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**Epithelial ovarian cancer: An overview**

Desai A *et al.* Epithelial ovarian cancer: An overview

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**Abstract**

Ovarian cancer is the second most common gynecological cancer and the leading cause of death in the United States. In this article we review the diagnosis and current management of epithelial ovarian cancer which accounts for over 95 percent of the ovarian malignancies. We will present various theories about the potential origin of ovarian malignancies. We will discuss the genetic anomalies and syndromes that may cause ovarian cancers with emphasis on BRCA1/2 mutations. The pathology and pathogenesis of ovarian carcinoma will also be presented. Lastly, we provide a comprehensive overview of treatment strategies and staging of ovarian cancer, conclusions and future directions.

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**Key words:** Epithelial ovarian cancer; BRCA1; Chemotherapy

**Core tip:** Epithelial ovarian cancer (EOC) is one of the most common gynecological cancers. We present a number of theories on the origin of EOC including the recent hypothesis that the fallopian tube is the primary site of most serous carcinomas. We also discuss genetic anomalies that may cause ovarian cancer. The pathology of ovarian cancer by malignant transformation of the epithelium of the ovarian surface, peritoneum or fallopian tube is also presented. Finally we provide an overview of ovarian cancer treatment options, comparing various chemotherapy regimens and future predictive biomarkers and functional assays for targeted therapy for BRCA1 associated EOC.

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**INTRODUCTION**

Amongst gynecologic malignancies ovarian cancer is the second most common and the #1 cause of death[1]. In this article we review the diagnosis and current management of epithelial ovarian cancer which accounts for over 95 percent of the ovarian malignancies[2]. The clinical presentation of epithelial ovarian cancer can either be acute or subacute. Acute cases present with conditions such as pleural effusion, small bowel obstruction (SBO) and venous thromboembolism. Subacute cases may present with non specific symptoms such as abdominal fullness, bloating, an adnexal mass, vague pelvic or abdominal pain and gastrointestinal symptoms.

In the following review, we initially present various intriguing theories about the potential origin of ovarian malignancies. Subsequently, we discuss in depth genetic anomalies and syndromes that may cause ovarian cancers with emphasis on BRCA1/2 mutations (section II). Next, the pathology and pathogenesis of ovarian carcinoma is presented (Section III). Finally, we provide a comprehensive overview of treatment strategies and staging of ovarian cancer (Section IV), conclusions (Section V) and future directions (VI).

**ORIGIN**

The cellular origin of epithelial ovarian cancer is not well known thus hampering the development of effective early detection methods. Sir Spencer Wells in 1872 claimed that epithelial ovarian cancers arose from ovarian surface epithelial (OSE) cells[3]. This hypothesis is supported by Cheng’s work on HOX genes[4], which shows that ectopic expression of *HOXA9*, *HOXA10* and *HOXA11* genes in mouse ovarian surface epithelial cells (MOSEC) followed by intraperitoneal injection into mice resulted in the establishment of cancers of serous, endometrioid and mucinous subtypes, respectively. Inclusion cysts lined by OSE were considered as precursors for epithelial ovarian cancers in the past[4]. However the above theory has been refuted by a number of studies[5]. For example, a prospective study of 48230 postmenopausal women who had no family history of ovarian cancer but had annual pelvic ultrasounds was conducted in 2010. Investigators found that after a median follow-up of 6 years there was no increase in the development of epithelial ovarian cancer in women who had inclusion cysts in their initial study. Yet in another study[6] it has been proposed that ovarian cancers arise from secondary Mullerian tract structures as they are indistinguishable from adjacent mesothelial cells lining the peritoneum.

However, in the last 5-10 years, several studies have proposed that epithelial ovarian cancers should no longer be considered as a single disease entity. For example, high-grade serous ovarian cancers (HGSOC), which represent the most common type of invasive epithelial ovarian cancer, are exemplified by the ubiquitous presence of TP53 mutations[7]. In a detailed analysis of the fallopian tubes of patients who underwent prophylactic salpingo-oophorectomies, histologic studies showed that tubal lesions were present in almost 100% of cases of early serous cancers associated with familial *BRCA* mutations. This lends evidence to the hypothesis that fallopian tube cells may play an important role in the genesis of BRCA-associated HGSOC. Kindelberger *et al*[8] have proposed that cancer cells are shed from the tubal epithelium and implanted on the surface of the ovary and most likely become trapped within the surface inclusion cysts to produce ovarian or primary peritoneal carcinomas.

