

Research Progress on High-risk Factors, Prevention and Treatment of Ovarian Cancer

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Abstract: Based on the relevant international literature of the past five years, this paper summarizes the research progress in the fields of risk assessment, chemoprevention, and early screening. The high-risk factors for ovarian cancer are complex and diverse, and genetic factors, hormonal reproductive factors, and lifestyle factors all play a role in its occurrence.

Keywords: Risk Assessment; Chemoprevention; Early Screening; Genetic Factors; Hormonal Reproductive Factors

1. Introduction

According to the latest statistics from the World Health Organization's International Agency for Research on Cancer (IARC), there were approximately three hundred ten thousand new cases of ovarian cancer and two hundred thousand deaths worldwide in 2020. Among them, more than 70% of patients had already developed to the late stage (FIGO stage III/IV) when diagnosed, missing the best time for treatment. What is more noteworthy is that despite the continuous advancement of medical technology in recent years, the 5-year survival rate of patients with advanced ovarian cancer is still less than 30 percent, significantly lower than other gynecological malignancies such as cervical cancer (66%) and endometrial cancer (81%) [20]. This severe clinical situation highlights the urgency and challenge of ovarian cancer prevention and treatment. In-depth exploration of its high-risk factors and the development of effective prevention strategies have important scientific value and clinical significance for fundamentally reducing the incidence and mortality of ovarian cancer. This article will systematically explain the multi-dimensional high-risk factors of ovarian cancer, such as genetics, hormones, and lifestyle, and focus on the importance of prevention and a detailed review of research progress in risk

assessment, chemical prevention, early screening, etc. in recent years. At the same time, it will also explore the latest developments in related treatment fields to provide a theoretical reference for the comprehensive prevention and treatment of ovarian cancer.

2. High-risk Factors for Ovarian Cancer

The development and progression of ovarian cancer is a complex, multi-factorial, multi-step process, with risk factors involving genetics, hormones, reproduction, lifestyle, and other aspects. Genetic factors are recognized as important high-risk factors for ovarian cancer, among which BRCA1 and BRCA2 gene mutations are the most critical. Women carrying BRCA1 mutations have a lifetime risk of ovarian cancer of up to 39%-46% [1], and BRCA2 mutation carriers have a risk of 12%-23% [1]. In addition to BRCA1/2, mutations in mismatch repair genes (such as MLH1, MSH2, MSH6, and PMS2) associated with Lynch syndrome (hereditary non-polyposis colorectal cancer) also significantly increase the risk of ovarian cancer. The lifetime risk of ovarian cancer in such patients is approximately 9%-12% [9]. In recent years, genome-wide association studies (GWAS) have discovered several ovarian cancer susceptibility loci, such as single nucleotide polymorphisms (SNPs) located in regions such as 8q24, 9p22.2, and 17q21.31. Although the effects of these loci alone are weak, their combined effects may increase the risk of ovarian cancer [17]. Hormones and reproductive factors play a complex role in the occurrence of ovarian cancer. Early menarche (≤ 12 years old) and late menopause (≥ 55 years old) are considered risk factors, which may be related to the prolonged exposure of ovarian epithelial cells to ovulation-related damage and repair processes [19]. In contrast, pregnancy and breastfeeding have a clear protective effect. Each full-term pregnancy can reduce the risk of ovarian cancer by approximately 15%-20% [21],

and the extension of breastfeeding duration may further enhance this protective effect [21]. The use of oral contraceptives (OCs) is another important modifiable protective factor. Several studies have confirmed that long-term use of OCs (e.g., use for more than 5 years) can reduce the risk of ovarian cancer by approximately 50 percent, and this protective effect can persist for many years after discontinuation of the drug [6]. The mechanism may be related to inhibiting ovulation, reducing repeated damage to the ovarian epithelium, and regulating hormone levels. Lifestyle and environmental factors are also receiving increasing attention. Obesity, especially central obesity, may increase the risk of ovarian cancer by affecting hormone levels (such as estrogen, insulin, insulin-like growth factor), chronic inflammatory state, and oxidative stress, especially for endometrial carcinoma and clear cell carcinoma subtypes [2]. Regarding dietary factors, the current evidence is not completely consistent, but some studies suggest that high animal fat intake may increase the risk, while a diet rich in vegetables and fruits, increased dietary fiber intake, and appropriate vitamin D supplementation may have a certain protective effect [21]. In addition, local pelvic application of talc was once thought to increase the risk of ovarian cancer, but recent meta-analysis results show that this association may not exist or is only weakly associated, and further research is needed to confirm it. Previous gynecological diseases and pelvic surgery history may also affect the risk of ovarian cancer. Endometriosis, especially ovarian endometriosis, has been identified as a precursor to endometrioid carcinoma and clear cell ovarian cancer.

