Ovarian cancer is the most lethal gynecologic cancer. Early-stage diagnosis is difficult, and chemotherapy treatments often are not durable. Despite challenges, progress has been made since the 1990s; healthcare professionals now have an increased understanding of the disease biology and can identify hereditary ovarian cancer and provide screening recommendations. The recognized importance of complete staging, cytoreductive surgery, and new effective treatments has made an improvement in five-year survival.

At a Glance
- Ovarian cancer is the most lethal gynecologic cancer.
- Most patients with ovarian cancer are diagnosed at advanced stages of disease.
- Improvements in staging, cytoreductive surgery, and adjuvant therapies have improved five-year survival.

Pathophysiology

The primary method of ovarian cancer metastasis is by the exfoliation of cells that implant along the surfaces of the peritoneal cavity; lymphatic and hematogenous dissemination also occurs but is less common. The exact molecular events that trigger the development of ovarian cancer have not been determined; however, epithelial ovarian cancer develops because of the malignant transformation of the epithelium on the surface of the ovary. The origin of ovarian cancer centers on reproduction and ovulation. Two general hypotheses of ovarian cancer pathogenesis are the incessant ovulation theory and the excess gonadotropin secretion theory. Incessant ovulation theory postulates that the risk of ovarian cancer is directly related to the number of ovulatory cycles and the repetitive trauma and repair ovulation causes (Fathalla, 1971). The excess gonadotropin secretion theory proposes that excess secretion of gonadotropin promotes high estrogen concentration, which may lead to epithelial proliferation and possible malignant transformation (Cramer & Welch, 1983).

Risk Factors

Genetics, hormones, reproduction, and lifestyle have been implicated as risk factors for ovarian cancer. Most ovarian cancer is not attributed to a specific cause. The most significant risk factor, hereditary ovarian cancer syndrome, increases the possibility of developing ovarian cancer by 25%–50% (Daly & Obrams, 1998). Women have a 4%–5% increased risk if a single family member was diagnosed with ovarian cancer, whereas those with two or more family members have a 7% increased risk (Daly & Obrams). Other hereditary syndromes are site-specific ovarian cancer, breast-ovarian cancer, and the family...
cancer syndrome (i.e., Lynch syndrome II) (see Figure 2). Breast-ovarian cancer syndrome causes almost 90% of hereditary ovarian cancers and usually is associated with mutations in BRCA1 or BRCA2 genes (Boyd & Rubin, 1997; Piver, 2002).

Hormonal risk factors include nulliparity, infertility, early (i.e., before age 12) menarche, late menopause (i.e., after age 50), and endometriosis. Environmental and lifestyle risk factors are diet (although no definite association between specific foods has been identified) and obesity. Perineal talc exposure also is a risk factor, which most likely resulted from the asbestos contamination of talcum powder (Wong, Hempling, Piver, Natarajan, & Mettlin, 1999). No definitive reason has been given for why Western industrialized countries have a higher incidence rate (Whittemore, Harris, & Itnyre, 1992).

Prevention

Risk factors must be defined more clearly to counsel women about risk reduction and prevention. Currently, women who have hereditary syndromes or a family history of ovarian cancer may take preventive action by using oral contraceptives or undergoing risk-reducing surgery (Martin & Cherry, 2006). Oral contraceptives decrease a woman’s risk of developing ovarian cancer by 30%–60% after as little as three to six months (Daly & Obrams, 1998). Parity, breast-feeding, tubal ligation, and oophorectomy also have been identified as risk-reducing factors (Whittemore, 1994). The general population is advised to receive an annual rectovaginal pelvic examination; however, screening tests sensitive and specific enough to detect ovarian cancer do not yet exist. For high-risk women, a CA-125 blood test and transvaginal ultrasound may be recommended. CA-125 is a glycoprotein found in blood serum, which is most reliable when used to track the status of the disease. The CA-125 blood test is less effective as a screening tool because it detects only 50% of stage I cancers (Bast et al., 1998). Another method is a transvaginal ultrasound, which affords a better image of the ovaries than abdominal ultrasound. Proteomic screening is one of the more sensitive and specific screening tests expected to be used for ovarian cancer detection in the future. Proteomics documents the consequences of the genetic change, including protein mutation, rearrangement, loss, amplification, or silencing of genes (Boyce & Kohn, 2005). Clinical trials currently under way will provide the needed validation and standardization of proteomic testing (Ozols, 2002). Current recommendations for women with hereditary cancer syndromes are a pedigree analysis, transvaginal ultrasound, and CA-125 blood test every 6–12 months from age 25–35. High-risk women are advised to receive an oopherectomy after childbearing or no later than age 35 (Rebbeck et al., 2002). Healthcare professionals should consider age, reproductive plans, and the extent of the risk identified when providing preventive suggestions to high-risk women.

