

**2010 State of the State  
of Gynecologic Cancers**

*Eighth Annual Report to the Women of America*



**Gynecologic  
Cancer  
Foundation**



HONORING THE PAST  
CELEBRATING THE PRESENT  
EMBRACING THE FUTURE

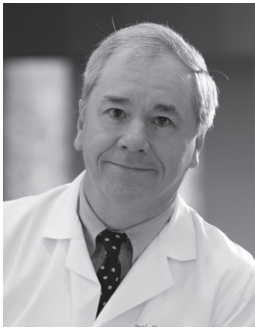
*Celebrating its 20th Anniversary in 2011*

The Gynecologic Cancer Foundation was established by the Society of Gynecologic Oncologists in 1991 as a 501(c)(3) not-for profit organization whose mission is to ensure public awareness of gynecologic cancer prevention, early detection and optimal treatment. In addition, the Foundation supports research and training related to gynecologic cancers. GCF advances this mission by increasing public and private funds that aid in the development and implementation of programs to meet these goals.

To learn more about the Foundation and gynecologic cancers, visit GCF's Women's Cancer Network at [www.wcn.org](http://www.wcn.org).

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## A Letter to the Women of America

The Gynecologic Cancer Foundation (GCF) is pleased to publish the eighth edition of *The State of the State of Gynecologic Cancers: A Report to the Women of America*. Like the seven editions that preceded it, the report provides information about each of the major reproductive cancers and the advances that have been made during the past year. In addition, this year's report focuses on clinical trials and their importance to the advances in the care of women with gynecologic cancers.

Throughout 2010, GCF is undertaking a variety of approaches to increase knowledge about clinical trials with the hope that more women will enroll. This report is the cornerstone of that effort.

It is our hope that the report will provide women who are undergoing treatment with information that will help them talk with their treatment team about clinical trial options if appropriate. We also hope that policy makers will appreciate the importance of continued funding for clinical research as a result of the information presented here.

And last, we salute the thousands of women who have participated in clinical trials and dedicate the *2010 State of the State of Gynecologic Cancer: Eighth Report to the Women of America* to them with the deepest appreciation.

Sincerely,

David M. Gershenson, MD  
Chairman  
Gynecologic Cancer Foundation



# The Value of Clinical Trials

## *A Message from Dr. Philip DiSai, Chair, Gynecologic Oncology Group*

Clinical trials have been undertaken by both industry and individual researchers with the objective to develop novel therapeutic agents and at times to obtain FDA approval for their general use. Publicly funded clinical trials have also played a key role in advancing the science of caring for patients with cancer, particularly by addressing questions that are vital to patient care but which may not be a top priority of industry. An example of such a trial is a comparison of effectiveness and toxicity of different treatment options that are already approved for clinical use. The National

Cancer Institute (NCI) supports a large network of clinical trials through several mechanisms. The largest component of the NCI network is the Clinical Trials Cooperative Group Program, which consists of ten Cooperative Groups that involve more than 3,000 institutions and 14,000 investigators that collectively enroll more than 25,000 patients onto clinical trials each year.

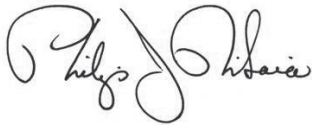
One of the ten Cooperative Groups is the Gynecologic Oncology Group (GOG), which has been active since 1970 and enrolls three to four thousand patients each year in Phase I, Phase II, and large Phase III trials. The GOG is a unique organization with seventy primary research sites and two hundred affiliated sites in the United States and several foreign countries. The GOG is truly a multi-disciplinary organization, composed of surgeons, medical oncologists and radiation oncologists, who all share a focused interest in gynecologic cancer. Over the past forty years the research conducted by GOG has played a key role in defining the nature of the malignant processes affecting women with cancer, the best methods of staging these cancers, and in defining the current standards of care for treatment of women with gynecologic cancers.

The Gynecologic Oncology Group has achieved many advances in the last four decades that have resulted in a change in the standard of care for treating gynecologic cancer. A series of clinical trials conducted by the GOG, beginning with Protocol 33, defined the spread pattern of endometrial cancer and led to a radical change in the surgical approach. This eventually resulted in revision of the staging system which forms the basis of all treatment for women with this disease. Results from three separate, Phase III GOG protocols established the value of chemotherapy combined with radiation in the treatment of cervical cancer. All three studies compared the effect of radiation therapy given with low-dose chemotherapy versus the effect of radiation therapy alone in the treatment of women with advanced stage cervical cancer and concluded that combined treatment was superior, which has led to this becoming standard of care for cervical cancer therapy worldwide. An analysis by the GOG of several trials in women with ovarian cancer confirmed the value of aggressive cyto-reductive surgery in combination with chemotherapy to increasing survival. Results of two GOG Phase III clinical trials in ovarian cancer are considered so significant that these trials, GOG-0111 and GOG-0158 were recently nominated to be included in the ImpACT Project list of the most important randomized controlled trials performed in the fields of medicine and public health since 1948. Both GOG-0111 and GOG-0158 confirmed the value of multi-agent chemotherapy that includes paclitaxel for ovarian carcinoma and established this treatment as the new standard of care for women with this disease. Also for the treatment of ovarian cancer, the GOG completed three randomized clinical trials comparing intraperitoneal chemotherapy with standard intravenous chemotherapy that demonstrated the superiority of intraperitoneal therapy regimens. Less toxic intraperitoneal drugs are currently being studied to optimize this approach. This year, at the 2010 American Society of Clinical Oncology Annual Meeting, the GOG reported the results of an international Phase III trial in which the addition of a novel targeted therapy, bevacizumab, to initial

chemotherapy treatment with carboplatin and paclitaxel demonstrated superiority as measured by improved progression-free survival for women when the bevacizumab was given as maintenance therapy following chemotherapy for a total of fifteen months. The effect of this new treatment on overall survival for women with ovarian cancer will be analyzed at a later date.

In summary, the efforts of the Gynecologic Oncology Group have been highly successful in demonstrating the value of clinical trials. The thousands of women with gynecologic cancer who have participated in GOG trials have been a key factor in our ability to conduct studies that have advanced the standard of care in gynecologic malignancies. We look forward to working with the National Cancer Institute, our investigators, research institutions, and our patients to continue to conduct clinical trials that will improve treatment for women affected by gynecologic cancer.

Sincerely,

A handwritten signature in black ink, reading "Philip J. DiSaia". The signature is written in a cursive, flowing style with a large initial "P".

Philip J. DiSaia, MD  
The Dorothy Marsh Chair in Reproductive Biology  
Professor, Department of Obstetrics and Gynecology  
Director, Division of Gynecologic Oncology  
Chair of Gynecologic Oncology Group



## “Hope Springs Eternal”

*By Kathleen Appollo, RN, BSN, OCN, Clinical Research Nurse, Memorial Sloan Kettering Cancer Center, New York*

“Hope springs eternal,” a proverb penned by Alexander Pope, was no more a characteristic of people in 1733 than it is today. Hope, and its resulting optimism, is necessary for leading a purposeful and fulfilling life. It encourages one to think that life will be improved in some way, especially when faced with a great adversity. Hope is a powerful tool in the fight against cancer. For the woman battling a gynecologic cancer, hope is generated by a treatment plan to eradicate the disease.

Participation in a clinical trial may be a method to increase and bolster hope in several important ways: 1) a clinical trial frequently offers a treatment which is thought to be as good as or possibly better than the standard treatment; 2) it may offer a new drug with potential superior action, which could not otherwise be obtained; and 3) it may offer a treatment plan for one who has exhausted all standard treatment options.

When a woman is considering participation in a clinical trial, detailed information and education about the trial are paramount to ensure her understanding and willingness to participate. Initially, a detailed patient history and baseline tests are obtained to be certain that strict eligibility requirements are followed. Next, she needs to know the details of the treatment plan including the schedule of interventions or drug administration, and tests that are required during the trial and follow-up period. She also needs to be aware of potential side effects of the treatment, especially of those which may impact her quality of life.

Fears about safety may be alleviated by knowledge that care is delivered under very high standards with rigid guidelines requiring frequent evaluations of treatment outcome and side effects. Extensive instructions are outlined for withholding medication or for dose changes based on side effects. These changes allow for the treatment to be personalized, since each participant will experience individual reactions.

Women participating in a clinical trial often develop a deep bond with the treating team because they are intensely monitored by the same staff members over the course of the trial. During a particularly stressful time in their lives, these bonds offer a great support to complete the trial and manage the side effects.

Participation in a clinical trial may be a good option for a woman who is seeking exposure to the latest treatment options with access to a high level of care. It also may provide her with an increased sense of hope, a potent weapon in the arsenal of her cancer care.