Recently Kurman *et al*[9] hypothesized that the fallopian tube is the primary site of most serous carcinomas. Evidence supporting this hypothesis includes: (1) more than 50% of sporadic pelvic high grade serous carcinomas have serous tubal intra-epithelial cancers (STIC), (2) STICs have also been found in 10%–15% of fallopian tubes prophylactically removed from women with BRCA mutations, (3) 92% of STICs have been shown to have *TP53* mutation similar to those found in concordant HGSC samples, (4) STIC oncogene productions such as cyclin E1, Rsf-1, and fatty acid synthase, are also overexpressed in HGSCs, and (5) STICs have been found to be present in prophylactic salpingectomy specimens in the absence of carcinoma which lends evidence against the view that STICs are formed due to metastasis from adjacent HGSCs.

**GENETIC ANOMALIES AND SYNDROMES**

Individuals from families with multiple cancers, cancers occurring at an early age, and two or more primary cancers in a single individual have a higher risk of hereditary ovarian cancer syndromes. A recent Cancer Genomic Atlas (TCGA) project analyses of mRNA expression, miRNA expression, promoter methylation, and DNA copy number in 489 high-grade serous ovarian adenocarcinomas (HGS-OvCa) revealed TP53 mutations in almost all tumors 965). Approximately 13% had germ line mutations in BRCA1 or BRCA2 and a small percentage had somatic mutations in NF1, RB1 and CDK12[10]. Analysis also showed four ovarian cancer transcriptional subtypes, three miRNA subtypes, four promoter methylation subtypes and signatures associated with survival 965). Furthermore pathway analyses showed defect in homologous recombination, Notch and FOXM1 signaling was involved in the pathophysiology of serous ovarian cancer[10].

The majority of hereditary ovarian cancers are associated with mutations in tumor suppressor genes, *BRCA1* and *BRCA2*. BRCA1 (Breast cancer type 1 susceptibility protein) encoded by BRCA1 gene (located on the long arm of chromosome 17) is a nuclear-cytoplasmic shuttling protein, and many cancer-associated mutations have altered subcellular localization of BRCA1 protein[11]. BRCA1 also plays a role in DNA repair by transcription regulation, chromatin remodeling, homologous recombination, and cell cycle regulation. *BRCA1* mutations function as either truncating or missense mutations interfering with critical regions of the gene such as the RING finger motif or BRCT region of the gene. BRCA2 (Breast cancer type 2 susceptibility protein) is encoded by *BRCA2* gene (located on long arm of chromosome 13), plays a crucial role in repair of double stranded DNA breaks. It has been observed that the risk of ovarian cancer is higher in women with BRCA1 mutation as compared to BRCA2 mutation[12,13]. The cumulative risk of ovarian cancer by age 70 is estimated to be 40%-50% for BRCA1 mutation-carriers and 10%-25% for BRCA2 mutation carriers[14]. Furthermore, BRCA1 mutations are also associated with earlier onset[12]. In one study, the average age at diagnosis of ovarian cancer in BRCA1 and BRCA2 mutation carriers was 52 and 62 years respectively[15].

BRCA associated cancer risks are determined by the mutation location and genetic variation of the BRCA1 and BRCA2 gene function. Mutations occurring within the central region of the BRCA2 gene, called the ovarian cancer cluster region, compared to mutations in the 5’ or 3’ region, may be associated with a significantly higher risk of ovarian cancer in women[16].