Diagnosis and Presentation

Ovarian cancer symptoms exist but often are ignored. Indicators most frequently reported are lower abdominal discomfort or pain, dyspepsia, early satiety, abdominal distention or bloating, a change in bowel habits, urinary frequency or incontinence, weight loss, and vaginal bleeding (Igoe, 1997). In a large, retrospective study of more than 1,700 women with ovarian cancer, only 5% reported having no symptoms of the disease prior to diagnosis. More than 70% of women reported having symptoms for three or more months (Goff, Mandel, Muntz, & Melancon, 2000).

An ovarian mass found while conducting a physical examination should be investigated in menopausal and postmenopausal women.

Hereditary Breast Ovarian Syndrome

- Most common
- Three family members with early-onset (i.e., < 60 years of age) breast or ovarian cancer with at least one family member with ovarian cancer

Site-Specific Ovarian Cancer

- Three of more family members with ovarian cancer at any age and no relatives with breast cancer diagnosed younger than age 50

Hereditary Nonpolypsisis Cancer C

- Three or more first-degree relatives with colon or endometrial cancer with at least two individuals diagnosed with colon cancer at the age of 50 or younger

Figure 1. Cellular Classification


Figure 2. Hereditary Syndromes in Ovarian Cancer

Note. Based on information from Piver, 2002.
women. For premenopausal women, investigation is dependent on the size of the mass. Most masses are 4 cm or less and do not indicate a malignancy; however, a mass 10 cm or more is suspicious (Curtin, 1994). A transvaginal ultrasound, CA-125 blood test, chest x-ray, and computed tomography scan may be ordered as part of the diagnostic workup (Eriksson & Frazier, 2000).

**Treatment**

**Surgery**

Surgery is the primary approach to diagnosis and treatment, but it should be performed by a gynecologic oncologist who will strive to achieve an optimal debulking, leaving no tumor greater than 1 cm (Eisenkop, Friedman, & Wang, 1998). The surgical procedure includes a vertical midline abdominal incision approach with an abdominal hysterectomy, bilateral salpingo-oophorectomy, scraping of the under surfaces of the diaphragm, omentectomy and peritoneal cytology, multiple peritoneal biopsies, pelvic and para-aortic lymph node sampling, and multiple random biopsies. Optimal debulking surgery can improve patients’ responses to chemotherapy and relieve their symptoms. The International Federation of Gynecology and Obstetrics surgical staging and American Joint Committee on Cancer staging classifications are presented in Table 1. Worldwide presentation of ovarian cancer by stage follows 23%-33% stage I, 9%-13% stage II, 46%-47% stage III, and 12%-16% stage IV (Heintz et al., 2001; International Federation of Gynecology and Obstetrics, 2003). In some patients, complete surgical staging is not possible. For those patients, subsequent debulking surgery may be necessary after chemotherapy (National Comprehensive Cancer Network [NCCN], 2007).

Major prognostic factors for ovarian cancer are age, stage, performance status, histologic tumor type, and histologic grade. Tumor stage is the most important prognostic variable (Karlan, Markman, & Eifel, 2005). Patients with stage I disease with well- or moderately well-differentiated tumors have a five-year survival rate greater than 90%. Rates decline with stage; patients with stage III have a 35% five-year survival rate, and patients with stage IV have less than a 10% survival rate (Karlan et al.). In addition, clear cell, mucinous, and poorly differentiated tumor types have poorer prognoses than other tumor types (Karlan et al.).

**Early-Stage Disease**

Chemotherapy is recommended for all stages of ovarian cancer, with the exception of certain stage I patients. Patients with stages I and II ovarian cancer are designated as favorable and low risk or unfavorable and high risk following surgery (see Figure 3). Low-risk patients are differentiated from high-risk patients because they have a 90% five-year survival rate and therefore do not require further treatment (Young, 2003). High-risk patients have a 25%-40% recurrence rate and must receive chemotherapy following surgery (Vergote et al., 2001). Chemotherapy regimens studied most extensively in early-stage patients are cyclophosphamide and cisplatin, chromic phosphate therapy (32P), and paclitaxel and carboplatin (NCCN, 2007). A 10-year follow-up of the intraperitoneal 32P versus combination chemotherapy revealed a 35% relapse when using 32P as opposed to 28% when using chemotherapy (Young et al., 2005). Platinum-based regimens are the preferred adjuvant for high-risk patients with early-stage ovarian cancer because chemotherapy has a lower cumulative recurrence rate and 32P has more complications (Young et al.). Platinum-based adjuvant therapy can reduce the risk of relapse for high-risk patients, resulting in a disease-free interval for

