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REVIEW ARTICLE

A REVIEW ON OVARIAN CANCER

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ABSTRACT

A cancer that begins in the female organs that produce eggs (ovaries).Ovarian cancer often goes undetected until it has spread within the pelvis and stomach. At this late stage, ovarian cancer is more difficult to treat and can be fatal cancer that forms in tissues of the ovary (one of a pair of female reproductive glands in which the ova, or eggs, are formed). Most ovarian cancers are either ovarian epithelial cancers (cancer that begins in the cells on the surface of the ovary) or malignant germ cell tumor (cancer that begins in egg cells).Around two in ten women with advanced-stage ovarian cancer are effectively cured and survive at least 12 years after the treatment as per the research. Your response to cancer therapy and chances for a cure depend on the type and the staging of ovarian cancer at the time of diagnosis back pain - Many sufferers of ovarian cancer will experience excruciating back pain. If the tumour spreads in the abdomen or pelvis, it can irritate tissue in the lower back for all types of ovarian cancer taken together; about 75% of women with ovarian cancer live for at least one year after diagnosis. Around 46% of the women with ovarian cancer can live five years after diagnosis if the cancer is defected in earlier stages.

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INTRODUCTION

Ovarian cancer is the most lethal gynaecologic cancer worldwide, and the median age at diagnosis is around 63 years in most developed countries. It is more common in older than younger women. The incidence and death rates due to ovarian cancer are higher in developed than in developing countries. Nevertheless, the incidence rates and related deaths in Western Europe and Northern America have either declined or plateaued since the beginning of the 21st century. Incongruously, ovarian cancer incidence and the related mortality rate have increased in industrial and some developing countries, especially those that have witnessed economic transition. This could be due to westernized lifestyle, a significant decrease in the number of pregnancies, decreased family size and the reliance on milk formula to feed new babies instead of breastfeeding. The majority of ovarian cancers arise from the epithelium cells.Ovarian cancer is an asymptomatic disease; thus despite the development in screening technology, surgical procedures and chemotherapy, most ovarian cancer cases are only identified at advanced stages.[1]

MATERIALS AND METHODS

The current article has reviewed English literature for epidemiological, pathological and genetics related studies on ovarian cancer. The main aim of the present study is to explore, update and expand on the current risk factors and epidemiology of ovarian cancer. Following the definition of the main aim of the current study, we have used a set of keywords including ovarian cancer, aetiology of ovarian cancer, epidemiology, prevalence, incidence, morbidity, mortality and risk factor in the search for related articles. In order to evaluate risk factors for ovarian cancer, we looked at every factor separately and thoroughly in order to define factors with the strongest relationship, controversial factors and those that are weakly related. Additionally, duties such as searching for related articles, and collecting and summarizing the main outcomes were divided between authors equally. We first conducted a broad search in order to collect all available articles on ovarian cancer from 1970 to the end of 2022. In order to do so, we performed a deep internet search, using PubMed, Google Scholar, Scopus and Web of Science databases.

Later, we narrowed our search and included only full-text, English articles on ovarian cancer between 1990 and 2022. We considered well-designed clinical and epidemiological studies including prospective and retrospective cohorts, case control studies and other observational studies on ovarian cancer. Furthermore, we included high quality reviews, meta-analyses and systemic reviews. However, case reports, clinical and epidemiological studies with methodological errors and/or those with weak study design were not considered. Studies with vague and/or conflicting conclusions were also excluded. Opinions on this review's topic have been discussed deeply and shared with other experts and colleagues in the field of gynaecology oncology.[2]

The Aetiology of Ovarian Cancer: Ovarian cancer is a cancer of postmenopausal women, and it is rare in women below the age of 40 years. Thus, it is classically described as a disease of older women. The median age for women with ovarian cancer ranges from 60 to 65 years in most developed coun- tries. As life expectancy has increased in most countries worldwide, and because the incidence rate of ovarian cancer increases with age, more and more postmenopausal women will have ovarian cancer.Approximately 90% of ovarian cancers develop from ovarian surface epithelial cells. The aetiology and precursor lesions of epithelial cancers are multifactorial, partially because epithelial cancers tend to have a complex and heterogeneous histology that defies a simple biological explanation. Nevertheless, about 10–15% of ovarian cancer is due to genetics, including mutations in BRCA genes, hereditary nonpolyposis colon cancer or Lynch syndrome and Peutz-Jeghers syndrome. Furthermore, the initiation of the disease is influenced by specific reproductive variables as well as familial or personal characteristics. Ovarian cancer is a complex disease because it can develop at all ages and from different cell types in the ovary, including oocytes, granulose cells, theca interstitial cells, and the surface of epithelium. Thus, the classification of ovarian cancer is difficult, even if attention is confined to epithelial cancer.

