Mutation of effective genes in ovarian cancer

Several studies have reported a significant correlation between gene mutations and cancer clinical phenotype, which indicates the importance of gene mutations as prognostic and therapeutic targets. The four gene mutations most frequently associated with epithelial OC are

BRCA1/2, TP53, PIK3CA, and KRAS. It should be noted that the frequency of these mutations has been reported in different types of epithelial OC (35-37). In high-grade serous ovarian cancer (HGSOC), the P53 mutation is reported to be the most common type of mutation with 55%. Meanwhile, BRCA mutation, which is responsible for most hereditary OCs, increases up to 40%. Mutations in different genes have been reported in different types of ovarian cancer (38). A review showed that more than one-fifth of ovarian tumors are hereditary, and in about 80 percent of these cases, the genetic abnormality is a mutation in BRCA genes. However, several suppressor genes and oncogenes are related to hereditary ovarian cancers. Findings have reported mutations in mismatch repair (MMR) genes in Lynch syndrome, the P53 gene in Li-Fraumeni syndrome and several genes with a dual role in hereditary ovarian cancers (39).

Based on a study, it was observed that gene expression profiling is a very effective tool in the discovery of new molecular markers in ovarian cancer patients. Changes in tumor suppressor gene expression, proto-oncogenes, pro-apoptotic genes, genes related to chromatin remodeling and genes related to carcinogenesis were observed. However, the relationship between these markers and patient survival and clinical outcomes was not observed (40). Another study evaluating the relationship between human epidermal growth factor receptor and clinicopathological characteristics of epithelial ovarian cancer showed that HER2/neu was positive in a quarter of patients, which is significantly associated with cancer marker CA 125 before treatment. However, longer follow-up is needed to analyze survival and establish HER2/neu as a prognostic marker for epithelial ovarian cancer (41). Based on another study in 2022 to provide evidence of susceptibility genes in epithelial ovarian cancer, it was seen that pathogenic variants in BRCA1 and BRCA2 genes are responsible for a significant part of hereditary EOC. In addition, mutations in PV genes involved in the MMR pathway account for 10–15% of hereditary EOC. Identification of women with hereditary EOCs has a significant clinical advantage in terms of chemotherapy regimen planning and development as well as the use of targeted therapies (42).

Effective genes in polycystic syndrome mutation

PCOS leads to chronic anovulation and hyperandrogenism expression, this condition has been one of the most controversial cases in female endocrinology for years. Based on the studies, the expression of some genes has changed in PCOS patients and caused signal transmission pathways that control steroidogenesis, insulin secretion, steroid hormone function, gonadotropin function and regulation, energy action and homeostasis, and inflammation to undergo fundamental changes (43). Steroidogenesis enzymes belong to the complex family of cytochrome P450 and play a vital role in steroid conversion and convert androgen to estrogen. The deficiency of these enzymes affects ovarian function and increases androgen levels. Any abnormality in cytochrome P450 increases the risk of developing PCOS (44). During several studies, mutations in cytochrome family genes such as CYP17A1, and CYP19A1 have been observed in PCOS (45-47). Based on a 2022 study on polycystic ovary syndrome with a genetic approach, it was reported that early diagnosis and treatment of PCOS can be beneficial for patients because, with a genetic approach, long-term treatments can be postponed or avoided. Early detection of polycystic ovary syndrome with comorbidities helps to identify specific treatments for an individual patient's phenotype, which requires continuous progress in genetic and pathophysiological research (48).

Mutation of genes effective in breast cancer

Until now, various mutations have been reported in different genes effective in cell proliferation, and mutations combination related to BRCA1 and BRCA2 genes is the cause of approximately 80% of patients with hereditary breast cancer. Findings have shown that women who have a family history of breast cancer are subjected to genetic tests, in most cases mutated BRCA1 and BRCA2 genes are identified in them. Statistics show that about 50 to 60 percent of women who have these genes develop this disease from the age of 70 years and above (49-52). Various other genes such as p53 and others also play a role in causing breast cancer (53,54). PIK3CA E545K and PIK3CA N345K are other gene mutations that have been reported in 8% to 10% of breast cancer types (55,56). H1047R (PIK3CA), E545K (PIK3CA), E17K (AKT1), and N345K (PIK3CA) are other types of mutations in breast cancer that affect cell differentiation and proliferation functions (57). Of course, tumor mutational burden (TMB) increases with age, and this can be the basis of tumorigenesis (58). For this reason, with time passage, older people are more likely to get breast cancer. Identifying common genes affecting hormonal behavior and cell differentiation can help to understand the relationship between malignant and metabolic diseases.

