

**2007 State of the State
of Gynecologic Cancers**

Fifth Annual Report to the Women of America



**Gynecologic
Cancer
Foundation**

About the Society of Gynecologic Oncologists and the Gynecologic Cancer Foundation

The Society of Gynecologic Oncologists (SGO) is a national medical specialty organization of physicians who are trained in the comprehensive management of women with female reproductive cancers. Gynecologic oncologists are obstetricians-gynecologists with an additional three to four years of training. SGO's purpose is to improve the care of women with gynecologic cancer by encouraging research, disseminating knowledge to raise the standards of practice in the treatment and prevention of gynecologic malignancies, in cooperation with other organizations interested in women's health care, oncology and related fields.

The Society's membership is primarily comprised of gynecologic oncologists, as well as other related medical specialists such as medical oncologists, radiation oncologists and pathologists. SGO members provide multi-disciplinary care including chemotherapy, radiation therapy, supportive care and surgery.

For more information about SGO and the field of gynecologic oncology, please visit www.sgo.org or contact the Society at 312.235.4060.

The Gynecologic Cancer Foundation (GCF) is a 501(c) 3 not-for-profit organization whose mission is to ensure public awareness of gynecologic cancer prevention, early diagnosis and proper 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.

For more information about GCF, its educational materials or research grants, please visit www.thegcf.org or contact Executive Director Karen Carlson by phone at 312.578.1439 or by e-mail at kcarlson@thegcf.org. For additional information on gynecologic cancers or for a referral to a gynecologic oncologist or a related specialist, please call the toll-free GCF Information Hotline at 800.444.4441.

GCF is a 501(c)(3) non-profit organization under the U.S. Internal Revenue Code.



For more information about women's cancers, visit GCF's Women's Cancer Network Web site:

www.wcn.org

Log on for a confidential risk assessment to learn about your risk for developing gynecologic and breast cancers. Additional information of interest to women and cancer survivors is also available on the site.

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A Letter to the Women of America

The Gynecologic Cancer Foundation (GCF) is pleased to publish the fifth edition of *The State of the State of Gynecologic Cancers: A Report to the Women of America* to mark September 2007 as Gynecologic Cancer Awareness Month. Like the four editions that preceded it, the report provides information about each of the major reproductive cancers plus a special section, this year focused on the important topic of quality of life in women with gynecologic cancer.

GCF would like to open this report to the women of America by highlighting the passage of the Gynecologic Cancer Education and Awareness Act of 2005 (H.R. 1245/S.1172), known as “Johanna’s Law.” Years of collaborative and dedicated efforts were brought to a successful conclusion in January 2007 when President Bush signed into law this legislation which commits federal dollars for support of critically needed education about gynecologic cancers. More information about the law can be found in the legislative summary at the conclusion of the letter.

When GCF first began to consider the development of this annual report, it was thought that all women, but especially those who are living with a gynecologic cancer, would benefit from hearing from experts each year about what these experts thought were the most important scientific advances in each cancer during the past year.

This year’s report again will provide these scientific updates of importance. However, there is an advance to report this year that is remarkable because it is based upon collaboration between survivors of ovarian cancer and researchers, facilitated by GCF.

The Ovarian Cancer Consensus Symptoms Consensus Statement, which is reprinted at the end of this letter, positively debunks the myth that ovarian cancer is a “silent killer.” We now know that this cancer “speaks” to women in its earliest stages, when chance of cure is over 90 percent.

Only a few years ago, there was no scientific evidence to suggest a set of symptoms for this, the most deadly reproductive cancer. However, women living with ovarian cancer anecdotally began to discuss common symptoms they had noticed before their diagnosis. GCF, through its Allied Support Group consisting of 26 national gynecologic cancer advocacy groups and federal agencies, connected these women with researchers, like SGO/GCF member Dr. Barbara Goff. Dr. Goff and her colleagues listened to these women and began to develop the evidence you see footnoted at the bottom of the statement.

In September 2006, GCF’s Allied Support Group again played a pivotal role. With the accumulating evidence about symptoms, it issued a “call to action,” asking GCF to take the lead in developing a consensus about these symptoms that could then be widely distributed to women. The Society of Gynecologic Oncologists and the American Cancer Society joined GCF as originating organizations, joined by members of the Allied Support Group and other advocacy organizations as endorsing organizations — now totaling 38.

GCF released the Ovarian Cancer Symptoms Consensus Statement to the press on June 13, 2007, and thanks to widespread media coverage, by the end of the day thousands of women across the country were made aware that ovarian cancer is not a “silent killer.”