The latest WHO classification lists five major histotypes of ovarian cancer: high-grade serous carcinoma, low-grade serous carcinoma, mucinous carcinoma, endometrioid carcinoma and clear cell carcinoma. Because these histotypes arise from different cells of origin, cell lineage-specific diagnostic immunohistochemical markers and histotype-specific oncogenic alterations are used to confirm the morphological diagnosis. Compared with tumours of other organs, ovarian neoplasms are composed of heterogeneous histologic types; not only epithelial tumours but also sex-cord stromal tumours and germ cell tumours develop. While the exact mechanism of ovarian cancer is still not yet elucidated, several theories have been proposed to describe disease development and aggression.[3]

The epidemiology of ovarian cancer: The incidence rate of the disease is lower than in other gynaecologic cancers; however, it is the most fatal of all gynaecologic cancers and accounts for more than two thirds of all deaths due to gynaecologic cancers, mainly because most cases are diagnosed at later stages. Worldwide, the prevalence of ovarian cancer varies markedly, being highest in Western Europe and Northern America, intermediate in Southern and Eastern Europe and South America and lowest in the Middle East and Asia. Generally, the differences between countries of highest and lowest prevalence of ovarian cancer can be explained by racial, reproductive, socioeconomic and cultural differences. The higher prevalence of ovarian cancer in developed compared with developing countries can be due to many factors. The first is the significant increase in life expectancy in developed countries. The second is the significant decrease in fertility rate (decreased family size) in comparison with some developing countries where large families still exist and women still have the motivation for a higher numbersof pregnancies. Further, women of developed countries are less prone to practise breastfeeding, which was found to be protective against ovarian cancer and its protective effect can last for almost 30 years after stopping. Thirdly, in developed countries, westernized lifestyle has a major impact on increasing most types of cancers including ovarian cancer. In addition, increased daily intake of fatty diet and dense caloric food, which is common in developed countries, is also connected to most types of cancers. The increased prevalence of being overweight and obesity in developed countries has a significant correlation with cancer incidence. In women with ovarian cancer, obesity is mostly related to a decrease in quality of life and the five-year survival rate.[3]

In developed countries, ovarian cancer incidenc varies across different racial and ethnic groups. African American women are 40% less prone to develop ovarian cancer compared to White American women. Part of these variations is due to the existence or the absence of BRCA1 and BRCA2 mutations, which is more prevalent in Ashkenazi Jews. Generally, BRCA1 mutations were significantly more common in White (2.9%) than Black (1.4%) cases and in Jewish (10.2%) vs. non-Jewish (2.0%) cases. In contrast, BRCA2 mutations were slightly more prevalent in Black women (2.6%) than their White counterparts (2.1%) and were more frequent in non-Jewish (2.3%) compared to Jewish women (1.1%). Factors such as number of children, cigarette smoking and dietary fat may also contribute to the racial differences. Furthermore, the results can be influenced by the methodology or type of epidemiological studies. While prospective cohort studies may under-evaluate the relationship between dietary fat and ovarian cancer, over-evaluation of this relationship is one of the major drawbacks in retrospective cohort and case control studies due to recall bias. Indeed, recall bias is always expected when risk factors (i.e. diet type) are assessed after cancer has been diagnosed.

In the USA, death rates due to ovarian cancer represent 4% of the total death rate due to women's cancers, whereas death due to breast cancer accounts for 15% of the total death due to women's cancers. The differences between races may expand to include significant differences in age at diagnosis, stage at diagnosis and survival rate. Black women are usually diagnosed at a later stage and their five-year survival rate is less (40.7% vs. 44.1%) than in White women. African American women had the worst survival rate compared to all other ethnic groups in the USA. Compared to White American women, African Americans have a 56% higher mortality rate [HR = 1.56 (95% CI: 1.01–2.39)], and Hispanics 41% higher [HR = 1.41 (0.98–2.04)], while Asian women have a survival rate that is 11% higher than that of White women [HR = 0.89 (0.61–1.31)].[4]

Established risk factors: Established risk factors are closely associated with disease incidence rate; thus it has classically been used to identify and to predict individuals and families at risk.