---

**Table 1. Gynecologic Cancer Staging**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Growth limited to the ovaries</td>
</tr>
<tr>
<td>IA</td>
<td>Growth limited to one ovary, no ascites; no tumor on the external surface, capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>Growth limited to both ovaries, no ascites; no tumor on the external surface, capsule intact</td>
</tr>
<tr>
<td>IC*</td>
<td>Tumor stage IA or IB but with tumor on the surface of one or both ovaries, with capsule ruptured, with ascites present containing malignant cells, or with positive peritoneal washings</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension or metastases to the uterus or tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extention to other pelvic tissues</td>
</tr>
<tr>
<td>IIC*</td>
<td>Tumor either stage IIA or IIB with tumor on the surface of one or both ovaries, with capsules ruptured, with ascites present containing malignant cells, or with positive peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes, superficial liver metastases equal stage III, tumor limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum</td>
</tr>
<tr>
<td>IIAA</td>
<td>Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces</td>
</tr>
<tr>
<td>IIBB</td>
<td>Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm diameter; nodes negative</td>
</tr>
<tr>
<td>IICC</td>
<td>Abdominal implants greater than 2 cm in diameter, or positive retroperitoneal or inguinal nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal lover metastases equals stage IV</td>
</tr>
</tbody>
</table>

*To assess the impact prognosis of the different criteria for allotting cases to stage IC or IIC, it would be of value to know whether the source of malignant cells was (i) peritoneal washings or (ii) ascites, and whether rupture of the capsule was spontaneous or caused by the surgeon.*

approximately 80% (Young). Trimbos et al. (2003) published an analysis of two parallel, randomized clinical trials that enrolled patients with early-stage ovarian cancer. Patients were randomly assigned to receive platinum-based adjuvant chemotherapy or observation until chemotherapy was indicated. Overall survival improved by 8% for patients who received immediate chemotherapy, indicating that platinum-based chemotherapy improved overall and recurrence-free survival. The Gynecologic Oncology Group (GOG) recently compared three cycles of the recommended standard chemotherapy regimen (i.e., paclitaxel and carboplatin) to six cycles. No difference in overall survival has been reported; however, patients receiving the three-cycle regimen had a statistically insignificant higher relapse rate. Standard therapy remains three cycles of carboplatin (area under the curve = 6–7.5) and paclitaxel (175 mg/m²) (Bell et al., 2003).

A subsequent GOG trial is comparing three cycles of paclitaxel and carboplatin to three cycles followed by weekly low-dose paclitaxel (40 mg/m²) (National Library of Medicine, 2007). The purpose of the study is to determine whether low-dose paclitaxel has antiangiogenic properties; markers of angiogenesis are being collected as part of the study. Women with early-stage disease need further treatment to improve outcomes, and clinical trials must continue to better define which women need the therapy and the best regimen.

**Advanced Disease**

Advanced disease (i.e., stages III and IV) requires combination chemotherapy following surgical staging because ovarian cancer is sensitive to chemotherapy. In the 1990s, the combination of paclitaxel and cisplatin was found to have an improved and complete response rate and an increase in progression-free and overall survival (McGuire et al., 1996; Piccart et al., 2000). Later, carboplatin was introduced as a replacement for cisplatin because of its ease of outpatient administration and better side-effect profile. A randomized GOG clinical trial demonstrated that carboplatin and paclitaxel, when directly compared to cisplatin and paclitaxel, showed no difference in progression-free or overall survival and was less toxic (Ozols et al., 2003). Clinical trials continue to study paclitaxel and platinum therapy in various combinations and comparisons. GOG 132 was a three-part trial that compared high-dose cisplatin versus cisplatin and paclitaxel as well as cisplatin and paclitaxel versus high-dose paclitaxel. The study found no difference in median survival; however, the platinum-containing regimens had a superior response rate and progression-free survival (Muggia et al., 2000). The International Collaborative Ovarian Neoplasm (ICON) group provided additional insight into the treatment of ovarian cancer by conducting large-scale clinical trials. The ICON (1998) group compared carboplatin to the combination of cyclophosphamide, doxorubicin, and cisplatin (CAP). No significant difference in survival between the two groups was found, although CAP was more toxic. In 2002, the ICON group compared single-agent carboplatin, carboplatin and paclitaxel, and CAP. Overall survival was similar, leading the authors to conclude that single-agent carboplatin and CAP were as effective as paclitaxel and carboplatin. The ICON group (2002) study was limited by design; women with all stages of disease were included, the extent of primary surgery was not defined or restricted, and the data were not audited by an independent data-monitoring committee.