But the job of increasing awareness has just begun. In a recent national poll of 700 women ages 40–65 commissioned by GCF, only 4 percent of women interviewed say they would recognize the signs and symptoms of ovarian cancer, while 42 percent report being very concerned about their own level of risk for developing ovarian cancer. GCF is committed to closing this information gap about ovarian cancer and we need your help to do so. Please read the consensus statement carefully and then share your new knowledge about the symptoms of ovarian cancer with your family, friends and colleagues.

Before closing, I would like to again note the ongoing efforts by the gynecologic cancer community in the legislative arena that are aimed at encouraging additional government support of gynecologic cancer research, education and training:

- *Johanna's Law: The Gynecologic Cancer Education and Awareness Act of 2005 (H.R. 1245/S.1172)* On January 12, 2007 President Bush signed into law this bill that funds a national campaign to raise awareness about gynecologic cancers among women and their health care providers. Administered through Centers for Disease Control and Prevention and the Office of Women's Health at the Public Health Service, this campaign will arm women with the basic facts about early warning signs of gynecologic cancers.
- *Comprehensive Cancer Care Improvement Act of 2007 (H.R. 1078)* introduced by Congresswoman Lois Capps (D-CA) would provide for coverage of comprehensive cancer care planning under the Medicare program, and to improve the care furnished to individuals diagnosed with cancer by establishing a Medicare hospice care demonstration program and grants programs for cancer palliative care, and symptoms management programs, provider education and related research.
- *Cancer Screening, Treatment & Survivorship Act of 2007 (H.R. 2353/S. 1415)* introduced by Congresswoman Janice Schakowsky (D-IL) and Senator Tom Harkin (D-IA) this legislation would amend the Public Health Service Act and the Social Security Act to improve screening and treatment of cancers, provide for survivorship services, and for other purposes.
- *Cancer Testing, Education, Screening and Treatment Act (H.R. 1030)* introduced by Congresswoman Maxine Waters (D-CA) would authorize the Secretary of Health and Human Services to make grants to qualifying health centers and non-profit organizations for programs providing cancer screening, counseling and treatment for low-income, minority individuals who are at-risk for cancer.
- *Genomics and Personalized Medicine Act of 2007 (S.976)* introduced by Senator Barack Obama (D-IL) to secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase safety of drugs and identify novel treatments.
- *Access to Cancer Clinical Trials Act of 2007 (H.R. 2676)* introduced by Congresswoman Deborah Pryce (R-OH) to amend the Public Health Services Act, the Employee Retirement Income Security Act of 1974, and the Internal Revenue Code of 1986 to require group and individual health insurance coverage and group health plans to provide coverage for individuals participating in approved cancer clinical trials.

As is customary, I close by asking each of you to use the knowledge provided in this report to maintain your health. At GCF we are guided by the belief that where there is knowledge there is hope. Please help us create hope for the early diagnosis of ovarian cancer by sharing information about its symptoms.

Sincerely,



Karl C. Podratz, MD, PhD
Chairman
Gynecologic Cancer Foundation

Ovarian Cancer Symptoms Consensus Statement

Historically ovarian cancer was called the “silent killer” because symptoms were not thought to develop until the chance of cure was poor. However, recent studies have shown this term is untrue and that the following symptoms are much more likely to occur in women with ovarian cancer than women in the general population.^{1,2} These symptoms include:

- Bloating
- Pelvic or abdominal pain
- Difficulty eating or feeling full quickly
- 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.³ Several studies show that even early stage ovarian cancer can produce these symptoms.²⁻⁶

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.²⁻⁵ 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.¹

References

- ¹ Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care. *JAMA* 2004;291:2705-12. Level II-2
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- ³ Goff BA, Mandel L, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis: results of a national ovarian cancer survey. *Cancer* 2000;89:2068-75. Level III
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- ⁶ Goff BA, Mandel L, Drescher CW, Urban N, Gough S, Schurman K, Patras J, Mahony BS, Anderson M. Development of an ovarian cancer symptom index. *Cancer* 2007;109:221-7. Level II-2

Originating Organizations:

Gynecologic Cancer Foundation
Society of Gynecologic Oncologists
American Cancer Society

Date

January 23, 2007
February 15, 2007
April 30, 2007

Endorsing Organizations:

CancerCare
Conversations: The International Newsletter For Those Fighting Ovarian Cancer
EyesOnThePrize.org
FORCE: Facing Our Risk of Cancer Empowered
Gilda's Club Worldwide
Gynecologic Oncology Group
In My Sister's Care
International Gynecologic Cancer Society
Lynne Cohen Foundation for Ovarian Cancer Research
National Coalition for Cancer Survivorship
National Cervical Cancer Coalition
National Ovarian Cancer Coalition
Ovarian Cancer Canada
Ovarian Cancer National Alliance
Ovarian Cancer Research Fund
SHARE: Self-help for Women with Breast or Ovarian Cancer
Society of Gynecologic Nurse Oncologists

May 29, 2007
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June 1, 2007
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June 5, 2007
May 29, 2007

Additional Endorsing Organizations:

Alliance for Women's Cancer Awareness
Cancer Awareness Team, Akron, Ohio
Marsha Rivkin Center for Ovarian Cancer Research
Minnesota Ovarian Cancer Alliance
Oasis of Southern California
Ovar'Coming Together
Ovarian and Breast Cancer Alliance of Washington
Ovarian Awareness of Kentucky
Ovarian Cancer Alliance of FL
Ovarian Cancer Alliance of FL — Gulf Coast
Ovarian Cancer Alliance of FL/Space Coast
Ovarian Cancer Alliance of Oregon and SW Washington
Ovarian Cancer Orange County Alliance
R.O.A.R! (Responsible Ovarian Awareness Required)
R.O.C.C.S. Research for Ovarian Cancer and Continued Survival
Sandy Rollman Ovarian Cancer Foundation, Inc
St. Louis Ovarian Cancer Awareness
The Chicago Ovarian Cancer Alliance
The Ovarian and Gynecologic Cancer Coalition/Rhonda's Club
Treasure Coast Ovarian Cancer Alliance
Tri-State Ovarian Cancer Alliance

July 3, 2007
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June 18, 2007
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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 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 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 or chemotherapy. The choice of therapy 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 78,000 new cases diagnosed and approximately 28,000 deaths from gynecologic cancers in the United States during 2007.¹

¹ American Cancer Society. Cancer Facts & Figures, 2007. Available at: http://www.cancer.org/docroot/stt/stt_0.asp. Accessed April 19, 2007.

Quality of Life in Women with Gynecologic Cancers

By Vivian E. von Gruenigen, MD

Quality of life (QOL) reflects how a disease and its associated treatments influence the life of an individual. Each gynecologic cancer is unique in its symptoms and effects on QOL. Cancer may be treated by surgery, chemotherapy, and/or radiation therapy. In addition to determining whether cancer therapies are tolerable and provide clinical benefit, it is imperative to understand how cancer and its treatment affect a woman's quality of life.

There are more than 1 million gynecologic cancer survivors in the United States. Advances in the early detection and treatment of gynecologic cancers have improved survival for many patients. In addition, over 78,000 women will receive a new diagnosis of gynecologic cancer this year, and receive surgery and other treatments, including chemotherapy and radiation. As cancer research has progressed, investigators have learned that it is important to treat the whole individual and not just the disease.

Quality of life (QOL) research studies physical, social and family concerns, and how they relate to a woman's experience with gynecologic cancer. There are standard questionnaires given to women to study QOL as part of clinical trials; however, because these issues are so important to a women dealing with cancer, some physicians use QOL questionnaires routinely in their practice to help them care for their patients. Research tells us that QOL issues in cancer patients differ according to the primary site of the cancer. For example, a woman with ovarian cancer would be asked about the impact of discomfort due to abdominal bloating, whereas an endometrial cancer patient may be asked about fatigue and inconvenience due to vaginal bleeding. In addition to studying QOL in patients with cancer, researchers also explore how cancer affects the QOL of caregivers.

Advances in Quality of Life

In this section, issues and advances in the QOL concerns will be explored for the three most common female reproductive cancers — endometrial, ovarian and cervical cancers.

Endometrial cancer is the most common gynecologic cancer in the United States and obesity is a significant risk factor for the development of the disease. In addition, obesity may decrease a woman's overall QOL as well as QOL related specifically to cancer treatment. A recent prospective study reported that approximately 70 percent of women with early stage endometrial cancer are obese. The incidence of endometrial cancer in the United States is rising and it is likely that this is secondary to increasing obesity.