## Conversance in the Language of Clinical Trials

*By Mary Scroggins, Patient Advocate and Writer, Chair, GOG Patient Advocate Committee, and President and Co-founder of In My Sisters Care*

In 1996, as a woman newly diagnosed with Stage 1A ovarian cancer, I was distraught after learning that little research was underway on my rare cell type — clear cell. Although I didn't know much about clinical trials, I knew just enough to believe that my long-term survival might hinge on trial participation and outcomes.

Fourteen years later, I am even more invested in the clinical trial process and in educating cancer survivors on what trials are and are not, and on how to access them. Mostly, I simply want every survivor to know that a trial *might* be an important option and thus to have the opportunity to participate. Every survivor will not participate in a trial (only about 3% of those eligible currently do), but every survivor should be knowledgeable enough about trials to have a productive two-way conversation when her physician brings up the subject and to initiate the conversation when appropriate if her physician does not.

Participation in a trial, which is always voluntary, *might* benefit the individual participant — although that is not a trial's primary purpose — but it *will* help to add to our body of knowledge and thus move us closer to preventive strategies, new therapies and even perhaps a cure. However, even the most well designed trial with the most promising potential to benefit patients will yield nothing usable or useful unless patients are “invited” and willing to enroll in it.

So, I start from the premise that patients and researchers are equal partners in the clinical trial enterprise, with patients at the center of all research. Trials are not treatments per se, but well-designed trials answering important questions are precursors to the development of new therapies, and to improved survival and quality of life. I'd call those compelling reasons to become conversant in the language and the culture of clinical trials. I strive to be more fluent.

# Commonly Asked Questions

## What are gynecologic cancers?

Gynecologic cancers are the uncontrolled growth and spread of abnormal cells originating in the female reproductive organs, including the cervix, ovaries, uterus, fallopian tubes, vagina and vulva.

## What causes gynecologic cancers?

There are many factors that cause gynecologic cancers. Medical research has discovered that some classes of genes, called oncogenes and tumor suppressor genes, promote the growth of cancer. The abnormal function of these genes can be acquired (e.g., through smoking, aging, environmental influences) or inherited. Almost all cervical cancers and some cancers of the vagina and vulva are caused by a virus known as HPV, or Human Papillomavirus.

## Can gynecologic cancers be prevented?

Screening and self-examinations conducted regularly can result in the detection of certain types of gynecologic cancers in their earlier stages, when treatment is more likely to be successful and a complete cure is a possibility. Diet, exercise and lifestyle choices play a significant role in the prevention of cancer. Additionally, knowledge of family history can increase the chance of prevention or early diagnosis by determining if someone may have a gene which makes them susceptible to cancer.

## Who should treat gynecologic cancers?

Gynecologic cancers should be treated by a specialist with advanced training and demonstrated competence, such as a gynecologic oncologist.

A gynecologic oncologist is a board-certified obstetrician/gynecologist who has an additional three to four years of specialized training in treating gynecologic cancers from an American Board of Obstetrics and Gynecology-approved fellowship program. This subspecialty program provides training in the biology and pathology of gynecologic cancers, as well as in all forms of treatment for these diseases, including surgery, radiation, chemotherapy and experimental treatments.

## How are gynecologic cancers treated?

Gynecologic cancers are treated by using one or more of the following: surgery, radiation therapy and/or chemotherapy. The choice of therapy(s) depends on the type and stage of the cancer.

## Who is at risk?

Every woman is at risk for developing a gynecologic cancer. It is estimated that there will be about 83,000 new cases diagnosed and approximately 28,000 deaths from gynecologic cancers in the United States during 2010.<sup>1</sup>

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<sup>1</sup> American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

# Cervical Cancer

## State of Cervical Cancer

*Cervical cancer is a cancer that begins in the cervix, the part of the uterus or womb that opens to the vagina. It is the part of the uterus that dilates and opens fully to allow a baby to pass into the birth canal. The normal cervix has two main types of cells: squamous cells that protect the outside of the cervix and glandular cells that are mostly inside the cervix which make the fluid and mucus commonly seen during ovulation. Cervical cancer is caused by abnormal changes in either of these cell types in the cervix, and is the only gynecologic cancer that can be prevented by regular screening and appropriate vaccination. Since nearly all cervical cancers are caused by persistent infection with the Human Papillomavirus (HPV), vaccinating women and young girls before they become sexually active (currently recommended at 11 and 12 years of age) leads to the greatest prevention of pre-cancer and cancer. Early vaccination along with regular Pap tests and HPV testing when recommended is now the best way to prevent cervical cancer. Cervical cancer usually affects women between the ages of 30 and 55.*

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**Symptoms:** Bleeding after intercourse, excessive discharge and abnormal bleeding between periods. Most women will have no symptoms and will be alerted by an abnormal Pap test.

**Risk Factors:** Infection with high-risk HPV has been shown to cause virtually all cervical cancers. However, HPV is very common and most women with HPV will never get any significant cervical disease. Other risk factors include smoking; weakened immunity due to HIV infection or taking medicines for chronic diseases, such as lupus, or following an organ transplant; and becoming sexually active at a young age. Failure to get regular gynecologic examinations with Pap testing takes away the opportunity for early diagnosis through cervical cancer screening. A recent study shows that even for women with HIV, thought to be at high risk for cervical cancer, appropriate screening with Pap tests may eliminate the increased risk.

**Screening/Prevention:** Over the last 50 years, routine use of the Pap test to screen for cervical cancer has reduced deaths from the disease by 74%. A Pap test is a standard way healthcare providers can check to see if there are any changes in the cervical cells that might cause concern. The Pap test involves looking at a sample of cells from the cervix under a microscope to see if there are any that are abnormal. It is a good test for finding not only cancer, but also finding cells that might become cancerous in the future.

Usually, healthcare providers perform the Pap test as part of a routine pelvic exam. It is important for women to know if a Pap test was performed because it is possible to have a pelvic exam without a Pap test. It is also important that women know and understand their Pap test results and follow through with any recommendations made by their healthcare provider. Some abnormal Pap tests will be followed by colposcopy (examination of the cervix using a magnifying device to see the cervix more clearly) and biopsy of any abnormal appearing areas on the cervix. Any pre-cancerous areas can then be seen and treated as recommended by the healthcare provider.

Current cervical cancer screening guidelines support the use of HPV testing at certain times in combination with Pap testing. In non-adolescent women, HPV testing is done automatically when a Pap test is diagnosed as ASC-US (atypical squamous cells of undetermined significance). If high-risk HPV is present in these cells, then a pre-cancerous abnormality is more likely and colposcopy will be recommended. In women over 30, HPV testing with a Pap test can determine who is not at risk of having pre-cancer of the cervix. A negative HPV test with a negative Pap test can allow Pap screening to occur in three years. Active research

is underway to evaluate the role of HPV testing and HPV type-specific testing in primary cervical cancer screening. As described below, the role of HPV testing may be expanded in the future.

Major educational efforts are being directed toward the appropriate approach to cervical cancer screening in adolescent girls (less than 21 years of age). Sexually active girls and young women frequently have HPV infections and will even have abnormal Pap tests. Many of these young women will have spontaneous resolution of their infections and abnormal Pap test without the need for their gynecologists to intervene. In December 2009, the American College of Obstetricians and Gynecologists published revised guidelines recommending cervical cancer screening before age 21 should be avoided because it could lead to unnecessary and potentially harmful overtreatment in a group of women at very low risk for developing cervical cancer.

One of the most significant advances in the fight against cervical cancer is the development of HPV vaccines. In June 2006, one of these vaccines was approved by the FDA for use in 9-26 year old women and girls. In large clinical trials, the vaccine was found to be very effective in protecting women from developing pre-cancerous lesions of the cervix, vulva and vagina. A second vaccine was approved by the FDA in October 2009. Early vaccination with regular screening, which includes a Pap test and HPV test when recommended according to standard guidelines, is now the most effective way to prevent cervical cancer.

*Incidence:* It is estimated that there will be about 12,200 new cases of invasive cervical cancer diagnosed and approximately 4,210 deaths in the United States during 2010.<sup>2</sup>

## Advances in Cervical Cancer

The most active area of research and advances in cervical cancer remains the continued development of HPV vaccines. Increasing knowledge of ways to prevent HPV infection and increase access to care are key to continuing advances in cervical cancer. Critical to the rapid progress made in recent years in cervical cancer prevention has been the detailed understanding that HPV is the cause of nearly every cervical cancer and pre-cancer.

