Ovarian carcinoma: An overview of current status

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Abstract: Ovarian carcinoma is one of the leading causes of morbidity and mortality associated with carcinomas affecting women. It comprises a heterogeneous group of neoplasms that represents the seventh most lethal malignancy in women worldwide, and is a major cause of death from gynecological carcinoma. Specific to different geographical locations all over the globe, there are variations in the magnitude and trends of ovarian carcinoma, and the scenario of the disease keeps changing. As such, it is necessary to update and review the existing study on ovarian carcinoma. Reviews on ovarian carcinoma from 2000 to 2015 were extracted from PubMed and Google Scholar, and a few selected landmark studies that incorporated old data were also included. The focus of the present study is to consolidate an updated global view on epithelial ovarian carcinoma, the most prevalent type of ovarian carcinoma. This article covers the epidemiology, types, diagnosis, prognosis, and treatment of epithelial ovarian carcinoma.

Keywords: ovarian carcinoma; epidemiology; diagnosis; prognosis; treatment


Introduction

Ovarian carcinoma comprises a heterogeneous group of neoplasms that represents the seventh most lethal malignancy affecting women worldwide (and eighteenth most common carcinoma overall) and is a major cause of gynecological carcinoma-related death in the western world. Previously, it has been suggested that the origin of most ovarian carcinomas is from the ovarian surface epithelium or postovulatory inclusion cysts formed after follicular rupture and repair ¹ ² . There are many hypotheses on the occurrence of ovarian carcinoma among women. According to the “incessant ovulation” hypothesis, a wound is created during every ovulation, which results in increased cell proliferation to repair the epithelial cells. This may result in the increased likelihood of DNA damage and carcinogenic mutation ³ ⁴ . In another hypothesis regarding gonadotropin-based stimulation, the incidence rate of ovarian carcinoma increases after menopause with increased levels of gonadotropin ⁵ ⁸ . According to the inflammation hypothesis, inflammation may be involved during the process of ovulation, which is associated significantly with ovarian carcinoma ⁹ . Meanwhile, the hormonal hypothesis proposes that the ovarian surface epithelium is stimulated by excess androgen and hence, increases the risk of ovarian carcinoma; however, progesterone stimulation has demonstrated protective effect and reduces the chances of carcinoma ⁶ .

Approximately 75% of women present with the disease are diagnosed in advanced stages ¹⁰ . On the basis of histology, ovarian carcinoma is classified into three main categories based on the ovarian tissues that cause carcinoma: epithelial ovarian tumor (which covers the ovary and its subtypes that include serous, mucinous, endometrioid, and clear cell), germ cell tumor (cells that become ova and its subtypes including dysgerminoma, immature teratoma, and yolk sac tumor), and sex cord-stromal cell tumor (which produces hormones with subtypes of malignant granulose cell tumor and Sertoli-Leydig cell tu-
The relative frequencies of the subtypes of ovarian carcinoma are shown in Figure 1. The maximum frequency (approximately 85%) of ovarian carcinoma is found within the epithelial cells. Serous tubal intraepithelial carcinoma is a relatively recent finding in understanding the development of ovarian carcinoma and it represents the precursor lesion in high-grade serous ovarian carcinoma.

**Figure 1.** Relative frequencies of ovarian carcinoma sub-types

The cause of ovarian carcinoma is unknown; however, a positive family history of breast and ovarian carcinoma is found to be the strongest risk factor based on epidemiologic studies. There are many factors that contribute to the poor prognosis of ovarian carcinoma patients such as localization within the peritoneal cavity, absence of early symptoms, difficulty in complete eradication by surgery, and chemotherapy resistance among patients, resulting in a five-year survival rate of 45%. Antibody therapy, immune checkpoint inhibitors, vaccine strategies, adoptive cell therapy, and combinatorial immunotherapy are all used for the treatment of the disease.

There are numerous review papers discussing ovarian carcinoma’s origin and its development, types and subtypes, diagnosis, prognosis, and treatment. As such, there is a need to review and update existing information on ovarian carcinoma. The focus of the present study is to consolidate the updated global view on epithelial ovarian carcinoma (EOC) as it is one of the most prominent gynecologic carcinomas. This review covers the epidemiology, diagnosis, prognosis, and treatment of epithelial ovarian carcinoma.