Because ovarian cancer is a multifaceted disease, the identification of an individual at high risk is based mainly on medical background, with family history being the most important risk factor. Risk factors for ovarian cancer include older age, genetics, family history, history of other cancers, nulliparity, late menopause, HRT, tobacco smoking and dietary fat.[5]

Genetics: Ovarian cancer is part of a phenotype of two distinct familial cancer syndromes. These are hereditary breast/ovarian syndrome and Lynch syndrome (or non-polyposis colorectal cancer). These mutations are associated with higher risk of ovarian cancer, representing 10% of epithelial ovarian cancer causes and tend to promote ovarian cancer development at a younger age. Although breast cancer mutations BRCA1 and BRCA2 are mostly observed among Ashkenazy Jews, previous studies have detected these mutations in different ethnicities as well. Compared with a lifetime risk of 2% for the general population, the average cumulative risks by age 70 for ovarian cancer among BRCA1 or BRCA2 mutations is 59% (95% CI: 43–76) and 16.5% (95% CI: 7.5–34) respectively, in line with what was reported later. Corresponding breast cancer lifetime risks were 72% for BRCA1 and 69% for BRCA2 carriers. These results have provided solid evidence that the risk of cancer in women with BRCA1/2 mutations increases with an increasing number of affected first and/or second-degree relatives, suggesting that genetic or other familial related factors modify cancer risks for BRCA1/2 mutation carriers. In patients diagnosed with ovarian cancer due to BRCA gene mutations, 84% of patients were reported to be BRCA1 carriers while the rest (16%) were BRCA2 carriersBRCA2gene carriers it reaches its lowest effect around this point. Not surprisingly, triple negative patients (oestrogen receptor–, progesterone receptor–, and human epidermal growth factor receptor 2–) are mostly associated with the BRCA1 mutation, in accordance with what was reported previously for women with breast and ovarian cancer.[6]

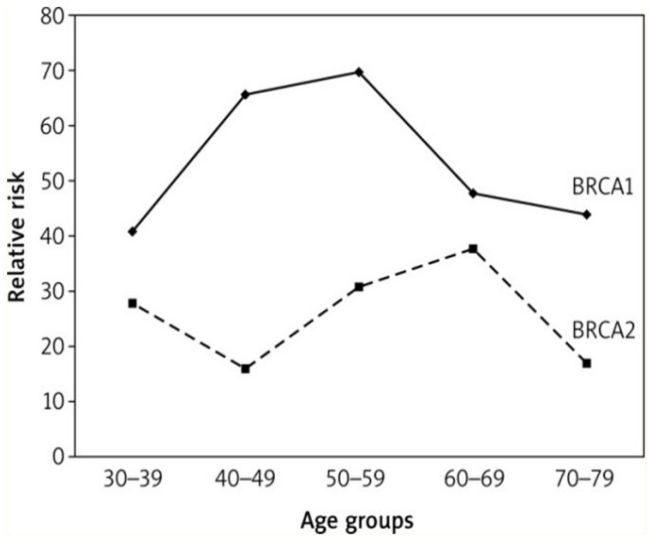

Fig.1. BRCA1 mutation carriers display a higher risk towards the development of ovarian cancer across all age groups

However, when a deleterious mutation exists (i.e. cancer), the number of mutant receptors increases and cells continue to grow and divide abnormally. At the cellular level, EGFR plays a key role in cancer development and metastasis, promoting tumorigenesis and survival.

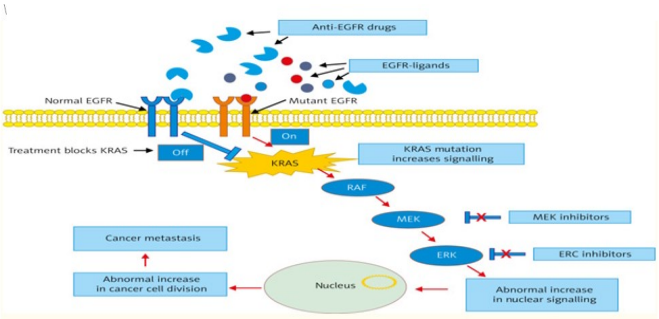

Fig.2. Pathwayanalysis demonstrating drug resistance in patients with KRAS mutation. KRAS mutation contributes to the resistance through constitutive activation of epidermal growth factor receptor (EGFR) downstream signalling cascades regardless of EGFR blockade. In normal EGFR, the use of anti-EGFR drugs blocks KRAS and stops cancer cells' division and metastasis, while in mutant EGFR, anti-EGFR drugs are not effective.[6]