Over 40 types of HPV have been identified in vaginal, vulvar and cervical diseases. Of these, approximately 15-18 are known to be cancer-causing types. Two types in particular, HPV 16 and 18, are the most common HPV types associated with cervical cancer. HPV 16 causes nearly 60 percent of all cervical cancers and HPV 18 causes an additional 10 to 20 percent. HPV types 16 and 18 are the most important HPV types to include in a vaccine designed to prevent the development of cervical cancer. Both of the existing HPV vaccines protect against infection with HPV types 16 and 18.

The results of several large clinical trials demonstrate the effectiveness of vaccines to prevent HPV infection and HPV related disease. When widespread vaccination has been achieved, cervical cancer should be reduced by over 70%. Because HPV vaccination is so effective at preventing cervical pre-cancer and cancer, especially if given to girls before they become sexually active, several medical organizations, including the Advisory Committee on Immunization Practice, the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists, recommend routine vaccination of young girls 11 and 12 years of age, ideally before first intercourse, and young women age 13-26. Newer vaccines that provide immunity against a greater number of HPV types are under development with the hope of preventing over 90% of cervical cancer.

<sup>2</sup> American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

More girls and young women need to be vaccinated to achieve this goal. The barriers remain access to care, patient and provider education, and attitudes toward the HPV vaccine. The HPV vaccine is available through most public health facilities and government sponsored insurance programs. Most private insurers will provide some coverage for the cost of the HPV vaccine.

Several recent clinical trials investigating HPV DNA testing for cervical cancer screening will play a role in determining future recommendations for Pap testing and cervical cancer screening programs. The FDA has approved two additional HPV tests for use in cervical cancer screening. Both new tests detect limited subtypes of high-risk HPV DNA that are both sensitive and specific for the detection of CIN III. This gives clinicians another option in HPV testing that may be used in accordance to current guidelines for management and triage of Pap test results. Several studies have reported the impact of using HPV testing as a replacement of Pap test, or in combination with Pap testing. In general these studies show that HPV testing may be more cost effective than conventional Pap test based screening. These studies may reshape cervical cancer screening programs in the future.

As mentioned above, in 2009 the FDA approved a second prophylactic HPV vaccine. Recently published clinical trials data shows that this bivalent vaccine effectively prevents pre-cancerous cervical lesions caused by HPV types 16 and 18, and that this protection continues for at least 6.4 years, according to the most recent report updating immunogenicity and efficacy. An additional report shows that the bivalent vaccine offers cross protection to prevent pre-cancers caused by HPV types 31, 33 and 45. Results from a study of the quadrivalent HPV vaccine in women between 24–45 years of age, were recently reported. This study found that the vaccine effectively prevents infection, and cervical/genital disease from HPV types 6, 11, 16 and 18 in women who have not been previously exposed to these HPV types in this older age group.

Clinical trials are currently ongoing to study the role of HPV vaccines in treating women already infected with HPV and women who have cervical cancer. These vaccines work differently and are more complex than the vaccines for prevention. But since cervical cancer is far from being fully eradicated, clinical trials of vaccines that treat as well as prevent cervical cancer are important.

Progress continues to be made in developing better treatments for women with invasive cervical cancer. Fertility-sparing surgery called trachelectomy (removing the cervix and cancer but keeping the uterus to allow a woman to carry a pregnancy) continues to be an option for select women with early-stage cervical cancer. Traditionally performed through a vaginal incision, the procedure is now being done through abdominal incisions and by laparoscopic (minimally invasive) and robotic surgical approaches. These advances are giving more young women in this country access to surgical management of cervical cancer that preserves an important part of their quality of life.

For women with advanced-stage cervical cancers, treatment with a combination of radiation therapy and chemotherapy remains the standard of care. The National Cancer Institute issued a clinical alert in 1999 to emphasize the importance of combination therapy for the treatment of advanced cervical cancer. A long term follow-up of women who participated in the clinical trials that tested combination therapy confirms that those treated with radiation and chemotherapy continue to have a higher survival rate than women treated with radiation alone. Further, studies suggest that continued additional chemotherapy after radiation may improve survival even further. New studies have also identified alternative chemotherapy drugs that improve survival with potentially fewer harmful side effects from the drugs that have been traditionally used with radiation.

### *Clinical Trials in Cervical Cancer*

For women with early-stage cervical cancer who are treated with radical hysterectomy, the Gynecologic Oncology Group (GOG) recently opened two prospective randomized clinical trials: 1) GOG 0263 to evaluate the role of combined radiation and chemotherapy vs radiation treatment alone for women considered at intermediate risk for recurrence; and 2) GOG-0724 to evaluate the role of continuing chemotherapy alone after combined chemoradiation treatment in women considered at high risk for recurrence. It is hoped that results of these studies will provide further guidance to physicians and patients as to which women with early stage cervical cancer need treatment after surgery.

Recent advances in the ability to detect cervical cancer when it has spread outside of the pelvis include the new data demonstrating the accuracy of PET/CT scans to find disease that has spread away from the cervix, especially cancer located in lymph nodes outside the pelvis. The GOG recently opened GOG 0233, a study that evaluates the utility of preoperative FDG-PET/CT and special MRI scans to detect lymph node spread of cancer in women with advanced stage disease who will undergo surgery for accurate staging. Improved imaging of cervical cancer allows more accurate and targeted planning of the boundaries for radiation treatment, which minimizes effects of radiation on normal tissues.

A continuing challenge in the treatment of cervical cancer is finding effective therapy for women whose cancer recurs after being treated initially with surgery, or the combination of radiation and chemotherapy. In 2009, the GOG reported the results of a clinical trial that showed a biologic agent called bevacizumab, that blocks new blood vessel growth in cancer, was effective in shrinking tumors in some women with recurrent cervical cancer. Based on the encouraging results of that trial, the GOG recently activated GOG protocol 0240, a prospective randomized trial designed to study the effect of combining bevacizumab with paclitaxel/cisplatin vs topotecan/paclitaxel chemotherapy on survival in women with recurrent cervical cancer.

# Ovarian Cancer: Epithelial

## State of Epithelial Ovarian Cancer

*Ovarian cancer, the seventh most common cancer among women, usually starts on the surface of the ovary in cells that are called epithelial cells. About 85 percent to 90 percent of ovarian cancers are epithelial ovarian cancers.*

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*Symptoms:* Bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly and/or urinary symptoms (urgency or frequency).

Women with ovarian cancer report that symptoms are persistent and represent a change from normal for their bodies. The frequency and/or number of such symptoms are key factors in the diagnosis of ovarian cancer. Several studies show that even early-stage ovarian cancer can produce these symptoms.

Women who have these symptoms almost daily for more than a few weeks should see their doctor, preferably a gynecologist. Prompt medical evaluation may lead to detection at the earliest possible stage of the disease. Early-stage diagnosis is associated with an improved prognosis.

Several other symptoms have been commonly reported by women with ovarian cancer. These symptoms include fatigue, indigestion, back pain, pain with intercourse, constipation and menstrual irregularities. However, these other symptoms are not as useful in identifying ovarian cancer because they are also found in equal frequency in women in the general population who do not have ovarian cancer.

*Risk Factors:* The risk of epithelial ovarian cancer increases with age, especially around the time of menopause. A family history of epithelial ovarian cancer is one of the most important risk factors. Infertility and not bearing children are also risk factors for getting ovarian cancer, while pregnancy and the use of birth control pills decrease the risk. A personal history of premenopausal breast cancer or a family history of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer or premenopausal breast cancer are important risk factors.

*Screening/Prevention:* Currently, there is no widely accepted and effective screening test for epithelial ovarian cancer. High-risk women may be candidates for screening using transvaginal ultrasound and CA125 blood tests on an annual or biannual schedule, though the benefits of such screening is unproven. For most women, ultrasound and CA125 screening is not recommended because false positive results can lead to unnecessary surgery.

*Incidence:* Ovarian cancer ranks fifth in cancer deaths among women and causes more deaths than any other reproductive cancer. It is estimated there will be about 21,880 new cases diagnosed and approximately 13,850 deaths from ovarian cancer in the United States during 2010.<sup>3</sup>

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<sup>3</sup> American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

## Advances in Epithelial Ovarian Cancer

### *Basic Biology*

The ability to make key advances in the screening, prevention and treatment of epithelial ovarian cancer lies in the ability to clearly understand its biology. Assisting in this effort is the Cancer Genome Atlas Project (TCGA), launched by the National Cancer Institute and the National Human Genome Research Institute in 2005. The TCGA is presently unraveling the genetic alterations associated with epithelial ovarian cancer in addition to lung and brain cancer. Research conducted within TCGA has in this past year identified four distinct molecular subtypes of the deadly brain cancer glioblastoma multiforme; the first results of studies detailing the genetic alterations associated with epithelial ovarian cancer are soon to be reported. Recent studies presented at the American Society of Clinical Oncology profiled the molecular characteristics associated with response to specific treatments or resistance to therapy. These studies will eventually lead to technology that will allow clinicians to individualize therapy for women affected by ovarian cancer.