Overweight and obese women in the general population, with a history of endometrial cancer, or with active disease are at a greater risk of dying. A recent publication in the *New England Journal of Medicine* assessed the risk of death for overweight cancer patients. Endometrial cancer patients who were obese had a greater than 2-fold risk of death. Those women who were morbidly obese (body mass index of greater than 40) had a greater than 6 times the risk of death. This was the highest obesity-related risk of death seen for all cancers. Another study from the Gynecologic Oncology Group (GOG) published in the journal *Cancer* looked at how

being obese affected the survival of women with endometrial cancer. Intriguingly, this study revealed that obese endometrial cancer patients had a higher mortality from causes not related to their cancer. Thus, ensuring that other adverse health effects of obesity are being minimized and monitored while the patient receives cancer care may be the key to protecting longevity and QOL in this group of women.

Obese endometrial cancer patients often have significant co-existing medical conditions, such as hypertension, cardiovascular disease and diabetes, all of which affect many aspects of QOL. Two recent studies have revealed that obese endometrial cancer survivors also have lower QOL related to mood. However, QOL was higher in endometrial cancer survivors who exercise. Understanding this connection, physicians and patients can mutually develop a comprehensive plan of care that incorporates exercise whenever permissible around cancer care treatments.

Moving beyond the effects of obesity, all women with endometrial cancer are concerned with how their treatment will affect their QOL. In 2006, investigators from the GOG prospectively compared QOL outcomes in patients with advanced endometrial cancer treated in two different ways. Following surgery, half of the patients were treated with whole abdominal radiation and half with chemotherapy using two of the most active drugs in this disease, doxorubicin and cisplatin. The chemotherapy treatment group had better survival compared to the radiation treatment group; however, the QOL concerns were different in the two groups. A condition called neuropathy, numbness in the fingers and toes, was significantly worse at the completion of chemotherapy treatments and 6 months later when compared to the women who received radiation therapy. For individual patients, understanding the survival implications in the context of specific QOL issues for each reasonable therapeutic option may help guide selection of therapy.

QOL in **ovarian cancer patients** is affected by surgery and chemotherapy. In 2006, researchers at the University Hospitals of Cleveland prospectively followed ovarian cancer patients from before surgery and into remission. Not surprisingly, they found that surgery had a large impact on physical QOL and fatigue. This pattern continued during chemotherapy and did not resolve until the patient was off therapy and in remission. This information is useful in guiding newly diagnosed patients in making realistic plans for family, work and social needs.

In 2007, the GOG measured QOL during and after intraperitoneal (IP) versus intravenous (IV) chemotherapy in women with ovarian cancer. During active treatment, women getting IP therapy experienced more disruption of their QOL, including having more abdominal discomfort and neuropathy, compared with the women who received IV therapy. Although most of the negative impact of IP treatment on QOL resolved, neuropathy remained a problem for IP patients one year after treatment.

There is less QOL research on ovarian cancer survivors than in women who are in active treatment. However, a GOG study from 2002 revealed that ovarian cancer survivors have fear of follow-up diagnostic testing and a fear of recurrence. In addition, over 50 percent were interested in support programs during therapy. A more recent GOG study found that in survivors of ovarian germ cell tumors, confidence and social support played a significant role in QOL.

Women at high risk for ovarian and breast cancers also face specific QOL concerns. For these women cancer prevention options include the surgical removal of both ovaries. In some women, this surgery may be advised even as young as their early 30s in order to reduce cancer risk. High-risk women must consider the side effects and health consequences of early estrogen loss versus the stress of living with the fear of developing cancer and the very real risk of dying of ovarian cancer. An ongoing GOG trial is now evaluating the global health and QOL effects of these decisions. Participating women answer multiple questions about their health and well-being before and at intervals after their risk-reducing surgery. Others, who choose to participate in careful monitoring rather than surgery, answer the same questions over time. In the future, the results of this study will allow high-risk women to face this complex decision aided by the experience and detailed reports from hundreds of women who faced similar risk.

Overall, most **cervical cancer** survivors report a good QOL. However, for women with advanced cervical cancer who are treated with a combination of radiation and chemotherapy, there is concern for reduced QOL and sexual functioning when compared to women with early stage disease that is treated by surgery alone. For those patients needing treatment with chemotherapy, there does not appear to be a difference in effect on QOL based upon which drugs are used. The significant impact of QOL assessment was evident in a recent GOG trial involving a four-drug regimen that appeared to be active in the treatment of cervical cancer. Though probably effective, this four-drug regimen was abandoned due to excess, and sometimes life-threatening, side effects.