Family history: Compared to families with no history of ovarian cancer, previous studies have reported a three- to four-fold higher rate of ovarian cancer among first-degree relatives diagnosed with the disease. This risk is, however, a lifetime risk; the familial risk may decline with the age at which the relative was affected and with the age of the woman at risk. Familial clustering of ovarian cancer with other cancers is most often attributable to a shared genetic basis of cancer and environmental factors. Mutations in BRCA1/2, which confer a significant risk for ovarian cancer, also predispose individuals to breast, prostate and other cancers. A previous study showed that the RR of ovarian cancer among sisters of women diagnosed with ovarian cancer before the age of 55 years was 5.2 in comparison with 3.6 for sisters of women diagnosed after the age of 55 years.[6]

Ovarian Cancer Treatment: Treatment for OC includes surgical removal of the tumor (cytoreductive surgery) and systemic chemotherapy. Since the mid-1970s, platinum compounds have formed the basis for chemotherapy. Initially, this was cisplatin, which, however, was associated with a range of adverse effects. Therefore, second-generation platinum compounds soon began to be developed, resulting in the 1989 introduction of carboplatin, which is just as effective as cisplatin but has fewer serious adverse effects, especially primarily in terms of nephrotoxicity. The addition of targeted therapies in the 2010s brought the possibility of a better safety profile, but even this therapy is not without serious adverse effects. PARP inhibitors, which have generally been found to be safe and well tolerated, are associated with a risk of serious hematological toxicities. Bevacizumab, another targeted drug, increases the risk of even fatal gastrointestinal perforation, and so patients that have a history of treatment for inflammatory bowel disease, or bowel resection, should be excluded from such therapy. In addition, hypertensive patients should be closely monitored.

According to established guidelines, cytoreductive surgery is followed by postoperative (adjuvant) chemotherapy with paclitaxel and carboplatin. Patients are usually administered six to eight cycles every 21 days. Contraindications for a combination of paclixatel and carboplatin are poor overall performance status (PS ≥ 3 according to WHO), significant comorbidities (heart failure, ischemic heart disease,

neuropathy, etc.), uncontrollable hypersensitivity to the medication, and high biological age. Pegylated liposomal doxorubicin (PLD) can be used as an alternative to paclitaxel, but it has demonstrated a higher incidence of hematological and dermatological toxicity and stomatitis. However, it causes less neurotoxicity and alopecia. In patients with poor performance status, comorbidities, and high age, it is to be expected that they will have difficulty enduring combined systemic treatment in full three-week doses and it is less likely that they will complete the course of therapy. In this case, a weekly form of combined therapy can be administered alternating paclitaxel and carboplatin, or monotherapy with carboplatin.In some cases, treatment begins with preoperative (neoadjuvant) chemotherapy followed by surgery. This method may be considered for patients with advanced ovarian cancer (stages III–IV), for whom the surgeon decides that radical removal is not possible, or if a patient is unable to undergo surgical treatment due to comorbidities. The purpose of preoperative therapy is to improve the patient's status or clinical response that would increase the likelihood of radical surgery. The same combination of drugs is applied in three to six cycles, after which interval surgery follows with maximum cytoreduction and three to four cycles of postoperative systemic therapy. A schematic diagram showing a treatment algorithm for advanced OC is shown in Figure 3.[7]

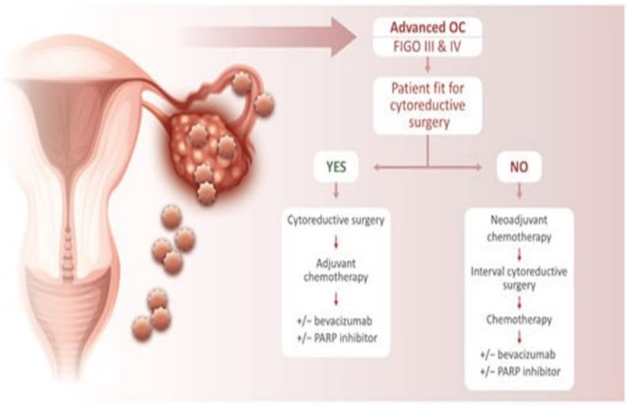

Figure 3. Treatment algorithm for advanced OC

Resistance to Treatment

Resistance to Platinum-Based Chemotherapy: The first-choice platin (Pt) used at present for clinically managing OC is carboplatin. It replaced cisplatin as a result of its superior safety profile. There are a greater number of studies on cisplatin due to its status as an older medicine, but cisplatin and carboplatin are considered to operate in a similar manner to create an antineoplastic effect. Consequently, the chemoresistance mechanisms may also be similar. Nonetheless, caution is advised because they have different chemical structures; this aspect is reflected in their differing pharmacokinetic parameters. Chemoresistance occurs in 20% to 30% of patients during primary treatment. The remainder of patients respond well to treatment, but in 80%, the median progression-free survival is only 18 months. When retreating patients that have relapsed after more than 12 months, only 50% respond to treatment. The percentage is even lower (10–20%) in patients that relapsed less than 6 months after initial treatment. With each new recurrence, the interval to the next recurrence tends to be shorter, and the likelihood of resistant disease tends to increase.