Clinicians already appreciate that epithelial ovarian cancer in patients with mutations in the BRCA genes is associated with distinct clinical attributes and response to therapy. Of note, investigators reported this year that epithelial ovarian cancer patients with germline mutations in the BRCA1 and BRCA2 genes more frequently developed metastasis to the liver, spleen, and lung compared to those with non-hereditary ovarian cancer. In general, patients with a BRCA mutation who develop ovarian cancer have a more favorable prognosis; however, a study reported at the Society of Gynecologic Oncologists Annual Meeting demonstrated that ovarian cancer patients with a specific variation in the DNA sequence at one of 5 locations in the BRCA1 gene have significantly shorter survival than patients without this specific DNA change. A separate study at this meeting reported that secondary mutations may occur in ovarian cancer patients with BRCA mutations that restore the BRCA gene function and confer resistance to platinum chemotherapy. Collectively, these studies demonstrate the evolving role of the BRCA genes in determining prognosis and directing treatment for women with BRCA associated ovarian cancers.

Over the past few years, investigators have also been unraveling the role of microRNA's (miRNA) in epithelial ovarian cancer. miRNA's are 25-nucleotide-long non-coding RNA's that inhibit the translation of messenger RNA into protein in the cell. Several studies have noted altered expression of various miRNA's, most notably those in the miRNA 200 family, in patients with ovarian cancer. miRNA's are thought to play a role in the initiation of ovarian cancer and response to therapy. Ongoing research is further clarifying the potential of miRNA's as prognostic markers and/or therapeutic targets.

### *Screening and Early Detection*

In addition to identifying women at genetic risk for developing ovarian cancer, the development of an effective screening strategy would significantly reduce the mortality commonly associated with ovarian cancer. The preliminary results from the Prostate, Lung, Colorectal and Ovarian Cancer screening trial (PLCO) and the United Kingdom Collaborative Trial of Ovarian Cancer Screening trial (UKCTOCS), the two largest prospective randomized trials to evaluate screening for ovarian cancer, have demonstrated both the potential and the limitations of utilizing CA-125 and pelvic ultrasound as a screen for ovarian cancer. The final results of these studies are eagerly awaited. A recent study presented at the American Society of Clinical Oncology demonstrated promising results when a strategy that employed annual CA125 levels analyzed by the Risk of Ovarian Cancer Algorithm (ROCA) followed by transvaginal ultrasound was used to screen postmenopausal women at average risk for ovarian cancer and provided credence to the approach being evaluated in the UKCTOCS study.

Investigators have recently reported the potential value of multi-marker assays for the detection of ovarian cancer. Studies of blood specimens taken from patients prior to the development of ovarian cancer demonstrated increases in levels of three proteins, CA-125, HE-4, and mesothelin, 1 to 3 years prior to

diagnosis. Other studies showed that a four-biomarker panel, which included CA-125, HE-4, CEA, and VCAM-1, had promising sensitivity for detecting both early and advanced stage ovarian cancer. The potential of utilizing a symptom index in combination with blood levels of CA-125 and HE-4 as means of predicting ovarian cancer has also been evaluated. The recent FDA approval of OVA1, a five-biomarker serum panel (b2-microglobulin, apolipoprotein A1, CA-125, transferrin, transthyretin), as a lab test for predicting cancer in a woman with a pelvic mass further demonstrates the potential of a multi-marker assay approach as a means of screening for ovarian cancer. Additional studies are planned to validate the potential of these multi-marker assays as a useful screening strategy for epithelial ovarian cancer.

### *Treatment*

In general, the management of patients with advanced stage epithelial ovarian cancer involves a combined surgical and chemotherapeutic approach. Long-term follow-up of the European Organization of Research and Treatment of Cancer's (EORTC) Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial in patients with ovarian cancer confined to the pelvis recently demonstrated better long-term survival in those patients who were adequately staged. For patients with advanced ovarian cancer, removing both upper abdominal and pelvic disease in order to render a patient optimally debulked remains the primary goal of treating surgeons. Neoadjuvant chemotherapy and interval debulking have been increasingly employed in ovarian cancer patients with significant medical illnesses or findings suggesting unresectable disease. Results of the EORTC trial comparing these two approaches were recently published and showed that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary surgery followed by chemotherapy as a treatment option for women with bulky advanced ovarian cancer, but also showed that complete resection of all visible cancer is the most important factor in improving survival in ovarian cancer no matter what the timing of the surgery in relation to chemotherapy.

In early stage ovarian cancer, long-term follow-up of the EORTC ACTION study reported this year demonstrated the benefit of adjuvant chemotherapy in patients who were not thoroughly staged, and data presented at the Society of Gynecologic Oncologists Annual Meeting demonstrated no significant benefit to the addition of 24 weeks of paclitaxel after 3 cycles of standard chemotherapy in this group of patients. A recent publication also suggested that the recurrence rate in patients with early stage serous ovarian cancer was lower when 6 rather than 3 cycles of chemotherapy were administered.

One of the major advances in advanced epithelial ovarian cancer in this past year was presented at the 2010 American Society of Clinical Oncology Annual Meeting. The results of a Gynecologic Oncology Group (GOG) Phase III trial showed that progression free survival was improved when women with epithelial ovarian cancer were treated with intravenous paclitaxel and carboplatin in combination with the anti-angiogenic agent bevacizumab and then administered a maintenance course of bevacizumab. The impact of this strategy on long-term survival remains to be determined. Additionally, the results of trials using bevacizumab in combination with a platinum-based regimen for patients with recurrent ovarian cancer will soon be available. Studies evaluating other anti-angiogenesis agents have demonstrated promising results and these agents may eventually be incorporated into the care of most ovarian cancer patients at some point in their treatment course.

### *Clinical Trials in Epithelial Ovarian Cancer*

Several new strategies for the treatment of ovarian cancer are being evaluated in ongoing randomized controlled clinical trials. The GOG is currently testing whether giving paclitaxel in a dose-dense, weekly course rather than an every 3-week course will improve outcome in patients with advanced ovarian cancer. Intraperitoneal chemotherapy treatments that have fewer side effects than those currently used in the standard treatment of optimally debulked ovarian cancer are being evaluated in a separate GOG trial. These dose dense and intraperitoneal chemotherapy strategies are also being studied in combination with concurrent and maintenance bevacizumab. Another ongoing trial is evaluating the benefit of giving intravenous paclitaxel

for an additional 12 months in advanced ovarian cancer patients who have achieved a complete response to conventional chemotherapy.

New trials have recently been activated that will evaluate new treatment strategies in rare ovarian tumor types. The GOG will compare the efficacy of oxaliplatin and capecitabine to paclitaxel and carboplatin with or without bevacizumab in patients with mucinous ovarian cancer. In addition, the multi-targeted tyrosine kinase inhibitor sunitinib will be evaluated in a Phase II study in women affected by clear cell ovarian cancer. Additional trials are under development for low grade serous carcinomas of the ovary.

Given new insights regarding the role of alterations in the BRCA genes in ovarian cancer, several early phase clinical trials are continuing to evaluate PARP inhibitors both alone and in combination with chemotherapy. PARP enzymes play a critical role in DNA repair, and ovarian cancer cells with BRCA mutations appear to be responsive to PARP inhibitors. There are plans to evaluate PARP inhibitors in the combination with chemotherapy and bevacizumab in patients with newly diagnosed disease. Currently there are many ongoing trials evaluating novel biologic agents that have been identified in preclinical studies to target biologic pathways unique to ovarian cancer. These promising targeted therapeutics will further spur the development of a personalized approach to and more effective treatments for ovarian cancer patients, particularly as improvements are made in the ability to molecularly characterize an individual patient's ovarian cancer.

# Ovarian Cancer: Germ Cell and Stromal Cell

## State of Germ Cell and Stromal Cell Cancers

*Germ cell and stromal cell ovarian cancers are rare ovarian cancers. Germ cell cancer starts in the cells that form eggs in the ovary, and stromal cell cancer begins in the cells that produce female hormones and hold the ovarian tissues together.*

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*Symptoms:* Germ cell and stromal cell cancers can cause pain or discomfort at the beginning stages. Stromal cell cancers can secrete hormones like estrogen or testosterone, and cause symptoms of abnormal uterine bleeding, new onset acne and facial hair growth. Germ cell cancers can become very large and can cause pain or abdominal distension. Some germ cell cancers may produce HCG, the pregnancy hormone, leading to a false positive pregnancy test.