**Epidemiology**

The incidence of ovarian carcinoma is greater in high income countries compared to middle and low income countries. In 2012, approximately 239,000 cases were recorded, which account for nearly 4% of all new cases of carcinoma in women (2% overall). Around the world, the incidence rate of ovarian carcinoma is 11 per 100,000 in Central and Eastern Europe, 5 per 100,000 in Africa, 11.7 per 100,000 in the US, 5.2 per 100,000 in Brazil, and 4.1 per 100,000 in China. In Europe, approximately 65,697 new cases are estimated every year with 41,448 deaths. It has been reported by the US Center for Disease Control and Prevention that about 20,000 women are diagnosed with ovarian carcinoma every year and 14,500 die every year from the disease. In the past five decades, although the mortality rate for many solid tumors has decreased, the mortality rate for ovarian carcinoma remained static with an overall five-year survival rate of 44.2%. A woman’s lifetime risk of developing invasive ovarian carcinoma is 1 in 75, and the lifetime risk of dying from it is 1 in 102.

In Germany, approximately 9,600 women develop malignant ovarian tumors every year and 5,500 women died from ovarian carcinoma. Epithelial ovarian carcinoma (EOC) is responsible for the death of 14,030 out of 22,240 diagnosed cases in the US, and the cure rate of this disease was found to be less than 40% owing to the advanced stage of the disease at the time of diagnosis. The aforementioned data succinctly illustrate ovarian carcinoma as one of the most serious gynecologic malignancies, responsible for the highest number of fatalities. Different morphological subtypes of ovarian carcinoma possess different pathogenesis with distinct molecular alterations, different natural history, and prognosis.

In India, the ovarian cancer incidence (age-adjusted rate per 100,000) in different population-based cancer registries is reported to range from 1.7 to 15.2 for the year 2012 to 2014. An increasing trend of this cancer has been observed since 1982 to date. The projected number of cases for this cancer in India for 2015 and 2020 are 45,231 and 59,276, respectively.

**Risk factors**

Multiple factors are involved in the prevalence of ovarian carcinoma; among these factors, a positive family history of breast and ovarian carcinomas is one of the strongest risk factor proven by epidemiologic studies. Age and other environmental factors could also be associated with the risk of getting the disease. Nonetheless, there is no clear evidence to date on the association between industrial exposure of carcinogens or therapeutic radiations and ovarian carcinoma. In contrast, various reproductive factors, e.g. (multi) parity and oral contraceptive use, breast feeding, tubal ligation, and hysterectomy are involved in the decreased risk of ovarian carcinoma. Ovarian carcinoma appears to be part of the family’s phenotype of germ line mutations in
BRCA genes (BRCA1 and BRCA2) and it is responsible for 30% lifetime risk of developing ovarian carcinoma in women up to the age of 70 years old\textsuperscript{[41]}. A significant reduction in the occurrence of ovarian carcinoma owing to the use of oral contraceptives has been reported previously and this reduction is related to the alteration of the BRCA1 and BRCA2 genes. The overall benefits and harm of oral contraceptives depend on the duration of use and time\textsuperscript{[42,43]}. The gene expression profile involves genetic instability with the mutation of genes (PTEN, ARID1A, CTNNB1, KRAS, BRAF, ERBB2, TP53), over expression of genes (HNF-1 beta, HER2/neu, AKT, HLA-G, APO-E), or microsatellite instability that is associated with type I and type II ovarian tumors\textsuperscript{[18]}. Women being treated for infertility are highly prone to experiencing ovarian carcinoma due to the increased levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH)\textsuperscript{[44,45]}.