Research has also shown that the BRCA1 Associated Ring Domain 1 (BARD1) protein which binds to the BRCA1 protein stabilizes both proteins and targets the BRCA1 to sites where DNA strands are broken. Mutations in the *BARD1* gene may prevent the BARD1 protein from helping repair damaged DNA. Thus, BARD1 isoform expression is required for cancer cell proliferation, thereby making them cancer maintenance genes[17]. Studies also suggest that the BARD1 protein has other functions different from its partnership with the BRCA1 protein. The BARD1 protein interacts with another protein, p53 (which is produced from the *TP53* gene) to promote controlled cell death (apoptosis) and regulate cell division. Other potential functions of the BARD1 protein are under study.

Specific genetic modifiers of cancer penetrance, sometimes called modifier genes, may influence the expression of genes like BRCA1 or BRCA2. Genetic variation, particularly in the genes comprising endocrine signaling and DNA repair pathways, may modify BRCA-associated cancer risks. Another potential modifier gene in BRCA1 and BRCA2 mutation carriers is CYP1A1, which encodes an enzyme involved in the metabolism of polyaromatic hydrocarbons and in the hydroxylation of estradiol[18]. A particular allelic variant, found in 14 percent of carriers with cancer and 22 percent of unaffected carriers, reduced the risk of breast cancer by about 40 percent. Recently Qin *et al*[19] have shown that BRCA1 inhibits the growth of ovarian cancers by regulating Ubc9 binding. With the aid of live imaging of YFP, RFP-tagged BRCA1 and BRCA1a proteins they showed enhanced cytoplasmic localization of mutant BRCA1 proteins in certain types of ovarian cancer cells. The mutant BRCA1 proteins were found to be impaired in their capacity to inhibit growth of ES-2 ovarian cancer cells. Less commonly hereditary non polyposis colorectal cancer (HNPCC) which is caused by mutations in mismatch repair genes, MSH2, MLH1, MSH6, PMS1, and PMS2 is also associated with ovarian cancer[20]. Jones *et al*[21] analyzed 42 cases of ovarian clear cell carcinoma and found that 57% of these cases had mutations in ARID1A which suggests that aberrant chromatin remodeling contributes to the pathogenesis of ovarian clear cell carcinoma.

**PATHOLOGY**

Epithelial cancer of the ovary is thought to derive from malignant transformation of the epithelium of the ovarian surface, peritoneum, or fallopian tube. The exact molecular transformation events causing epithelial ovarian cancer are not known. Baylin and Herman[22] have shown that epigenetic phenomenon may also play a role. Mutations of the oncogenes HER2, C-myc, K-ras, Akt, and the tumor suppressor gene p53 have been observed[23-25]. The molecular pathways underlying cancer progression are also not well understood. Most research to date have shown that factors associated with reproduction and ovulation have the largest impact[26,27]. Some studies have shown that somatic mutations in BRCA1, BRCA2 and other genes can also lead to cancer progression.

Some of the theories for the pathogenesis of epithelial ovarian cancer include: (1) repeated ovulation with trauma[28,29], (2) increased estrogen concentrations as a result of excess gonadotropin secretion[30], (3) high androgen concentrations [30], and (4) stromal hyperactivity[31].

***Histopathology***

The classification of epithelial ovarian cancer is usually based on the origin of the tumor[32].

(1) About 75% of epithelial ovarian cancers are of the serous type. They simulate the lining of the fallopian tube. This histologic variant is often associated with concentric rings of calcification known as psammoma bodies. While there is no established grading scheme for serous ovarian cancer, recent work has suggested a two-tiered system -- low-grade and high-grade[33,34]. The work of Meinhold-Heerlein *et al*[35] has shown that low-grade serous carcinomas and serous tumors of low malignant potential involve similar genes and pathways that are distinct from high-grade serous carcinomas. These findings have led some to hypothesize that low-grade carcinomas represent the natural progression of an undetected serous ovarian tumor of low malignant potential.

(2) Mucinous tumors usually resemble intestinal or endocervical epithelium. Mucinous tumors are usually large with a median diameter of 18 to 20 cm and tend to remain confined to the ovaries[36]. Furthermore, primary ovarian mucinous tumors can be difficult to distinguish from metastatic mucinous tumors from the colon/rectum, appendix, cervix or pancreas.