Common genes involved in ovarian cancer, breast and polycystic syndrome

Hyperandrogenism and infertility often occur in polycystic ovary syndrome, and the occurrence of these disorders is also associated with breast cancer development. Also, endocrine abnormalities in PCOS, including long-term exposure to estrogen, progesterone deficiency, and androgen excess, can contribute to an increased risk of female cancers. Mutations in estrogen hormone receptors and long-term exposure of breast cells to estrogen are also associated with breast cancer (59,60). Elevated androgen levels, and increased insulin and IGF-I levels detected in PCOS can increase the progression of breast cancer. Because polycystic ovary syndrome is usually associated with an increase in androgen and insulin levels and causes high secretion of IGF-I. These conditions can also increase the development of breast cancer and cause direct stimulation of AR-positive cancer cells (61,62).

However, based on a study, it was observed that there was no relationship between polycystic ovary syndrome frequency and breast cancer. This may be due to the age of breast cancer patients in this study, who were mostly over 40 years old (63). Wen et al. (47) also investigated the causal relationship between genetically predisposed PCOS and breast cancer risk and concluded that polycystic ovary syndrome is probably a causative factor in the development of ER-positive breast cancer, which provides a better understanding of the cause of breast cancer and prevention

Table 1. Common genes involved in ovarian cancer, breast and polycystic syndrome.

Communication report	Gene name	Gene function	Year (Ref)
Gene mutations in breast cancer and polycystic syndrome	CYP11A	A key enzyme in synthesis and metabolism of androgens, cleaving side chain of cholesterol	1997 (45)
	CYP17A1	A key enzyme in the steroidogenic pathway	2016 (46)
	CYP19A1	Key proteins in production and regulation of steroid hormones such as cortisol, testosterone and estrogen	2015 (47)
	CYP1A1	Membrane hemoproteins exist in inner membrane of mitochondria of steroidogenic tissues such as liver, intestine, adrenal cortex, testis, ovary, breast and placenta.	1999 (65,66)
	CYP21A2	encoding the enzyme 21-hydroxylase (21-OHD)	2009 (67)
	CYP3A7	An enzyme from the cytochrome P450 family	1989 (68)
mutation of genes in ovarian cancer; Breast and polycystic syndrome	BRCA1	DNA repair or cell damage proteins	2007 (69)
	BRCA2	Encodes tumor suppressor proteins, repairs damaged DNA, regulates transcription of hormone-responsive genes, repairs damaged DNA	2013 (70)
Gene mutations in ovarian cancer and polycystic syndrome	OGN	OGN (Osteoglycin) is a Protein Coding gene	2022 (71)

of it (64). One of the important common mutations of this disease has occurred in BRCA1. The BRCA1 gene produces proteins that prevent the formation of malignant tumors in the body. These genes repair damaged DNA (49-51). As shown in Table 1, 9 mutated genes that are related to hormonal function have been observed jointly in ovarian cancer, breast cancer and polycystic syndrome. These genes can first confirm the association of genes with the risk of these malignancies.

Mutation and cancer control

When a series of mutations cause cells to continue to grow and divide out of control, normal cells turn into cancer cells. Many mutations are inherited from people. BRCA 1 and BRCA 2 are the cause of most hereditary breast cancer (51-53). Changes or mutations in cancer may be inherited or caused by environmental factors. It is believed that the metastatic process, which is the main cause of high mortality in advanced cancers, is mostly caused by epigenetic changes (72,73), therefore, effective strategies for hormonal regulation and reduction of oxidants in the body are important.

In the body of healthy women, genes effective in cell division and tumorigenesis function well. In addition to these cases, there is no family predisposition to defective genes in healthy people (72,74). Of course, family talent alone is not the main cause of cancer spread, but environmental factors and exposure to environmental pollution contribute to cancer spread. Mutations in BRCA genes have been observed in ovarian and breast cancer and PCOS patients (69,70). In general, identifying mutations in ovarian and breast genes in healthy women is important in preventive management. On the other hand, for patients with ovarian cancer, the identification of mutations may provide potential targets for biological agents and guide therapeutic decision-making (36). In addition to identifying mutations in people, lifestyle changes such as avoiding stress and exercising are probably effective in preventing infection.

Conclusion

Epidemiological data suggest that induction and biology of breast and ovarian cancer are related to estrogen exposure and its metabolism. Some studies have considered the risk of ovarian and breast cancer in polycystic patients. Gene expression profiling is a very effective tool in new molecular markers discovery in ovarian cancer patients. According to molecular findings, there are common mutations in BRCA genes in ovarian and breast cancer and PCOS patients. These mutations can confirm the risk of ovarian and breast cancer in PCOS patients, although long-term laboratory studies are needed to confirm this relationship. In addition, the presence of genetic mutations can be considered a predisposing marker in connection with the onset of ovarian and breast cancer, and this awareness can be effective in preventing them from developing in the future.

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