Types of epithelial ovarian carcinoma

The dualistic model categorizes EOC into two groups, designated as type I and type II\textsuperscript{[14,28]}. A better model of two broad categories, namely type I and type II of ovarian carcinogenesis, has provided the basis of new histopathological, molecular, and genetic studies\textsuperscript{[18]}. Type I tumors are slow-growing indolent neoplasms, and arise from a well-defined precursor, atypical hyperplasia. These tumors are confined to the ovary at the time of diagnosis and do not show TP53 mutations within a stable genome. However, in the case of type I tumor, somatic mutations are frequently found to be associated with certain genes\textsuperscript{[46]}. Type I tumor includes low-grade serous carcinoma, mucinous carcinoma, clear cell carcinoma, and endometrioid adenocarcinoma. Type II tumors are high-grade clinically with more aggressive neoplasms, genetically highly unstable, with a majority of them exhibiting TP53 mutations and diagnosed at an advanced stage. It has been reported in previous studies that type II tumors (which includes high-grade serous carcinoma) may originate from the epithelium of the fimbrial portion of the fallopian tube\textsuperscript{[47,50]} and/or the ovarian surface epithelium. The different types and subtypes of EOC are shown in Figure 2.

Type I tumor

Low-grade serous carcinoma. The classification of serous carcinoma as low-grade and high-grade has been adapted in United Kingdom\textsuperscript{[31]} and presently, many gynecological pathologists use this two-tiered grading system that was originally proposed by the MD Anderson Group (Houston, Texas, USA). Low-grade serous carcinoma is thought to arise in a well-defined adenoma-carcinoma sequence in a stepwise fashion, from a benign serous cystadenoma through a serous borderline tumor to an invasive low-grade serous carcinoma. In this type of tumor, there is no necrosis or multinucleation with moderate atypia, and less than or equal to 12 mitosis per 10 high power fields. Psammoma bodies are very common, with glands and papillae surrounded by clefts or non-epithelial lined space and intracytoplasmic mucin\textsuperscript{[52]}. Low-grade serous carcinoma is not associated with TP53 mutations; however, two-third of its cases are found to be associated with KRAS or BRAF mutation, which are found to be mutually exclusive\textsuperscript{[53]}.

Mucinous carcinoma. It is relatively uncommon, affecting patients from a wide range of age including occasionally children and adolescents\textsuperscript{[54,55]}. Smoking is found to be an important risk factor associated with benign, borderline, and mucinous carcinoma\textsuperscript{[56,57]}. The common features favoring metastasis in ovarian mucinous carcinoma include small and bilateral tumors, nodule pattern of ovarian involvement, destructive stromal invasion, single cell infiltration with signet ring cells, cells floating in mucin, extraovarian spread, and marked lymphovascular space invasion. Most of the ovarian mucinous carcinomas are of intestinal type; however, many of these contain goblet cells and even occasionally paneth or neuroendocrine cells. Similar to low-grade serous carcinoma, ovarian mucous carcinoma commonly exhibits KRAS mutations. However, unlike low-grade serous carcinoma, BRAF mutation is not a feature of ovarian mucous carcinoma\textsuperscript{[58]}.

Clear cell carcinoma. Clear cell carcinoma is mainly composed of cells with abundant clear cytoplasm and prominent cell membrane, existing approximately in equal frequency to endometrioid adenocarcinoma. Clear cell carcinoma is usually negative for estrogen receptor (ER), Wilms Tumor (WT1) and p53 genes (triple nega-
tive); however, it is usually negative or positive for the p16 gene. A majority of such carcinomas are endometrial in origin and are diagnosed at an early stage (stage I or II). Even though the prognosis of such carcinoma is relatively poor, the prognosis of a stage I disease is relatively good. Such neoplasms exhibit low proliferation index and they are resistant to the transitional chemotherapeutic agents used in the treatment of ovarian carcinoma[11]. Previously, no molecular events with regard to clear cell carcinoma were identified[59], but the ARID1A mutation has since been found to be involved in such cases[60].

Endometrioid adenocarcinoma. Endometrioid adenocarcinomas are low-grade tumors with a low staging (stage I); however, some of these tumors could potentially be high-grade and are usually unilateral, with 10% being bilateral. They usually arise from endometrial tissue implantation (especially an endometriosis cyst) or a pre-existing borderline adenofibroma[61,62]. In ovarian endometrioid carcinomas, mutations of the phosphatase and tensin homolog (PTEN), which are deleted from the chromosome 10 tumor suppressor, are found frequently[63]. Endometrioid adenocarcinoma of the ovary exhibits similar molecular events to that of uterine endometrioid adenocarcinoma, which include PTEN, β-catenin, KRAS, and PIK3CA mutations with microsatellite instability[64].