(3) Endometrioid tumors are hypothesized to sometimes arise from the foci of endometriosis. They are associated with slightly better survival when compared to serous adenocarcinoma, regardless of disease stage[37].

(4) Clear cell carcinomas can also sometimes arise from endometriosis. They derive their name as their histologic features include “clear cells”. Prognosis is poor due to an increased risk of venous thromboembolism and decreased response to platinum-and-taxane based chemotherapy regimens[38].

(5) Brenner tumors, also known as transitional cell tumors because histologically, they resemble transitional epithelium of the bladder. Majority of Brenner tumors are benign. Histologically, there are nests of transitional-type epithelial cells with longitudinal nuclear grooves lying in abundant fibrous stroma.

**TREATMENT**

There are basically three forms of treatment of ovarian cancer: (1) Surgery, (2) Chemotherapy, and (3) Radiation (rarely used). Surgery is considered the mainstay of treatment for ovarian cancer. Treatment is mainly based on the histologic subtype and the stage at diagnosis, which is determined surgically by a tumor reductive procedure including hysterectomy, removal of ovaries, removal of the omentum, and any other sites of disease feasible to remove. The goal of surgery is to reduce the tumor burden to no visible disease, though an “optimal” status is assigned if no residual lesions are larger than 1 cm. However, other studies[39] designate the status of maximal cytoreduction for tumors less than 3 cm. The following table lists the different stages of epithelial ovarian cancer: stage I: Cancer is confined to one or both of the ovaries; stage II: Either one or both the ovaries are involved and the cancer has spread to uterus and/or fallopian tubes or other sites in the pelvis; stage III: Either one or both the ovaries are involved and the cancer has spread to lymph nodes and/or sites outside the pelvis but is still within the abdominal cavity; and stage IV: Either one or both the ovaries are involved with distant metastasis.

***Stages I and II***

For stage I epithelial cancers, surgery alone is adequate. Here surgery is used for both staging and therapeutic purposes. Surgery includes hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Samples of the under surface of the diaphragm, peritoneal washings, pelvic/para-aortic lymph node samples are also examined for completeness. In high-grade ovarian cancer, adjuvant chemotherapy has led to better overall survival rates. Large clinical trials such as EORTC-ACTION and MRC-ICON1 involved patients with stage I and II ovarian cancer who were randomly assigned to adjuvant chemotherapy or observation[40,41]. In EORTC-ACTION, at least 4 cycles of carboplatin/cisplatin based chemotherapy were administered whereas in MRC-ICON1 patients received 6 cycles of single agent carboplatin or cisplatin or platinum-based chemotherapy. Data from both studies showed significant improvement in recurrence-free-survival (RFS) and overall survival (5 year survival figures were 82% with chemotherapy and 74% with observation with a 95% confidence-interval in the difference of 2%-12%).

***Stages III and IV***

In the case of stage III and IV cancers, surgery includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and debulking of any grossly visible tumor. Cytoreduction is an independent prognostic variable for survival[39,42]. In patients with optimal cytoreduction the median survival was 39 mo as opposed to 17 mo if the surgery was suboptimal[43].

Treatment options for patients with optimally cytoreduced stage III disease include conventional intravenous and/or intraperitoneal (IP) chemotherapy. The use of IP cisplatin has shown better progression free survival (PFS) and overall survival[44]. One of the recent studies GOG-0172 showed a higher median survival rate of 66 mo for patients receiving chemotherapy *via* the IP route as opposed to 50 mo in patients who received intra-venous cisplatin and paclitaxel (*P* = 0.03)[44]. Another study concluded that IP cisplatin works better on small tumors (< 1 cm) that are platinum responsive[45].

Therapeutic strategies for patients with sub-optimally cytoreduced stage III and IV disease include intravenous and/or IP chemotherapy plus additional cytoreductive surgery in some circumstances. The benefits of cytoreductive surgery have not been well established in advanced disease states. While one study performed by the EORTC showed better survival rates in patients who had debulking surgery after 4 cycles of cyclophosphamide and cisplatin[46]. Another study, GOG-0162, in patients who received paclitaxel and cisplatin with interval cytoreductive surgery did not show any survival benefit[47]. GOG 182-ICON5[48] compared the effectiveness of various combination chemotherapy regimens as first line therapy for patients with stage III/IV epithelial ovarian cancer who have undergone either optimal or sub-optimal cytoreductive surgery. The study shows that combining either carboplatin or paclitaxel with one of the follow new cytotoxic agents-gemcitabine, poly-ethylene glycol (PEG) liposomal doxorubicin and topotecan gave favorable results.