The relative risk of ovarian cancer can be increased by 2-3 times for lesions and risk factors [8]. In contrast, tubal ligation and hysterectomy (with ovarian preservation) may reduce the risk of ovarian cancer by reducing retrograde menstrual blood flow, changing ovarian blood supply or immune microenvironment [16].

3. Research Progress in the Prevention and Treatment of Ovarian Cancer

Ovarian cancer has an insidious onset and lacks specific early symptoms. Approximately 70% of patients are already in the advanced stage (FIGO stage III/IV) at the time of diagnosis [20]. Although initial treatment (cytoreductive surgery

combined with platinum-based chemotherapy) can achieve clinical remission in most patients, the recurrence rate is as high as 70percent-80percent, and the 5-year survival rate has long hovered around 30%-40% [20]. Therefore, prevention is of irreplaceable importance in improving the overall prognosis of ovarian cancer and reducing the social medical burden. Effective prevention strategies can reduce the occurrence of the disease at the source, and their social benefits are far greater than the treatment of advanced disease. Currently, research on the prevention of ovarian cancer mainly focuses on risk assessment and management of high-risk populations, chemical prevention, and primary prevention measures targeting the cause.

3.1 Risk Assessment and Management of High-risk Groups

Accurately identifying high-risk groups and conducting targeted management are the core links in ovarian cancer prevention. Genetic counseling and genetic testing are key means to identify individuals at high risk of hereditary ovarian cancer. The National Comprehensive Cancer Network (NCCN) guidelines recommend that individuals with a family history of breast cancer, ovarian cancer, pancreatic cancer, or prostate cancer, as well as people of a specific ethnic background (such as Ashkenazi Jews), should undergo genetic counseling and testing for related genes such as BRCA1/2 [15]. Genetic testing not only helps to clarify the diagnosis, but also provides important genetic information to the patient's family, enabling early detection and early prevention. Risk-reducing surgery (RRSO) is currently the most effective means of preventing ovarian cancer for BRCA1/2 mutation carriers and some Lynch syndrome patients. Studies have shown that BRCA1 mutation carriers who undergo bilateral salpingo-oophorectomy (RRSO) after childbearing can reduce the risk of ovarian cancer by about 90% and at the same time reduce the risk of breast cancer [18]. The timing of surgery is usually recommended between the ages of 35 and 40, or as soon as possible after childbearing, and individualized evaluation is required. However, RRSO also brings problems such as surgical risks, early perimenopausal symptoms, and potential long-term health effects (such as cardiovascular disease and osteoporosis). In recent years, risk-reducing

salpingectomy (RRST) has gradually attracted attention as an alternative or transitional option, especially for young women who wish to preserve ovarian endocrine function. Studies have shown that the fallopian tube may be one of the main origins of high-grade serous ovarian cancer (HGSC) [10], so fallopian tube removal may significantly reduce the risk of HGSC while preserving the ovaries. However, its long-term preventive effect and optimal surgical timing are still under further research and verification [10][11]. For high-risk women who do not accept or are not suitable for surgery, regular screening is an important monitoring method. However, there is currently no recognized and efficient ovarian cancer screening method. Traditional serum CA125 detection combined with transvaginal ultrasound (TVUS) has shown low sensitivity and specificity in large-scale population screening, which can easily lead to false positive results and overdiagnosis and treatment. The UKCTOCS study in the UK showed that CA125 combined with a risk-based algorithm (ROCA) for multi-stage screening could detect some early cases, but did not significantly reduce the mortality rate of ovarian cancer [13]. Therefore, the exploration of new, more sensitive and specific biomarkers has become a research hotspot. In recent years, the combined detection of circulating tumor DNA (ctDNA), microRNAs, circulating tumor cells (CTCs) and multiple protein markers has shown potential application prospects, but most are still in the preclinical or early clinical trial stage [4].

3.2 Chemoprevention

Chemoprevention aims to use natural or synthetic chemicals to inhibit, reverse or prevent the occurrence and development of precancerous lesions. Oral contraceptives (OCs) are not only an effective form of contraception, but their role in preventing ovarian cancer has been widely proven. A meta-analysis involving more than 200,000 women showed that the use of OCs for more than 5 years can reduce the risk of ovarian cancer by about 50%, and this protective effect can last up to 30 years after discontinuation of the drug [6]. For BRCA1/2 mutation carriers, the use of OCs has also been shown to reduce the risk of ovarian cancer and does not increase the risk of breast cancer or increases the risk very little. Therefore, it is recommended by the NCCN guidelines as a chemoprevention option before RRSO [15]. Its preventive mechanism