*Risk Factors:* There are no known risk factors for stromal cell cancer, although there is recent data suggesting that alterations in certain chromosomes may be associated with stromal cell cancers. Rare chromosome abnormalities can cause delayed puberty and menstruation, and an increased risk for germ cell cancers.

*Screening/Prevention:* There are no known prevention measures for germ cell and stromal cell cancers. Abnormal enlargement of an ovary might be noticed at the time of an annual pelvic examination, increasing the chance for early diagnosis and treatment. Girls who have not started menstruating by age 15 should be evaluated and part of this evaluation should include an analysis of the chromosomal abnormality that could predispose to a germ cell cancer.

*Incidence:* Only about five percent of ovarian cancers are stromal cell cancers and less than five percent of ovarian cancers are germ cell cancers. Stromal cell cancers are the most common hormonally active tumors. Germ cell cancers are usually found in adolescent girls and young women, with the average age of diagnosis being 18 years. Stromal cell cancers can be diagnosed at any age, with the average age of diagnosis being 45.

## Advances in Germ Cell Ovarian Cancer

### *Basic Biology*

The majority of ovarian germ cell cancers are diagnosed in children and young women less than age 30. A recent study from the Children's Oncology Group demonstrated that there was no increase in risk of an ovarian germ cell tumor in women with a family history of such tumors. Despite the lack of data supporting a role for family history in germ cell tumor risk, recent NCI studies suggest there may be a gene that when present increases a woman's risk for developing this rare type of ovarian cancer.

A recent study using SEER data evaluated the racial disparity in outcome observed in women affected by germ cell tumors. This study demonstrated that Caucasian women presented more frequently with dysgerminomas and malignant teratomas than African American women. Caucasian women were diagnosed more often with stage I disease and underwent more comprehensive surgical staging than African American women. Importantly, the outcome in African American women affected by ovarian germ cell cancer was significantly worse than noted in Caucasians, though race was not an independent factor when all other clinical factors were taken into consideration.

### ***Treatment***

Germ cell ovarian cancers are generally highly curable with a combination of fertility sparing surgery (removing the affected tube and ovary) and chemotherapy. A few patients with very early stage, low-grade germ cell tumors can be cured without chemotherapy treatment. The primary chemotherapy regimen used for germ cell ovarian cancer is bleomycin, etoposide and cisplatin and the long-term results of a clinical trial of observation in select ovarian germ cell tumors traditionally treated with chemotherapy are eagerly awaited.

### ***Clinical Trials in Germ Cell Ovarian Cancer***

Investigators in Europe are completing a study currently evaluating in newly diagnosed ovarian germ cell cancer patients the regimen of bleomycin and etoposide in combination with carboplatin rather than using these agents in combination with cisplatin. The Children's Oncology Group is also evaluating the role of paclitaxel, ifosfamide, and carboplatin, in young women whose germ cell tumor of the ovary is resistant to the standard chemotherapy agents.

## **Advances in Stromal Cell Ovarian Cancer**

### ***Basic Biology***

The most common stromal tumors are granulosa cell tumors. Studies continue to demonstrate that mutations in a gene called FOXL2 is critical for the development of granulosa cell ovarian cancer. The discovery that this mutated gene may be the cause of granulosa cell tumors could lead to drugs that could target the function of the protein associated with the FOXL2 mutation and hopefully block the growth of ovarian granulosa cell tumors in patients.

### ***Treatment***

Surgery to remove the primary site of cancer and staging to find out if there is spread to other sites is the accepted standard treatment for women with ovarian stromal tumors. Most patients will be found to have stage I disease and chemotherapy after surgery is not needed. Often patients in remission are followed periodically with serum Inhibin or Mullerian Inhibiting Substance. Recent studies have confirmed the value of blood tests for inhibin or Mullerian Inhibiting Substance for detecting recurrence and correlating with tumor volume in patients with granulosa cell ovarian cancer.

For those patients with advanced stage or unresectable recurrent granulosa cell ovarian cancer, treatment with bleomycin, etoposide and platinum has been the mainstay of treatment. Over the past decade, studies also have shown responses of granulosa cell ovarian cancer to treatment with paclitaxel and carboplatin. More recent studies have noted clinical responses in patients treated with the anti-angiogenesis agent bevacizumab, with GnRH agonists, or with aromatase inhibitors.

### ***Clinical Trials in Stromal Ovarian Cancer***

An important GOG study will compare in a randomized Phase II trial the activity of bleomycin, etoposide and platinum to that achieved with paclitaxel and carboplatin in patients affected by advanced stage or recurrent ovarian stromal tumors. Future trials will likely evaluate the efficacy of novel agents such as bevacizumab in combination with chemotherapy in this disease.

# Uterine Cancer: Endometrial Adenocarcinoma and Uterine Sarcomas

## State of Uterine Cancer

*The endometrium is the lining layer of the uterine cavity and most uterine cancers begin because of cancerous changes in that lining. In the most common type of uterine cancer, called endometrial adenocarcinoma, cells in the endometrial lining grow out of control, may invade the muscle of the uterus and sometimes spread outside of the uterus (ovaries, lymph nodes, abdominal cavity).*

*Uterine sarcomas represent a type of uterine cancer in which malignant cells form in the muscle of the uterus (leiomyosarcoma) or in the network of support cells in the uterine lining (endometrial stromal sarcomas and carcinosarcomas). Accounting for fewer than five percent of all uterine cancers, uterine sarcomas are much less common than endometrial cancer, but have a much more aggressive clinical behavior. These cancers can spread quickly to distant sites.*

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**Symptoms:** The most common warning sign for uterine cancer is abnormal vaginal bleeding, and recognition of this symptom often affords an opportunity for early diagnosis and treatment. In older women, any bleeding after menopause may be a symptom of uterine cancer. Younger women should note irregular or heavy vaginal bleeding because they may be symptoms of uterine cancer. Sarcomas can also produce pelvic pain or pressure. In addition, a rapidly growing fibroid during the post-menopausal period, should raise the suspicion of a leiomyosarcoma.

**Risk Factors:** Risk factors for endometrial cancer include use of estrogen without progesterone, obesity, diabetes, hypertension, tamoxifen use and late menopause (after age 52). Women who have not been pregnant also have a higher risk for endometrial cancer. A strong family history of endometrial or colon cancer may signal an inherited risk for getting endometrial cancer. Sarcomas are twice as common in black women as in women of other racial and ethnic groups, and having pelvic radiation therapy increases the risk of developing this rare type of uterine cancer.

**Screening/Prevention:** Women with postmenopausal bleeding or heavy, prolonged or unexpected bleeding during the menstruating years should have a biopsy of the endometrium to check for uterine cancer. For women without symptoms, there are no screening tests that are recommended on a routine basis. The Pap test is designed to find cervical cancers and its precursors, not endometrial cancer. Women can decrease their risk of endometrial cancer by exercising regularly, keeping blood sugar and blood pressure under control, and maintaining a healthy weight. Taking progesterone, either alone, or in combination with estrogen in birth control pills, lowers the risk of endometrial cancer. Progestin can prevent cancer from developing in women who have irregular menstrual cycles and infertility. There are no known methods to prevent uterine sarcoma.

**Incidence:** Cancer of the uterus is the most common reproductive cancer. It is estimated that there will be about 43,470 new cases diagnosed in the United States during 2010, and more than 95 percent of these will be endometrial adenocarcinomas, with approximately 1600 cases of uterine sarcoma. Approximately 7,950 women will die from uterine cancer in the United States during 2010.<sup>4</sup>

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<sup>4</sup> American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

## Advances in Uterine Cancer

Endometrial adenocarcinoma, which accounts for 95% of the over 43,000 new cases diagnosed this year, is fourth most common cancer in women, with only lung, breast and colon cancer being more frequent. Fortunately, most endometrial cancers are diagnosed in an early stage and the potential for cure is great.

Having appropriate surgery is the critical factor in curing endometrial cancer for two reasons: 1) it removes the primary site of the cancer (hysterectomy); and 2) it looks for spread of cancer outside the uterus (staging) by collecting biopsies and removing lymph nodes when indicated.

Gynecologic oncologists are the specialists with specific training in the management of uterine cancers, and have the surgical expertise to perform hysterectomy and lymph node dissections. Many believe that complete staging, which describes if and how the cancer has spread beyond the original site, helps women with endometrial cancer best understand their chances of being cured. Patients identified with cancer confined to the uterus frequently require no additional therapy, whereas those whose cancer has spread to the lymph nodes, ovaries, or within the abdominal cavity can be offered additional treatments, including radiation or chemotherapy, to reduce the chances of the cancer recurring.