A combination of carboplatin and a taxane (paclitaxel or docetaxel) is the standard chemotherapeutic agent for ovarian cancer with clinical response rates > 60% and median time to recurrence usually > 1 year. The combination of carboplatin and paclitaxel regimen is the standard worldwide and is sometimes used as induction chemotherapy, if patients are poor surgical candidates, or the surgeon feels that the primary surgery is not likely to be optimal. The SCOTROC trial[49] compared the use of either docetaxel or paclitaxel in combination with carboplatin as first line chemotherapy and found similar progression free survival in both cases therefore offering an alternative to paclitaxel.

Recently there have been a number of studies investigating the role of bevacizumab in first-line therapy for ovarian cancer following surgical cytoreduction. Bevacizumab is a humanized-monoclonal antibody against vascular endothelial growth factor (angiogenesis inhibitor). Two trials GOG-0218 and ICON7 have shown improvement in PFS when bevacizumab was added to initial chemotherapy and continued every three weeks for 16 and 12 additional cycles respectively[50,51]. However, overall survival has not been demonstrated, and therefore has not been adopted outside of recurrent disease or the clinical trial setting.

Eskander *et al*[52] have recently proposed a new strategy for combining maximal cytoreductive surgery with intra-operative hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of advanced stage epithelial ovarian cancer resulting in promising oncologic outcomes. Currently phase III clinical trials are ongoing to test the efficacy of combining cytoreductive surgery with HIPEC.

***Recurrent or persistent ovarian epithelial cancer***

Recurrent cancer has a wide range of presentations. Patients may present with abdominal distention or pain or symptoms related to sites where the cancer cells have spread to. The most common follow-up procedures include bimanual pelvic examination, serial measurement of CA125, laparotomy and repeating imaging studies. Platinum sensitive cancers (recurrence more than 6 mo since completion of primary therapy) are usually retreated with a combination of carboplatin and a taxane. The OCEANS trial[53] was conducted to test the efficacy and safety of bevacizumab with gemcitanine and carboplatin (GC) compared with GC alone (*i.e.*, bevacizumab replaced by a placebo) in platinum sensitive recurrent ovarian cancers. Results show a significant improvement in progression free survival when bevacizumab was used in combination with GC. Platinum resistant disease can be treated with one of several agents that typically provide response rates in the range of 10%-20%. These include bevacizumab, topotecan, gemcitabine, liposomal doxorubicin, and others. The AURELIA trial[54] was one of the first randomized phase III trials to demonstrate the benefit of combining bevacizumab with standard chemotherapy regimen resulting in increased progression free survival (6.7 mo *vs* 3.4 mo) in patients with platinum resistant ovarian cancer.

The NOVEL trial[55] proposed the idea of a “dose-dense” therapy for treating primary ovarian cancer. It is based on the hypothesis that a shortening of the time interval between the administrations of cytotoxic agents is able to achieve better cell kill. They compared the standard 3-weekly paclitaxel and carboplatin combination *vs* dose-dense weekly paclitaxel and 3-weekly carboplatin for advanced epithelial ovarian cancer and found that the progression free survival was significantly better in the former (28 mo *vs* 17.2 mo).

**CONCLUSION**

Among gynecologic malignancies ovarian cancer is the most lethal. The cellular origin of epithelial ovarian cancer is not well known. Early theories hypothesized that epithelial ovarian cancer arises from ovarian surface epithelial cells, while more recent ones have proposed that it should no longer be considered as a single disease entity but rather a diverse group of tumors with specific morphologic and genetic characteristics.