The problem of Pt resistance typically occurs in patients that receive neoadjuvant therapy with carboplatin before surgery. In their in vitro study, Matsuo *et al*. established a greater resistance to carboplatin in patients that received neoadjuvant therapy (33.3%) compared to patients that underwent primary cytoreductive surgery (9.2%). Similarly, Rauh-Hain *et al*. determined more frequent resistance to carboplatin in patients that received neoadjuvant therapy (88.8%) compared to patients that underwent primary cytoreductive surgery (55.3%). However, there is no consensus regarding a more suitable primary treatment. Some studies contest the superiority of primary cytoreductive surgery over neoadjuvant chemotherapy. The CHORUS randomized trialwhich included 550 patients, compared the results of both treatmentmethods. Among the patients, 276 underwent standard primary cytoreductive surgery, followed by adjuvant Pt-based chemotherapy, and 274 first received Pt-based neoadjuvant therapy, followed by interval cytoreduction. The second method has been connected with increased optimal debulking, reduced early mortality, and survival similar to that in standard treatment.[8]

Late menopause: The late age of natural menopause or the late-onset menopause begins by the age of 55 years and beyond. It is associated with a significant increase in the risk of ovarian cancer. However, the elevated risk is observed only among cases with endometrioid and clear cell tumours. Nevertheless, the total number of cycles during a woman's life is significantly associated with ovarian cancer risk. The age at the late onset of menopause carries intrinsic clinical and public health importance because the age at which natural menopause occurs may be a predictor of aging and health-related consequences (i.e. breast, ovarian and endometrial cancers).[9]

Radio therapy: The risk of ovarian cancer was found to be increased among women with breast cancer due to radiotherapy. This finding was supported by somebut not all the literature. Ionizing radiation can damage the cell membrane and cell constituents including the DNA molecule, leading to genomic instability and promoting cancer development. Thus, the risk of a second cancer due to radiation depends on the dose and period of radiation delivered to the normal ovaries. A low dose of radiation (e.g. mammography, computed tomography scan) causes an insignificant increase in DNA damage and or chromosome aberrations. Such damage may activate signalling pathways responsible on DNA repair. High radiation doses, used in treatment of certain cancer tumours, may cause irreversible damage in the DNA of healthy cells, and failure to repair such damage will initiate cancer development. Similarly, women with other types of cancers (e.g. breast cancer, lung cancer) may have increased risk of developing ovarian cancer due to unbearable doses during radiation therapy. Nevertheless, in women with BRCA1 and BRCA2 genes, there is still a great deal of controversy regarding the effects of low and high doses of radiation.[10]

Infertility: Infertility is the inability of a woman to conceive after one year or longer of unprotected sex, and the cause of this problem is divided equally between man and woman.
A previous study reported a 60% increase in the risk of ovarian cancer in a cohort of infertile women [standardized incidence ratio = 1.6 (95% CI: 0.8–2.9)], which is in line with later studies.It should be stated, however, that most studies in this field were unable to differentiate the underlying causes of infertility from the possible effects of fertility drugs.[11] [12]

CONCLUSION

Ovarian cancer is the sixth most common cancer and the fifth most common cause of gynaecologic cancer deaths in women of developed countries. Ovarian cancer is asymptomatic and is not easy to detect by physical or laboratory examination until late stages, and this leads to a significant decrease in survival rate. Established risk factors for ovarian cancer include older age, genetic mutations, family history of breast and ovarian cancer, individual history of breast or other cancers, nulliparity, HRT and dietary fat. Tobacco smoking is associated with a significant reduction in oestrogen level; thusit has a protective effect against female cancers except for mucinous tumours, where it is considered as a risk factor. The relationship between obesity and ovarian cancer is inconsistent, although some detected a slight positive association between obesity and ovarian cancer risk, while others found no relationship. The relationship between infertility, talc powder, radiotherapy and the risk of ovarian cancer is controversial. Neither fertility medications nor IVF is associated with ovarian cancer risk. However, the risk may increase when infertile women are exposed to extensive fertility medications/IVF for long periods and never get pregnant. Increasing women's awareness starts with education towards better understanding of the risk factors of ovarian cancer.

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