may include inhibiting ovulation, reducing ovarian epithelial damage, regulating the hormonal environment, and enhancing immune surveillance. In addition to OCs, other potential chemopreventive drugs are also under investigation. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin have shown potential in the prevention of various cancers due to their anti-inflammatory and cyclooxygenase (COX) activity inhibition effects. Some epidemiological studies suggest that regular aspirin use may be associated with a reduced risk of ovarian cancer, but the results are not completely consistent, and its optimal dose, duration of use, and safety still need to be further clarified [3]. Vitamin D is also considered to be associated with ovarian cancer risk due to its wide range of biological activities, including regulating cell proliferation, differentiation, and apoptosis. Some studies have shown that higher serum 25-hydroxyvitamin D levels are associated with a reduced risk of ovarian cancer, but there is also a lack of sufficient prospective research and intervention trial evidence [7].

3.3 Primary Preventive Measures Targeting the Ovarian Cancer

cause Promoting a healthy lifestyle is an important part of primary prevention of ovarian cancer. Encouraging women to marry and have children at an appropriate age and prolonging breastfeeding time is not only beneficial to the health of mothers and babies, but also reduces the risk of ovarian cancer. For women who need contraception, the rational use of OCs under the guidance of a doctor can achieve the dual benefits of contraception and ovarian cancer prevention. In addition, maintaining a healthy weight, avoiding obesity, reducing high-fat diets, increasing the intake of fruits and vegetables, quitting smoking and limiting alcohol, and exercising appropriately may all reduce the risk of ovarian cancer through various mechanisms. Reducing the medical risks associated with ovarian cancer is also worthy of attention. For example, for patients who need hysterectomy due to benign diseases, on the premise of fully informed consent, simultaneous removal of bilateral fallopian tubes (with ovarian preservation), namely “opportunistic salpingectomy”, can be considered to potentially reduce the risk of future ovarian cancer [16]. This strategy has begun to be promoted in some countries and regions, and its

long-term effects are being observed [16]. Early intervention for ovarian cancer precursor lesions is an important direction for future prevention research. There is increasing evidence that high-grade serous ovarian cancer may originate from the epithelial cells of the fallopian tube fimbria [10], and endometriosis is a clear precursor lesion of endometrioid carcinoma and clear cell carcinoma [8]. Therefore, identifying and treating these precursor lesions (such as serous tubal intraepithelial carcinoma (STIC) and ectopic endometrial lesions) may fundamentally prevent the occurrence of ovarian cancer. This requires more accurate early diagnosis technology and effective intervention methods, and relevant research is currently being actively explored [8][10].

4. Brief Review of Other Research Advances in Ovarian Cancer Treatment

Although this article focuses on prevention, progress in the field of ovarian cancer treatment is equally important. In terms of surgical treatment, robot-assisted laparoscopic surgery has shown the advantages of less trauma and faster recovery in the treatment of early ovarian cancer, but its application in advanced tumor cell reduction surgery is still controversial. In terms of chemotherapy, the application of hyperthermic intraperitoneal chemotherapy (HIPEC) after satisfactory tumor cell reduction surgery, and the emergence of new chemotherapy drugs such as poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors, have significantly improved the prognosis of some patients. In particular, PARP inhibitors (such as olaparib and niraparib) have made breakthrough progress in the first-line maintenance treatment and post-recurrence treatment of patients with BRCA mutations or HRD-positive ovarian cancer, ushering in a new era of precise targeted treatment of ovarian cancer [14][16]. Immunotherapy, such as immune checkpoint inhibitors (PD-1/PD-L1 inhibitors) monotherapy or combination therapy, is also being explored in ovarian cancer. Some clinical trials have shown certain efficacy, but its response rate still needs to be improved. Finding effective biomarkers to screen the advantaged population is the key [12].

5. Conclusion and Outlook

The risk factors for ovarian cancer are complex and diverse, with genetics, hormonal

reproductive factors, and lifestyle all playing a role. Given the dismal prognosis of ovarian cancer, the importance of prevention is self-evident. Currently, identification and management of high-risk individuals (particularly RRSO), chemoprevention (such as the use of OCs), and promotion of healthy lifestyles have achieved some success. Future research will focus on more precise risk prediction models, novel chemopreventive drugs, effective early screening technologies, and interventions targeting precursor lesions, as our understanding of the etiology, molecular mechanisms, and prodromal lesions of ovarian cancer continues to deepen. Combined with advances in novel treatments, these approaches are expected to significantly reduce ovarian cancer morbidity and mortality and improve women's health and well-being. Strengthening public education and raising awareness of ovarian cancer risk factors and the importance of prevention are also crucial components of ovarian cancer prevention and treatment.

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