Cervical cancer is known to disproportionately affect young women, often striking before childbearing is complete. Recent advances in fertility sparing surgery for early stage cervical cancer reflect the commitment of gynecologic oncologists to offer effective cancer therapy without the devastating effect of infertility for young women with cervical cancer. Preliminary data from an ongoing study of women who have been treated with fertility sparing surgery for cervical cancer shows that concerns and worries about their reproductive QOL persist long after they have completed treatment.

The traditional surgery for cervical cancer, known as a radical hysterectomy, produces numbness in the bladder, difficulty with bladder emptying and frequent constipation. Newer approaches to radical hysterectomy are being developed that allow preservation of the nerve branches to promote normal bladder and bowel function after cancer treatment. A recent report of nerve-sparing radical hysterectomy showed that women treated with this procedure resumed normal bladder function sooner than women treated with the standard radical procedure.

Finally, QOL studies have revealed, that similar to women with ovarian cancer, cervical cancer survivors are interested in counseling programs and support groups that can improve the psychological and social aspects of their QOL.

Summary

Quality of life for cancer patients is a topic integral to the progress made in cancer care. With advances in treatment, women with reproductive cancers are surviving longer and achieving a complete cure more frequently than in the past. The human spirit demands that life be fulfilling and suffering made manageable in order to make life worth living. Progress in cure rates have led to the new focus on quality of life in research, and today, clinical trials have built in QOL measures, so that researchers determine both benefits of a new therapy — and the “cost” in terms of QOL. By improving quality of life for women with gynecologic cancer, the quality of the experience is improved throughout the continuum of care. The ultimate goal is to improve a range of outcomes important to patients, caregivers, families and physicians, and improve both survival and quality of life for women with reproductive cancer.

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. Cervical cancer is caused by abnormal cellular changes in the cervix and is the only gynecologic cancer that can be prevented by regular screening. Now, in addition to screening, women can be protected by early vaccination with a new vaccine that targets the causative agent of cervical cancer, Human Papillomavirus (HPV). Early vaccination along with regular Pap tests and HPV testing when recommended by a health care provider is now the best way to prevent cervical cancer. Cervical cancer usually affects women between the ages of 30 and 55, but has been found as early as the teen years.

Symptoms: Bleeding after intercourse, excessive discharge and abnormal bleeding between periods.

Risk Factors: Infection with persistent 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 cervical disease. Other risk factors include smoking, HIV infection and starting to have sexual intercourse at a young age. Failure to get regular gynecologic examinations eliminates the opportunity for early diagnosis through cervical cancer screening.

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 percent. A Pap test is a standard way health care providers can check to see if there are any cervical cell changes 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, health care 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 the meaning of their Pap test results, and follow through with any recommendations made by their health care provider.

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, Gardasil[®], 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 precancerous lesions of the cervix, vulva and vagina. Early vaccination with regular screening, which includes a Pap test and HPV test when recommended according to standard guidelines, is now the most effective strategy to prevent cervical cancer.

Incidence: It is estimated that there will be about 11,150 new cases of invasive cervical cancer diagnosed and approximately 3,670 deaths in the United States during 2007.²

² American Cancer Society. Cancer Facts & Figures, 2007. Available at: http://www.cancer.org/docroot/stt/stt_0.asp. Accessed April 19, 2007.

Advances in Cervical Cancer

This 2007 *State of the State of Gynecologic Cancers* will be released roughly one year following FDA approval of the first vaccine for the prevention of cervical cancer. The past year has been marked by continued rapid progress in cervical cancer prevention, as well as steady progress in the treatment of cervical cancer. A key to the rapid progress in prevention has been the detailed understanding of the cause of cervical cancer. Due to major discoveries in molecular biology in the 1980's, HPV was identified as the cause of cervical cancer. Over 40 types of HPV have been identified in vaginal, vulvar and cervical diseases. Of these, approximately 15 are known to be cancer-causing types, and these types are responsible for virtually all cervical cancer and cervical precancerous lesions. 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 percent to 20 percent.