Another taxane agent, docetaxel, also has been studied in ovarian cancer. Phase II trials have indicated that docetaxel has a level of efficacy similar to paclitaxel; docetaxel also showed clinical activity in patients who were resistant to paclitaxel (Vasey et al., 2004). Toxicity profiles for docetaxel and neurotoxicity were different; patients taking docetaxel had less neurotoxicity, arthralgias, myalgias, and extremity weakness than those receiving carboplatin but more vomiting, diarrhea, neutropenia, and hypersensitive reactions.

The clinical trial results thus far have supported the use of a taxane-platinum compound for primary therapy in ovarian cancer. In the United States, guidelines from NCCN (2007) support the use of paclitaxel and carboplatin for six cycles of first-line therapy in advanced disease. The National Institute for Health and Clinical Excellence guidelines in the United Kingdom support the use of a paclitaxel-platinum compound or carboplatin therapy for advanced ovarian cancer treatment (Ozols, 2004). Almost 80% of previously untreated patients with advanced disease achieved a clinical complete response after platinum and taxane chemotherapy; however, 50%–70% ultimately relapsed (Karlan et al., 2005). The most recent and largest clinical study was GOG 182, a five-arm treatment schema that compared standard carboplatin and paclitaxel with the same regimen in sequential doublets or triplets, adding gemcitabine, topotecan, or liposomal doxorubicin. The study was closed in 2004 because accrual and events met planned interim analysis stopping points; results were reported in 2006. For the regimens evaluated, no evidence existed showing prolonged progression-free or overall survival when a third active cytotoxic agent was added (Bookman, 2006). The addition of a third agent did increase toxicities, but they were manageable (Bookman, 2006). Researchers concluded that carboplatin remains a standard of care for ovarian cancer.

Ovarian cancer has a long history of clinical trials using intraperitoneal chemotherapy because the disease is contained mostly in the peritoneal cavity even in its advanced stages. Clinical trials for optimally debulked disease combining intravenous
and intraperitoneal platinum and paclitaxel are described in “Evidence-Based Research for Intraperitoneal Chemotherapy in Epithelial Ovarian Cancer” on pp. 211–216.

**Maintenance and Consolidation Therapy**

Maintenance therapy must be considered in the treatment of patients with ovarian cancer. The disease, despite very high overall and complete response rates, has a relapse rate of 50%–75% (Karlan et al., 2005). Once relapse occurs, the disease is no longer curable; therefore, consolidation and maintenance therapy is heavily emphasized. A variety of agents, cytotoxic and hormonal, as well as radiation (i.e., intraperitoneal 32P or external beam) have been studied, but little or no improvement has been reported in overall survival in clinical trials (Karlan et al.). A GOG and Southwest Oncology Group trial followed 277 women who were assigned to either 3 or 12 cycles of continued paclitaxel after the completion of standard therapy. The study was closed early because progression-free survival favored the additional 12 cycles (Markman et al., 2003). The overall survival rate is difficult to assess because patients receiving three cycles of additional treatment were able to continue for 12 cycles after the study closed. At present, the clinical benefit of maintenance therapy is unknown. Extending treatment is associated with significant toxicities and is not recommended as a standard of care, but additional cycles are a focus of clinical trial investigation. Clinical trials also have shown improvements in progression-free or overall survival in studies of dose-dense therapy with platinum compounds or other consolidation therapy (Karlan et al.).

**Second-Look Surgery**

Second-look laparotomy is defined as surgical reexploration of women without symptoms or documentation of disease at the end of standard chemotherapy treatment. Controversy surrounds the surgical procedure, which is intended to detect residual disease in patients who have a negative computed tomography scan with a normal CA-125 blood test (Karlan et al., 2005). Although second-look surgery provides prognostic information, it does not improve outcomes, which was demonstrated in a GOG trial. More than 800 women received standard platinum therapy as well as paclitaxel and were asked to choose whether they wanted to undergo a second-look procedure after primary therapy. Women with a negative second look were followed without further treatment; those with positive results underwent tumor debulking and received additional therapy. Progression-free survival and overall survival were the same for second-look and non-second-look surgery groups (Greer et al., 2005). Second-look surgery currently is recommended only in the context of a clinical trial.