During the past few years, advances in surgery for endometrial cancer have focused on improving benefits while reducing risks. Enhancing the use of minimally invasive surgery (laparoscopic and robotic) and defining which patients will benefit most from removing pelvic and para-aortic lymph nodes have been active research topics.

In a large prospective, randomized clinical trial of over 2000 women with early stage endometrial cancer, the Gynecologic Oncology Group (GOG) found patients whose endometrial cancer was staged by laparoscopy had shorter hospital stays, fewer serious complications and better quality of life outcomes compared to those who were staged by traditional open surgery (laparotomy). The number of lymph nodes removed and the frequency of lymph nodes identified with cancer spread (metastasis) were comparable between the two surgery groups, suggesting that the types of surgery had similar accuracy for staging. Long-term results of this GOG trial reported at the 2010 annual meeting of the Society of Gynecologic Oncologists showed there was no difference in recurrence or survival rates between women staged by laparoscopy or open surgery. Although laparoscopic surgery was more difficult in patients who were extremely overweight or who had a large uterus, the favorable survival results and lower complication rates with laparoscopic staging seen in this trial establish minimally invasive surgery as a safe and effective option for the standard treatment of early endometrial cancer.

Robotic assisted laparoscopic surgery (RALS) has been increasingly integrated into the management of endometrial cancer in an effort to address some of the challenges identified with both laparoscopy and open surgery. RALS adds to standard laparoscopy three dimensional, high definition visualization, and increased mobility and precision of hand movements for the surgeon. As with standard laparoscopic surgery, the use of RALS by gynecologic oncologists in the treatment of endometrial cancer is increasing. Twenty-four percent of the recent SGO survey responders reported using robotic surgery in their practices and 66% stated they would increase their use of this technique during the coming year. Continued experience with the use of RALS to stage endometrial cancer patients reported by several groups of gynecologic oncologists in 2010 demonstrate that robot assisted laparoscopic surgery is technically feasible in the endometrial cancer population with results (amount of blood loss, operating times, complications and successful removal of lymph nodes) being the same or better when compared to patients treated by open or standard laparoscopic surgery. Although outcomes from the use of robotic surgery to stage endometrial cancer continue to be encouraging, no head-to-head comparison of robotic surgery to either standard laparoscopy or open surgery was reported in 2010.

In 2010, many gynecologic oncologists in the United States believe that the most accurate assessment of prognosis and appropriate treatment recommendations for women with endometrial cancer is made based on results of surgical staging that includes removal of pelvic and para-aortic lymph nodes (lymphadenectomy). Despite this commonly held perception among women's cancer specialists, lymph node dissection is performed in only 30–40% of all women having surgery for endometrial cancer in this country. There is controversy as to whether all, some, or none of the women having a hysterectomy to treat endometrial cancer should also have lymph nodes removed and the extent of the lymph node removal. Not in doubt, however, is the consensus that surgical removal of lymph nodes with pathologic review is the best available way to assess lymph node status. Detection of the spread of endometrial cancer to lymph nodes is one of the single most important predictors of outcome (recurrence and survival) for women with this disease. Women whose cancer has spread to the lymph nodes receive different treatments than those without spread. Debate has increasingly focused on identifying groups of patients who have the best chance to benefit from the surgical staging that removes lymph nodes.

In 2009, two large prospective randomized European trials compared hysterectomy with or without removal of pelvic lymph nodes. In both trials, patients received radiation therapy irrespective of whether their cancer had spread to the lymph nodes. In both studies, patients who had surgery to remove lymph nodes in addition to hysterectomy had the same risk of cancer recurrence and the same survival as patients who did not have their lymph nodes removed. Experts have identified a number of strengths and weaknesses in how these trials were done, and others have questioned whether these results from a group of European women can be applied to the treatment of women with endometrial cancer in this country. Until further research clarifies the important issues raised by the European studies, women with endometrial cancer should discuss with their gynecologic oncologist the risks and benefits of performing or not performing a node dissection as part of their initial surgery.

An important advance in the surgical staging of endometrial cancer is the incorporation of sentinel node mapping to identify the first (sentinel) nodes in the lymphatic chain which are at highest risk of having cancer spread. Identification and removal of these nodes can potentially avoid the side effects experienced by patients having a more extensive lymph node dissection including lymphedema (swelling of the lower extremities). Sentinel lymph node mapping involves the injection of either a radioactive solution or a blue dye into the cervix at the start of surgery which then travels to the closest group of lymph nodes that drain the uterus. The surgeon then identifies these sentinel nodes in the pelvis, using either a radiation probe or by visualizing the blue dye, and removes only the sentinel lymph nodes during the staging surgery. Although no large prospective trials of sentinel node mapping in endometrial cancer have been performed, results from small single-institution studies seem to indicate that this procedure is feasible and accurate in detecting the sentinel node. Larger studies are needed to determine whether sentinel node mapping is accurate for detecting whether endometrial cancer has spread to the lymph nodes

### *Clinical Trials in Uterine Cancer*

What to do after surgery has also been an important research focus in endometrial cancer. For most patients with low-risk disease confined to the uterus, the risk of recurrence is less than 10%, and survival is greater than 90%. For those patients with certain high-risk features (age greater than 70, high tumor grade or deep muscle invasion) the chance of cancer recurrence is higher. The potential benefits of treatments in addition to surgery have been studied in recent trials. Results of a randomized trial in over 400 patients that compared limited vaginal radiation therapy to more extensive pelvic radiation therapy showed lower recurrence, similar survival and better quality of life in the patients treated with vaginal radiation.

The Gynecologic Oncology Group (GOG) recently opened a large prospective randomized trial to compare pelvic radiation therapy to vaginal radiation followed by 3 cycles of chemotherapy in this group of women with high-risk, early stage endometrial cancer. This study, GOG-0249, is currently enrolling patients, and will try to determine if there is a benefit to these early stage patients of chemotherapy after surgery.

For women with advanced stage endometrial cancer whether outcomes can be improved by adding radiation to chemotherapy versus using chemotherapy alone is the focus of a new GOG study. This trial, GOG-0258, is currently open and will enroll over 800 patients whose stage III or IVA endometrial cancer has been optimally debulked with surgery to compare the recurrence-free and overall survival of those treated after surgery with cisplatin and tumor volume-directed radiotherapy followed by carboplatin and paclitaxel to the survival of those patients treated after surgery with carboplatin and paclitaxel alone. The benefit of adding cisplatin chemotherapy to pelvic radiation therapy for women whose endometrial cancer has recurred in the pelvis is also being studied by the GOG in an ongoing randomized clinical trial. New drugs which focus on blocking specific growth signals of cancer cells are being actively studied in endometrial cancer. Experimental agents which block growth pathways (mTOR inhibitors) or interfere with blood vessel development in tumors (anti-angiogenesis agents) have shown the most promise in treating patients with endometrial cancer. Several new clinical trials evaluate these interesting targeted agents in the treatment of women with advanced or recurrent endometrial cancer. The GOG recently completed protocol 0248 which was designed to determine the response rate in patients with advanced, persistent or recurrent endometrial carcinoma treated with the mTOR inhibitor temsirolimus with or without hormonal therapy comprising megestrol acetate and tamoxifen citrate.

Significant progress towards understanding the biology of endometrial cancers has been achieved by a large tumor banking study sponsored by the GOG. More than 4500 women with endometrial cancer nationwide have participated by donating portions of their tumor and blood obtained at the time of surgery so that researchers can identify promising biomarkers to predicting response and prognosis. These samples are being studied to answer important questions including why some cancers behave more aggressively and spread, and why some cancers respond better to other therapies. Progress in the treatment of uterine sarcoma also has occurred recently as a result of prospective clinical trials. Results of a large randomized trial conducted in Europe showed that pelvic radiation therapy offered little benefit for patients with early stage uterine carcinosarcoma or leiomyosarcoma. The GOG published results from two studies of patients with carcinosarcoma suggesting that 1) chemotherapy (ifosfamide plus cisplatin) was preferable to whole abdominal radiation therapy in women with stages 1-IV disease, and 2) the combination regimen of ifosfamide with paclitaxel was better than ifosfamide alone in patients with advanced or recurrent disease. As a result, chemotherapy has taken a much larger role in the management of uterine carcinosarcomas.