Histological differences in the ovarian cancers define a number of subtypes of epithelial ovarian cancer. Subtypes are named based on the tissue that they closely resemble and include serous, mucinous, endometrioid, clear cell, and transitional cell. Ovarian cancer is also classified as benign, borderline or malignant depending on the degree of epithelial proliferation and stromal invasion.

Treatment of epithelial ovarian cancer is based on the combination of surgery and chemotherapy. Over the past three decades, optimal surgical cytoreduction, followed by platinum-based chemotherapy has become the standard treatment for advanced ovarian cancer.

**FUTURE DIRECTIONS**

A recent NIH study discovered genomic similarities between basal-like subtype of breast cancer (triple negative breast cancer) and serous ovarian cancer[56]. Computational analyses show that both these cancers are susceptible to agents inhibiting blood vessel growth and chemotherapeutic drugs targeting DNA repair. However, more work is needed in this direction to determine how these findings may be used functionally and clinically.

Another area that has received attention recently is the impact of oxidative stress and *BRCA1* mutations in ovarian cancer. Oxidative stress induces DNA damage (as evidenced by increased 8-hydroxydeoxyguanosine or 8OHDG) correlates with poor outcomes in ovarian cancer[57]. Martinez-outschoorn*et al*[58] found that UWB1.289 cells, which contain mutant BRCA1, produce large amounts of hydrogen peroxide leading to oxidative stress and catabolic processes in adjacent stromal fibroblasts *via* stromal NF-κB activation. Catabolism in stromal fibroblasts was also accompanied by the up regulation of MCT4 and decreased Cav-1 expression which signify tumor microenvironment. Furthermore, the study also showed the effect of UWB1.289 could be negated by using the antioxidant N-acetyl-cysteine or by *BRCA1* gene replacement. This suggests that new trials are needed for cancer prevention using antioxidants in hereditary *BRCA1* mutations.

Another recent breakthrough in the treatment of recurrent ovarian cancer is in the use of vaccines derived from lysate-pulsed dendritic cells. Kandalaft *et al*[59] reported a study encompassing dendritic cell based autologous whole tumor vaccination and anti-angiogenesis therapy. They took the tumor lysate from patients with recurrent ovarian cancer. The patients were initially treated with intravenous bevacizumab and oral metronomic cyclophosphamide. This was followed by bevacizumab and the vaccination of dendritic cells with autologous tumor lysate, lymphodepletion and administration of a large number of vaccine primed T-cells. The study found that cellular immunotherapy may be used for treatment of recurrent ovarian cancer. However the study included only six subjects and the therapy was found to work for four of them. Thus more work is required in this direction to ascertain the benefits of such vaccines.

Some studies such as those by Bryant *et al*[60] and Farmer *et al*[61] have shown that BRCA-deficient cells are especially sensitive to chemical inhibitors of poly (ADP-ribose) polymerase (PARP), which plays a critical role in single stranded DNA break repair. The most studied PARP inhibitor Olaparib has shown good results[62] in initial studies in *BRCA1* mutated and sporadic ovarian cancer but further studies are needed.

There are a no clear indications for ovarian cancer screening. Testing is recommended for women at high risk such as those with a significant family history, but consultation with a genetic counselor is recommended to discuss limitations and alternatives to genetic testing. Potential screening tests include the blood test for CA-125 marker and transvaginal ultrasound. However these tests are neither sensitive nor specific for ovarian cancer. They may be abnormal in benign conditions such as endometriosis, menstruation, pregnancy, and cancers of fallopian tube, breast or the GI tract. Early results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) showed that combining annual CA-125 tests with ultrasound imaging was useful for detecting ovarian cancers at an earlier stage[63]. The full results of the trial are expected in 2015. Lastly the key to developing targeted therapies for EOC will depend on understanding the biological pathways and targets involved in the development of these cancers. Our results (unpublished work) suggest Ubc9 to be expressed at elevated levels in several ovarian cancers and BRCA1-mutant SEOC cells[19]. We have developed BRCA1 function-based cellular assays (Patent number US 8372580) where loss of Ubc9 binding by BRCA1 mutants can not only predict the risk for developing Triple Negative Breast Cancers and EOC, but it may lead to the development of targeted therapies for these cancers.

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