New HPV vaccines allow healthy girls and women to develop an effective immune response that protects them from being infected with the most dangerous HPV types, 16 and 18. Over 25,000 women have participated in studies of the vaccine Gardasil® and there have been over 27,000 participants in studies of a second vaccine, Cervarix®. Last year reports from clinical trials of the vaccines demonstrated that the vast majority of vaccinated participants were protected from getting infected with HPV types 16 and 18, and from having cervical precancerous lesions. This year, updates to the clinical trials were published, providing further details. One report described outcomes from 20,583 women ages 16–26 followed for an average of 3 years after study entry. Roughly half the group received active vaccine (Gardasil®) and half placebo. Researchers reported 99 percent effectiveness in preventing cervical disease associated with the HPV types found in the vaccines. However, effectiveness dropped to 44 percent in women already exposed to the HPV types found in the vaccine. In this mixed group of women, some previously exposed to the vaccine HPV types and some not, there was an 18 percent reduction in moderate and severe cervical pre-cancerous changes. While news outlets sometimes focused on the negative message of decreased effectiveness in HPV exposed women, it is important to embrace the positive message. The observed 44 percent reduction in HPV 16 and 18-related disease, even in women previously exposed to at least one of these types, substantially influences the risk of developing a deadly disease. This news should motivate women in the recommended age group to seek vaccination, even if they have already had sex. However, it also points out how highly effective the vaccine is in the girls who were vaccinated prior to sex, the most important age group to target for the vaccine. With increased use in girls ages 9–12, we will be able to maximize the effectiveness of this important cervical cancer prevention strategy. Further information supporting early vaccination comes from antibody studies in the youngest age groups included in clinical trials. A recent report describes HPV antibody levels in 10 to 14 year old girls who had antibody levels checked after receiving the recommended 3 doses of Cervarix® in a clinical trial. 100 percent of the 773 girls developed antibodies to HPV 16 and 18 and, notably, the antibody levels were approximately twice as high as those in the 15–25 year old age group. Cervarix® is currently being reviewed by the FDA for licensing in the United States. Similar high antibody levels in the youngest age groups were observed in clinical trials using Gardasil®. The consistency of this observation provides additional support for the recommended time to initiate the HPV vaccine series in the 9–12 year old age group.

With widespread use of these vaccines, it is expected that patient suffering and the economic burden from cervical cancer will decrease by up to 70 percent. These vaccines will also decrease the incidence of vaginal and vulvar pre-cancer changes since these conditions have been shown to be decreased by the vaccine. Clinical trials for new, 'second generation' vaccines, including a vaccine that protects against eight high-risk HPV types that can lead to cervical cancer, are underway. Eventually, it is expected that vaccines currently in development will protect women from the HPV infections that can cause 90 percent or more of cervical cancers. In addition to the second generation prophylactic vaccines, there are novel therapeutic vaccines currently in clinical trials that may help those women already infected with HPV and women with cervical disease. The ultimate impact of HPV vaccination will depend on how widely the vaccines are used and on the continued practice of regular cervical cancer screening according to established guidelines.

Regular cervical cancer screening saves women's lives because the Pap test can detect abnormal cells in the cervix and these cells can then be destroyed before they become invasive cancer. When moderate or severe pre-cancer changes are detected on Pap tests, women are typically treated using a minor surgical procedure called a LEEP or cone biopsy, to remove the abnormal areas of the cervix. Two recent studies from Europe evaluated the outcomes of pregnancies that occurred in women who were treated for pre-cancer of the cervix with a LEEP or cone biopsy. Pre-term delivery, low birth weight infants and premature rupture of the membranes were about two times more common in women who had these procedures than in women who had no treatment. These studies highlight the importance of the need for therapeutic vaccines to treat women already infected with HPV and those that already have cervical precancerous lesions with non-surgical methods. The findings of these studies should also be a reminder to pregnant women to make sure that their obstetric care provider knows of any prior treatment for abnormal Pap tests. Finally, the findings remind young women of the importance of protecting their health by minimizing the number of sexual partners, using condoms every time they have sex and taking advantage of the HPV vaccine.

Progress is also evident in advances occurring in the treatment of invasive cervical cancer. One of the changes involves a gradual shift in the manner in which radiation is delivered to treat cervical cancer. Many radiation experts are now utilizing a technique called intensity-modulated radiotherapy or IMRT. Delivery of radiation using IMRT allows the radiation oncologist more options for giving high-dose radiation treatment to areas of the tumor that need it most, and lower doses to areas where normal tissues are at risk of injury. Although so far there have been no reports from randomized clinical trials of IMRT, early results with this technique show that treatment success is at least as good with conventional radiation, and one recent report indicates that long-term side effects occurred 50 percent less often with IMRT than with conventional radiation treatment.