At the 2009 American Society of Clinical Oncologists (ASCO) meeting, investigators from the GOG reported promising preliminary results in a small group of patients with advanced or recurrent carcinosarcoma disease treated with a regimen of carboplatin plus paclitaxel. Based on these results, the GOG recently launched a trial of over 400 patients with newly diagnosed or recurrent uterine carcinosarcoma to determine if treatment with paclitaxel and carboplatin has similar effects on survival when compared to treatment with paclitaxel and ifosfamide. In addition, the study will determine if side effects, specifically neurotoxicity and infection, are more favorable as well as quality of life are improved with the combination paclitaxel and carboplatin compared to that of paclitaxel and ifosfamide.

For patients with leiomyosarcoma, the two drug combination of gemcitabine and docetaxel demonstrated important activity in both first and second-line treatment of patients with metastatic disease. To improve survival for these patients, the GOG recently opened GOG protocol 0250 a prospective trial that randomizes women with advanced or recurrent leiomyosarcoma to receive docetaxel and gemcitabine alone or in combination with the angiogenesis inhibitor bevacizumab.

Enrollment of patients in these GOG-sponsored prospective clinical trials has been very important for the recent advances in care of women with uterine cancer. GOG clinical trials currently available for enrollment can be found on GCF's Web site, the Women's Cancer Network, [www.wcn.org](http://www.wcn.org).

# Vaginal Cancer

## State of Vaginal Cancer

*Vaginal cancer originates in the vagina, usually in the squamous epithelium (lining). It is usually diagnosed in older women and radiation is the most common treatment.*

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**Symptoms:** Vaginal cancer, especially at precancerous and early stages, may not cause any symptoms. Common symptoms of more advanced stages include bleeding, pain, or problems with urination or bowel movements.

**Risk Factors:** Risk factors for vaginal cancer include HPV (Human Papillomavirus) infection, smoking, age (60 years and older), and prior treatment for cervical or vulvar cancer. The daughters of women who took DES (a hormone medication used many years ago to prevent miscarriage) while pregnant are at increased risk for both vaginal and cervical cancer.

**Screening/Prevention:** Many precancerous conditions and early vaginal cancers can be detected through routine pelvic exams and Pap tests. Because many vaginal cancers are associated with HPV types 16 and 18, vaginal cancer can be prevented by the vaccinations advocated for the prevention of cervical cancer. There is now both a quadrivalent vaccine and a bivalent vaccine approved by the FDA for the purpose preventing precancerous vaginal changes induced by HPV.

**Incidence:** Primary vaginal cancer is one of the rarest gynecologic cancers. It is estimated that there will be about 2,300 new cases diagnosed and 780 deaths from vaginal cancer in the United States during 2010.<sup>5</sup> Vaginal cancer accounts for about 3% of reproductive cancers.

## Advances and Vaginal Cancer Clinical Trials

Because of its rarity, vaginal cancer is not amenable to comparing one form of treatment with another in a large clinical trial. Therefore, much of what is understood in vaginal cancer treatment is borrowed from clinical trials in other related cancers, such as vulvar and cervical cancer.

Although most women with vaginal carcinoma are past child-bearing years, many women with DES-associated vaginal cancers are young. Standard treatments for vaginal cancer can cause young women to lose the option of having children, but a recent report showed that fertility-sparing surgery is possible in carefully selected patients, even when the vaginal tumor extends to and requires removal of the cervix. Another advance in surgical therapy for vaginal cancer includes the adoption of a minimally invasive approach. Surgeons are demonstrating that laparoscopic techniques for surgical evaluation with lymph node biopsy may be utilized to select patients with localized disease for tumor excision, or to precisely define radiation treatment fields to permit protection of normal organs during radiation treatment.

Visualizing vaginal cancer with imaging tests can be difficult because of the other organs located near the vagina in a woman's body including the uterus, bladder and rectum. One recent study evaluated magnetic resonance imaging (MRI) of vaginal cancer and showed that MRI correctly identified over 95% of the tumors, and correctly demonstrated disease that involved tissues beyond the vagina in 88% of patients. MRI staging correlated very well with survival. Thus, for patients with advanced disease, staging may allow a treatment plan to be enacted without need for surgery.

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<sup>5</sup> American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

Positron emission tomography (PET) in combination with MRI (or CT scans) may be an even better method to image vaginal cancer. A recent study evaluated PET prior to a planned radical surgery to remove recurrent cervical or vaginal cancer. PET was found to have a sensitivity of 100% and a specificity of 73% in detecting sites of cancer beyond the pelvis. These findings are particularly important for women with vaginal cancer because PET imaging may, in a non-invasive fashion, identify otherwise non-detectable metastasis, sparing some patients unnecessary surgical procedures and allowing others to receive radiation treatment to a smaller area.

Most patients with vaginal cancer are treated with radiation therapy. Radiation therapy alone is an effective treatment for early vaginal cancer; however, results with radiation therapy for more advanced vaginal cancers are not uniformly good and better treatments are needed. For some similar cervical and vulvar cancers, chemotherapy prescribed concurrently with the radiation therapy, has improved the response rates and overall survival. A recent study showed that by giving chemotherapy at the same time as radiation to women with vaginal cancer also improved the response and survival, with an acceptable level of side-effects. Side effects of radiation treatment for vaginal cancer include shortening and closure of the vaginal tube and remain a significant issue for these patients.

It is hoped that the integration of PET CT with other new imaging methods may also improve the accuracy of surgery or radiation treatment planning, resulting in improved survival and reduced treatment-related side-effects for women with vaginal cancer. Intensity-Modulated Radiation Therapy (IMRT) is a newer advanced type of high-precision radiation that is the next generation of 3-Dimensional Conformal Radiotherapy. IMRT's use in vaginal cancer has improved the ability to modify the radiation and conform to tumor shapes while avoiding treatment of vulnerable structures, such as the bladder and bowel.

The addition of simultaneous chemotherapy can also improve the effectiveness of radiation therapy for this disease. Since HPV is a risk factor for many vaginal cancers, it is hoped that the widespread use of HPV vaccines will reduce the incidence of this gynecologic cancer in the future.

# Vulvar Cancer

## State of Vulvar Cancer

*Vulvar cancer is caused by the growth and spread of abnormal cells within the skin of the labia and perineum.*

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*Symptoms:* Itching, burning, bleeding, pain, or a new lump or ulcer in the genital area are common symptoms.

*Risk Factors:* Infection with Human Papillomavirus (HPV) is a common cause of vulvar cancer in young women. Vulvar cancer in older women is associated with chronic vulvar irritation from any source.

*Screening/Prevention:* Protection from infection with HPV (Human Papillomavirus), including an HPV vaccination, reduces the risk of vulvar cancer. A quadravalent HPV vaccine and a bivalent vaccine have been approved by the FDA for this purpose. Examination of the vulva for changes by a woman at home or by her gynecologist during her yearly pelvic exam may lead to the detection of preinvasive disease or early vulvar cancer. Suspicious or unexplained changes on the vulva should be biopsied.

*Incidence:* Vulvar cancer is uncommon. It is estimated that there will be about 3,900 new cases diagnosed and approximately 920 deaths from vulvar cancer in the United States during 2010.<sup>6</sup> Vulvar cancer is usually diagnosed in the early stages and is most often cured with surgical treatment.

## Advances in Vulvar Cancer

Although vulvar cancer can often be cured with surgery, the side-effects of the procedures traditionally used to treat this rare cancer have a major impact on quality of life. Advances in surgical techniques and strategy have improved the lives of women with vulvar cancer by preserving sexual function, reducing surgical wound complications and reducing the condition of chronic swelling of the legs, called lymphedema. These advances have been achieved by performing less radical surgeries that preserve more of the normal tissue of the genital area.

Results from a recent study showed that cure rates for women with early-stage vulvar cancer treated with less radical surgery today are as good as the survival seen in women treated with the more extensive procedures that were standard 20 years ago. In spite of these improvements in surgery for vulvar cancer, problems remain, including accurate identification of patients whose cancer has spread to the groin lymph nodes and the lymphedema that results from inguinal femoral lymphadenectomy. Lifelong lymphedema, or chronic swelling in the legs, is especially frustrating for patients and care-givers because there are few effective treatments, and it is difficult to study because it is underreported. The Gynecologic Oncology Group (GOG) recently reported a randomized control trial in 150 vulvar cancer patients investigating whether the use of a sealant sprayed on the area of lymph node dissection at the time of surgery could reduce this common complication. Although the study found that using the sealant did not prevent lymphedema, the completion of this trial does demonstrate the feasibility of studying ways to decrease the rate of this disabling complication. The study identified that women undergoing treatment for vulvar cancer are at extremely high risk of developing lymphedema. The GOG is planning future trials to identify more effective methods to diagnose and prevent lymphedema in women having surgery for vulvar cancer.