Type II tumor

High grade serous carcinoma. High-grade serous carcinoma is more common than low-grade serous carcinoma. This type of tumor is high-grade in nature from the start, evolving quickly, and is found frequently at the advanced stage. It has been previously reported in the literature that a number of high-grade ovarian serous carcinomas actually originate from the epithelium of the distal fimbrial portion of the fallopian tube[65-68]. Necrosis and multinucleate cells are found within high-grade serous carcinoma in moderate to marked nuclear atypia, with greater than 12 mitoses per 10 high power fields. In such cases, TP53 mutation or p53 dysfunction is often implicated, and it appears to occur during early neoplastic development[69-71]. The survival rate of patients who underwent chemotherapy is significantly better with low-grade neoplasms compared to those with high-grade tumors[72].

Screening and diagnosis

The diagnosis of ovarian carcinoma at an early stage is very difficult owing to the absence of specific symptoms in patients, which results in decreased survival rate among patients[20]. Imaging is an important parameter for evaluating the extent and location of the spread of ovarian carcinoma and assessing its appropriate management, as encouraged by the International Federation of Gynecologists and Obstetricians (FIGO) committee[73]. Ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI) are routinely used imaging tools[19,20,74,75]. In addition, physical examination and trans-vaginal ultrasonography are used for the diagnosis of tumor and the cause of ovarian cysts is confirmed by exploratory laparotomy[74]. The screening of ovarian carcinoma can be improved using a combination of Symptom Index (SI) with a serum HE4 test or CA125 test[76]. The risk of ovarian cancer algorithm (ROCA) is a statistical algorithm used for the screening of EOC by calculating the risk of having a change-point based on a woman’s age and CA125 profile[77].

Different stages and grades

The staging system for ovarian carcinoma, which has been formulated by the International Federation of Gynecologists and Obstetricians (FIGO), is surgically based after diagnosis on whether the carcinoma is limited to the ovary or has spread to other parts of the body. This staging system was revised in 2014 and different sub-stages of IC (i.e. IC1, IC2, and IC3), IIIA (i.e. IIIA1 and IIIA2), and IV (i.e. IVA and IVB) were introduced, with stage IIC removed from the previous system[79].

Prognosis

Microarray studies have been used for the analysis of gene expressions in carcinoma cells[79] and seven microarray studies have been conducted for the prognosis of gene profiles in ovarian carcinoma cells[80]. In a recent study, different factors found associated with the prognosis of EOC include patient’s age, performance status, tumor stage and ascites, tumor grade, histopathologic subtype, obesity, surgical de-bulking, expression of genes (CYP4B1, CEPT1, CHMP4A), and immunological factors[21].

Treatment

In most low-risk cases that are diagnosed in the early stage, surgery alone is able to cure the disease without adjuvant chemotherapy[81]. However, adjuvant chemotherapy is found to be effective in patients with a high-grade disease staging (FIGO IC)[82]. Presently, the adjuvant therapy is found to depend on the tumor’s stage and grade rather than its type[13]. However, some side effects may occur as a result of chemotherapy such as hair loss, mouth sores, hand and foot rashes, menopause,
infertility, nausea, as well as vomiting. Sometimes, chemotherapy may also result in damages to the bone marrow, which leads to increased chances of infection. Therefore, chemotherapy is ineffective in patients who present these side effects, and other alternative treatments are needed for these patients. The survival rate of 10%–30% has been observed in women with advanced ovarian carcinoma (stage III–IV) using surgical cytoreduction (total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node removal, and omentectomy), followed by platinum-based chemotherapy. In another study, it was concluded that bilateral oophorectomy at the time of hysterectomy resulted in increased risk of all-cause mortality, fatal and nonfatal coronary heart disease, and lung carcinoma. A study conducted on platinum-sensitive patients diagnosed with ovarian carcinoma to compare the efficacy of single (platinum alone) versus combination chemotherapies (platinum plus paclitaxel) concluded that patients administered with the combination therapy had a significantly higher survival rate compared to those who received single chemotherapy. A recent study reported that one weekly dose of paclitaxel is less toxic than three weekly doses.