Surgical therapy for invasive cervical cancer is also changing, and the changes mean better quality of life and easier recovery for women with cervical cancer. Across the country, more gynecologic oncologists are treating cervical cancer with minimally invasive surgery in which the operation is performed using a camera and several small incisions through which surgical instruments are passed. Some gynecologic oncologists are utilizing robotic support to enhance the ability to perform minimally invasive gynecologic oncology surgery. As with IMRT, no randomized clinical trials have been conducted that compare the impact of minimally invasive

and robotic surgery to the standard surgery for cervical cancer. Several reports of cervical cancer patients treated with minimally invasive techniques both in the United States and internationally were published during the past year. The reports consistently show that minimally invasive surgery takes longer than traditional surgery through an abdominal incision, but that patient recovery time is shorter and cancer control rates appear identical.

Further advances in cervical cancer prevention and treatment are being achieved through ongoing research. Better vaccines, currently in clinical trials, will potentially protect a woman from additional cancer-causing HPV types. Progress is being made in the development of vaccines and immunotherapies for women already affected by cervical cancer and pre-cancer. With continued rapid advances in cervical cancer, this decade may mark the beginning of the end of cervical cancer.

For more information about cervical cancer, visit GCF's National Cervical Cancer Public Education Campaign Web site at www.cervicalcancercampaign.org.

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.

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.

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 CA 125 blood tests on an annual or biannual schedule, though the benefits of such screening is unproven. For most women, ultrasound and CA 125 screening is not presently advised due to problems with false positive results leading 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 22,430 new cases diagnosed and approximately 15,280 deaths from ovarian cancer in the United States during 2007.³

³ American Cancer Society. Cancer Facts & Figures, 2007. Available at: http://www.cancer.org/docroot/stt/stt_0.asp. Accessed April 19, 2007.

Advances in Epithelial Ovarian Cancer

The advances in the prevention, detection, treatment and surveillance of epithelial ovarian cancer described in this report are very encouraging. Progress continues on all fronts to overcome this disease. Cancer prevention continues to be an area of high priority within the National Cancer Institute (NCI). The Gynecologic Oncology Group (GOG), sponsored by the NCI, has responded to this challenge by instituting and/or completing a number of clinical trials in the area of chemoprevention (prevention using medication) and surgical prevention.

The GOG will soon launch a new clinical trial investigating the use of progestins as a chemopreventive agent in women at increased risk of developing epithelial ovarian cancer. Epidemiological evidence has shown that routine use of the combined estrogen-progestin oral contraceptive pill (OCP) offers a 30 percent-50 percent reduction in the risk of developing subsequent epithelial ovarian cancer, suggesting that an effective pharmacologic approach for the chemoprevention of ovarian cancer is possible. The evidence suggests that it is the progestin component of the OCP that has preventive biological effects on the ovarian epithelium. Patients recruited to this clinical trial will be women at high risk of developing ovarian cancer and planning to undergo surgery to have their ovaries and fallopian tubes removed to reduce their risk of ovarian cancer. This surgery is called “prophylactic oophorectomy” or “RRSO” (short for risk reducing salpingo-oophorectomy). In this study, the women will be treated with progestins for 6–8 weeks prior to surgery. At the time of surgery, the investigators will sample the ovarian tissue to study specific histopathological and molecular pathways that may be modified by the progestin medication. The goal of this study is to learn more about pathways that protect against ovarian cancer. Other agents that have been shown to modify preventive molecular pathways in laboratory and animal studies include non-steroidal anti-inflammatory agents and eicosanoids, of the omega-3 fatty acid family. These will be the next generation of agents to be studied within a clinical trial setting.

Approximately 10 percent-15 percent of epithelial ovarian cancers are hereditary, often related to mutations of the BRCA1 and BRCA2 gene. There is strong data to show that RRSO in this high-risk population can decrease both the risk of epithelial ovarian cancer and breast cancer by approximately 80 percent and 40 percent respectively. To confirm these findings, the GOG just completed a study of high risk women who requested risk-reducing salpingo-oophorectomy (RRSO) compared to high risk women that opted for longitudinal CA 125 screening with special emphasis on known BRCA1/2 mutation carriers. The main objective of the study was to define the risks and benefits of RRSO and determine, in a prospective manner, the incidence of ovarian, fallopian, breast and primary peritoneal cancer in this high risk population. The study will also quantify the accuracy of serial CA 125 tests in women who have elected not to undergo RRSO. The study was closed to accrual in November of 2006 and results are highly anticipated so as to guide high risk women with the difficult decision of how best to protect their health.