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<sup>6</sup> American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

One of the most significant recent advances is sentinel lymph node biopsy, which can improve detection of node metastases, and can reduce the risk of lymphedema in women having surgery for vulvar cancer. The sentinel lymph node is the node that is most directly connected to the main tumor through the lymph channels, and it is the most common site to which cancer cells spread. The sentinel lymph node can be found with a technique called lymphatic mapping. This strategy has been used successfully in patients with breast cancer and melanoma to improve the detection of metastatic disease, and avoid extensive lymph node resection and the associated lymphedema in some patients.

At the 2009 American Society of Clinical Oncology (ASCO) meeting, the results from a much-anticipated GOG study designed to validate the use of sentinel lymph node biopsy in vulvar cancer were presented. Five hundred ten women with vulvar cancer were enrolled in the study. In each woman participating in the study, sentinel nodes, identified with both blue dye and radioactive dye, were removed and examined to look for tumor spread. During the same surgery, the rest of the lymph nodes in the groin area were removed and results compared with the findings in the sentinel lymph nodes. Sentinel nodes were successfully identified in over 95% of patients, confirming that this technique is feasible and safe in women with vulvar cancer. This study confirmed the findings of a large Dutch study published in 2008 that followed 259 women with unifocal vulvar disease and negative sentinel lymph nodes for three years and concluded that sentinel lymph node biopsy is safe in many patients with early vulvar cancer (less than 4 cm). However, sentinel lymph node dissection alone is not advocated for larger lesions, multifocal lesions or women who have a positive sentinel node. These patients are best treated with a full lymph node dissection. Based on the encouraging results of the data to date, a woman with vulvar cancer should discuss with her gynecologic oncologist their experience with, and the risks of, a sentinel lymph node assessment given their personal clinical situation.

Further supporting the concept that less radical surgery is safe for vulvar cancer patients, GOG investigators performed a secondary analysis of a previous trial to determine whether groin recurrence was associated with the removal of fewer lymph nodes at the time of original surgery. Among 113 patients who underwent groin dissection, nine had a recurrence in the groin, but there were no significant differences in node counts between patients who had recurrence in the groin and those who recurred outside the groin. Investigators concluded that variations within other risk factors may make node counting itself an unreliable measure of surgical quality or risk for recurrence.

In general, cancers are divided into categories or stages, with the assignment within a stage based on the risk for recurrence. For vulvar cancer, the final stage depends on the pathologic review of the surgical specimens from the vulva and the regional lymph nodes. In 2009, FIGO announced the first major revision in staging for vulvar cancer since 1988. In the revised system, stage IA lesions do not require aregional lymph node evaluation because of the low risk of metastasis. Patients with stage IB have tumors with deeper invasion (greater than 1 mm), however the regional lymph nodes are negative. These patients remain in the stage I category as they have a low risk for recurrence. Stage II was reconfigured to include those patients with local extension to the urethra, anus or vagina, but still had negative lymph nodes. These patients have a lower risk of recurrence than the node positive Stage III patients with whom they were previously categorized. Stage III now includes those patients with lymph node metastases regardless of the size, location and extension of the primary vulvar tumor. The presence and extent of nodal involvement is the single most important factor in determining the risk for recurrence in vulvar cancer patients. Stage III is now subdivided by the size of the metastatic foci, the number of nodes involved and the presence of extracapsular spread. The new staging system will hopefully identify those patients at greatest risk for recurrence who would clearly benefit from adjuvant treatment.

Another area of progress is the treatment of vulvar cancer by using a combination of therapies for more advanced-stage tumors. This strategy holds great promise for patients who have large tumors or disease that has spread to lymph nodes. Results from a recent analysis of five vulvar cancer trials in women with advanced-stage cancer showed that treating women with the combination of chemotherapy and radiation

before surgery can shrink the size of the tumor and reduce the extent of surgical resection. This strategy helps preserve quality of life for patients who might have otherwise lost rectal, bladder or sexual function from radical surgery alone.

Another new technology being studied in the treatment of vulvar cancer is intensity modulated radiation therapy (IMRT). IMRT allows the radiation oncologist to vary the intensity of each beam of energy both in space and time, and provide a dose that more closely conforms to the contours of the tumor with less dose of radiation to normal tissues. A recent report of combining IMRT with chemotherapy for patients with locally advanced vulvar cancer before surgery, showed good tumor response and lower toxic effects to normal tissues, and is more commonly being utilized for these patients.

# Legislative Update

## Clinical Trials for Women with Gynecologic Cancer and Insurance Coverage

On June 7, 2000, President Clinton issued an executive order directing the Secretary of Health and Human Services to “explicitly authorize [Medicare] payment for routine patient care costs...and costs due to medical complications associated with participation in clinical trials.” The Health Care Financing Administration (now the Centers for Medicare & Medicaid Services, or CMS) responded to President Clinton’s order with the clinical trial policy national coverage determination (NCD) issued on September 19, 2000. This national policy requires Medicare to pay the routine costs of care received by Medicare beneficiaries who participate in clinical trials. Routine care costs include doctor visits, hospital stays, x-rays and scans, and clinical laboratory tests that are done as part of the treatment provided to a patient enrolled in a clinical trial. Research costs, including the time of the research doctor or nurse, analysis of research results and any laboratory tests done only for research purposes are not covered by Medicare, but are usually paid for by the organization or group sponsoring the clinical trial. The good news is that the routine costs of most of the clinical trials available for women with gynecologic cancer are covered by Medicare, including trials sponsored by the National Cancer Institute, the Centers for Disease Control, the Department of Defense and the Gynecologic Oncology Group. The bad news is that for women with gynecologic cancer who don’t have Medicare, the costs of participating in a clinical trial may not be covered by their health insurance. Although many states in the U.S. have passed legislation requiring private insurance companies to pay for the routine costs of clinical trials, until recently there was no national policy mandated such coverage.

## Enactment of the Patient Protection and Affordable Care Act of 2010 leads to Private Insurance Coverage of Routine Patient Care Costs in Clinical Trials

Prior to President Barak Obama signing the Patient Protection and Affordable Care Act (PPACA) of 2010 on March 23, 2010, private insurance coverage of routine patient care costs in clinical trials, depended on whether an individual state’s legislature had passed a law mandating coverage for clinical trials by the private insurance companies operating in their state.

As part of the PPACA health care reform legislation, a new provision was added to the federal Public Health Service (PHS) Act that will require group health plans and health insurers that offer individual or group health insurance products to provide coverage of routine patient costs associated with approved clinical trials beginning on or after January 1, 2014.

Under the new Federal law, “routine patient costs,” are defined as including all items or services that are consistent with coverage provided to a qualified individual who is not enrolled in a clinical trial. As with the existing Medicare coverage for clinical trials, this will include paying for doctor visits, hospital stays, scans and laboratory tests performed as part of treatment on a trial. Research only related costs, similar to the existing Medicare regulations, will not be covered by private insurance.

As with current Medicare coverage of clinical trials, this new Federal law defines an, “approved clinical trial,” as being a Phase I, Phase II, Phase III, or Phase IV clinical trial that is conducted in relation to the prevention, detection, or treatment of cancer or other life-threatening disease or condition. For women with gynecologic cancer, this means that beginning in 2014, private insurance will be required to pay for the routine costs of most clinical trials available including those sponsored by the Gynecologic Oncology Group.

The Federal government still has to write regulations to implement this new section of the health care reform law, but when all the details are worked out, passage of the PPACA of 2010 will expand access to participation in clinical trials for thousands of women with gynecologic cancer in the United States.

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## Medical Editor

Carol L. Brown, MD  
Associate Attending Surgeon  
Memorial Sloan-Kettering Cancer Center  
New York, NY

## Editor

Marsha Tanner Wilson, MPH  
Director of Communications  
Gynecologic Cancer Foundation  
Chicago, IL

## Contributors

Ronald D. Alvarez, MD  
Professor  
The University of Alabama at Birmingham  
Birmingham, AL

Richard R. Barakat, MD  
Chief-Gynecology Service  
Department of Surgery  
Memorial Sloan-Kettering Cancer Center  
New York, NY

Jay W. Carlson, DO  
Department of Gynecologic Oncology Service  
Mercy Hospital  
Des Moines, IA

Levi S. Downs, Jr., MD  
Assistant Professor  
Department of Obstetrics/Gynecology  
University of Minnesota  
Minneapolis, MN

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---



230 W. Monroe, Suite 2528  
Chicago, IL 60606

312.578.1439

[info@thegcf.org](mailto:info@thegcf.org)  
[www.thegcf.org](http://www.thegcf.org)  
[www.wcn.org](http://www.wcn.org)