**Recurrent Disease Treatment**

Although primary treatment of ovarian cancer has progressed, most patients relapse; second-line treatment can be beneficial but is not curative. A CA-125 blood test is a sensitive indicator of disease relapse, often preceding clinical findings, which presents challenges because clinicians and patients closely monitor glycoprotein levels in CA-125 blood tests. Patient anxiety and clinical dilemmas occur when levels are elevated without clinical evidence of disease. Prior patient response treatment influences the decision to start therapy. Patients with recurrent disease are considered to be either sensitive or resistant to primary platinum therapy. Sensitive patients have had a disease-free interval of more than six months and high probability of responding again to platinum-based treatment at the time of relapse. Resistant patients have progressed during platinum-based therapy, achieved stable disease as the best response prior to platinum therapy, or relapsed less than six months after completion of prior platinum therapy. Resistant patients generally do not respond to second-line platinum-based therapy and require other treatment agents (Karlan et al., 2005).

Second-line therapy for platinum-sensitive patients consisted of a single agent, carboplatin, until studies showed that a paclitaxel-platinum compound is superior. One study assigned patients to platinum-based monotherapy or platinum with paclitaxel. The results demonstrated an absolute two-year survival benefit of 7% and a five-month improvement in median survival with paclitaxel and platinum therapy (Parmar et al., 2003). Progression-free survival also favored paclitaxel-based therapy, with a 10% improvement in one-year progression-free survival and a three-month prolongation in median progression-free survival. Gonzalez-Martin et al. (2005) concluded that paclitaxel and carboplatin were tolerable and had a higher response rate than carboplatin monotherapy in platinum-sensitive recurrent ovarian cancer. Another study found that carboplatin and gemcitabine have a higher response rate, with a longer median progression-free survival than carboplatin (Pfisterer, Vergote, Du Bois, & Eisenhauer, 2005). Gonzalez-Martin et al. and Pfisterer et al. presented evidence that combination therapy is superior to single-agent therapy; the choice of which combination to use is based primarily on toxicity. Paclitaxel and carboplatin toxicity is primarily related to peripheral neuropathy as opposed to the hematologic toxicities associated with gemcitabine and carboplatin.

Platinum-resistant patients receive a new agent, which is most often single-agent therapy. Many active drugs may be considered, such as docetaxel, oral etoposide, liposomal doxorubicin, topotecan, gemcitabine, vinorelbine, tamoxifen, 5-fluorouracil plus leucovorin, hexamethylmelamine, melphalan, irinotecan, and ifosfamide (NCCN, 2007). Clinicians should assess treatments and subsequent toxicities. Patients who most likely will benefit from additional chemotherapy, single-agent or combination, include those with small-volume disease, good performance status, a long treatment-free interval, serous histology, and a low number of disease sites. Other factors to take into account are patients’ prior response to therapy, toxicity of prior treatment, toxicity profile, quality of life, comorbid illness, extent of disease, cost of therapy, and goals and preferences. Typically, healthcare professionals treat patients for two or three cycles, evaluate the response and toxicity, and make a decision about additional treatment based on results and patient symptoms.

**Conclusion**

Future ovarian cancer research will focus on developing better diagnostic methods and using earlier screening with more sensitive and specific markers. GOG’s recent five-arm chemotherapy
trial may provide direction for the use of doublets and triplets with newer agents in therapy (Bookman, 2006). New treatment targets, including antiangiogenic agents, monoclonal antibodies, hormonal agents, and small molecules that target key components in signal transduction pathways associated with cell growth, tumor vascularity, and invasive potential, are being investigated and should be incorporated into future clinical trials (Bookman, 2005). Molecular and targeted therapies are being tested in current clinical trials, combining chemotherapy with concurrent and extended antivascular endothelial growth factor therapy (National Library of Medicine, n.d.).

Caring for patients with ovarian cancer is challenging; patients often present at an advanced stage, have to receive repetitive cycles of aggressive treatment with little respite, and are shown dismal survival statistics. Despite difficulties, progress in the treatment of ovarian cancer continues to be made.

Author Contact: Virginia R. Martin, RN, MSN, AOCN®, can be reached at vr_martin@fccc.edu, with copy to editor at CJONEditor@ons.org.

References


Bookman, M.A. (2006). GOG0182-ICON5: 5-arm phase III randomized trial of paclitaxel (P) and carboplatin (C) vs combinations with gemcitabine (G), PEG-liposomal doxorubicin (D), or topotecan (T) in patients (pts) with advanced-stage epithelial ovarian (EOC) or primary peritoneal (PPC) carcinoma [Abstract 5002]. Journal of Clinical Oncology, 24(18, Suppl.), 256s.


Young, R.C. (2003). Early-stage ovarian cancer: To treat or not to treat. *Journal of the National Cancer Institute*, 95, 94–95.


**Receive continuing nursing education credit for reading this article and taking a brief quiz. See the Continuing Nursing Education in this issue for more information.**