The administration of cytotoxic drugs directly into the abdomen through intraperitoneal route increases the dose-intensity delivery to the residual tumor without any additional systemic toxicity. Most molecular targeted drug therapies have been developed with the aim of blocking the receptors, ligands, or pathways. A monoclonal antibody, bevacizumab, is found to be useful in the treatment of ovarian carcinoma by inhibiting the vascular endothelial growth factor (VEGFR). Nonetheless, bevacizumab is not a very effective treatment when used alone and hence, it is often used in combined chemotherapy in order to improve the outcome of ovarian cancer patients. Other anti-PD-L1 monoclonal antibodies such as BMS-936559, MPDL3280A, MEDI4736, and MSB0010718C have been developed to treat ovarian carcinoma by enhancing immune function, which results in the inhibition of ligand/receptor interaction. This inhibition further reduces the response of T-lymphocyte by inhibiting the kinases involved in T-lymphocyte activation via phosphatase activity and other signaling pathways.

The use of biomarkers has been encouraged for the selection of ovarian carcinoma cells, but the identification of such markers has been challenging. Currently, two markers have been identified, i.e., the mutation in BRCA gene, which is a marker for the deficiency of DNA repair through homologous recombination pathway; and folate receptor-α, which is overexpressed in this type of carcinoma. A new therapeutic concept for ovarian carcinoma involves optimal cytoreductive therapy, followed by molecular targeting therapy, intraperitoneal chemotherapy, and dose-dense chemotherapy. The investigation of immune checkpoints (the immune system being turned off by carcinoma cells) represents a potent therapy against ovarian carcinoma. Hormonal replacement therapy for carcinoma treatment has been reported by Lipkowitz and Kohn. Fertility Sparing Surgery (FSS) is another promising safe approach used to treat ovarian carcinoma. FSS therapy has been successfully used recently for the treatment of borderline ovarian tumors and early stage epithelial ovarian cancer. Although the use of FSS is very effective in preserving childbearing capacity, its application is controversial owing to the use of in vitro fertilization after surgery.

The use of BRAF inhibitors (veumafenib and dabrafenib) and MEK inhibitor (trametinib) offers a more hopeful option for ovarian carcinoma patients and these inhibitors are also used in rational pathway-targeted therapeutic combinations such as co-targeting PI3-kinase signaling, as well as dosing strategies to prevent or delay drug resistance and achieve long-term survival benefit. Poly(ADP-ribose) polymerase (PARP) inhibitors have been approved by the US Food and Drug Administration (FDA) as a monotherapy in patients previously treated with chemotherapy, and the inhibitors have also shown synergistic action with anti-angiogenic agents due to oxygenation changes. The use of these inhibitors has opened up a whole new treatment option for BRCA-deficient ovarian cancer patients in the US and Europe. The suppression of PTTG1 (pituitary tumor transforming gene) expression and the activation of p53 expression were shown by DNA-damaging drugs (doxorubicin and bleomycin), which induce cell cycle arrest to repair the damaged DNA. In addition, p53 also promotes programmed cell death by regulating cellular transcription. The first human trial of p53-targeting modified vaccinia Ankara (p53MVA) vaccine in patients with advanced refractory gastrointestinal cancers demonstrated enhanced T-cell recognition of p53 following vaccination. Anti-PD-1 immunotherapy drug nivolumab was found to be effective in a previous study conducted on patients of advanced platinum-resistant ovarian cancer.

Conclusion

Ovarian cancer is the most lethal malignancy in women, being the major cause of death with a high incidence rate to the extent of 15/100,000. The frequency of EOC is high among all types of ovarian cancer. EOC is divid-
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ed into two different types (i.e., Type I versus II) based on the risk factors involved, along with the stage and genes implicated during carcinogenesis. Ultrasound, CT, and MRI are the most commonly used techniques for the screening and diagnosis of ovarian cancer. Meanwhile, surgery, chemotherapy, or a combination of both is used for treatment purposes. Many newer therapies have also been introduced for the treatment of the disease. Currently, there is on-going research focusing on the development of new effective screening methods to detect the disease at an early stage.

**Author contributions**

SA and LS conceptualized the review and finalized the manuscript preparation. YL performed the literature search and drafted the manuscript.

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**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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