Although no accepted screening test has yet been developed, more knowledge was gained this year about using ultrasound and CA 125 to detect ovarian cancer in its early stages. Preliminary results of screening post-menopausal women in the large and important Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) were recently presented at the Society of Gynecologic Oncologists (SGO) Annual Meeting on Women’s Cancers™. In this study, over 39,000 women who have no symptoms of ovarian cancer are scheduled to have

transvaginal ultrasounds (TVU) done every year for 4 years, as well as a CA 125 blood test performed every year for 6 years. The interim results from the first 4 years show that most of the cancers found with TVU were early stage (77 percent Stage I/II), but most of those found with the CA 125 blood test were advanced (90 percent Stage III/IV). The chances that a woman with an abnormal screening test would actually have ovarian cancer, otherwise known as the positive predictive value of the test (PPV), remained low over the 4 years but showed improvement over time. These initial results show a high rate of unnecessary surgeries and a low rate of ovarian cancer detection. Since the impact on mortality is not yet known for this trial, such monitoring is not currently recommended outside the trial. However, completion of the PLCO trial is highly anticipated to help answer this important question and determine if such intense monitoring may be justified for this deadly cancer.

At the 2007 meeting of the American Society of Clinical Oncology (ASCO), another group of researchers reported on using serial CA 125 blood test results to predict a woman's risk of developing ovarian cancer. The researchers used a method of analyzing serial CA 125 blood tests over time called the Risk of Ovarian Cancer Algorithm or ROCA, to screen 2,300 women who had no symptoms, but were at high risk for developing ovarian cancer. The positive predictive value for ROCA as a screening test was 13 percent, and the sensitivity, or chances that a woman with ovarian cancer had an abnormal test, was 83 percent. These initial results are promising for high-risk women, but confirmation of the value of ROCA as a screening test in women who are not at high risk for ovarian cancer will be necessary. To this end, ROCA is currently being evaluated in a screening trial involving 200,000 postmenopausal women in the United Kingdom (UK Collaborative Trial of Ovarian Cancer Screening, UKCTOCS, www.ukctocs.org). The trial involves the serial measurement of CA 125 (ROCA) as the initial screen followed by transvaginal ultrasound for abnormal serial values. The trial is now closed and results are eagerly anticipated in 2011.

Surgery remains the cornerstone for treatment of epithelial ovarian cancer with early stage disease requiring methodical surgical staging, and advanced disease calling for a maximal surgical effort to remove as much tumor as possible ("debulk" the tumor) followed by chemotherapy. Two recent reports add to the growing number of studies supporting the critical role of the gynecologic oncologist in treating women with ovarian cancer. A study reporting collective data from 19 researchers around the world showed that appropriate staging and debulking of tumor were significantly more likely to be achieved when gynecologic oncologists performed ovarian cancer surgery compared to other types of surgeons. Data from the California Cancer Registry revealed that only 34 percent of women with ovarian cancer were treated by a gynecologic oncologist, and that those women were more likely to be treated according to the accepted standard of care including having surgery as their initial treatment and receiving chemotherapy after surgery. Both studies showed that survival for women with ovarian cancer was improved by having surgery performed by a gynecologic oncologist. Because of data from these and similar studies, an important focus of the continuing effort to improve care for women with ovarian cancer remains encouraging women and their health care providers to seek care from a gynecologic oncologist when ovarian cancer is suspected.

There was continued progress in the search for better treatments for ovarian cancer in the past year including advances in intraperitoneal therapy and the use of biologic agents that target specific pathways that tumor cells depend on to survive. Despite multiple trials in recent years

showing that chemotherapy, when given directly into the abdominal cavity (intraperitoneal or IP therapy) improves survival for women with advanced ovarian cancer, concerns persist within the oncology community regarding the increase in side effects of IP therapy compared to intravenous (IV) treatment. In response, studies aimed at minimizing the side effects of intraperitoneal (IP) chemotherapy while preserving the survival benefit are being conducted. At ASCO and SGO 2007 annual meeting, reports from two such studies were presented. In both studies, one substituting the platinum drug IP carboplatin instead of IP cisplatin and one using a lower dose of IP cisplatin, the side effects of the IP therapy were greatly reduced and early results regarding tumor control were promising.

It has been clearly demonstrated that a rising CA 125 above normal can lead to early detection of recurrent ovarian cancer 3–6 months ahead of any evidence of clinical disease (biochemical recurrence). What is less clear is whether detection of disease ahead of physical or radiographic findings adds a survival benefit. In fact, currently no data exists showing that giving chemotherapy early in patients with biochemical recurrent ovarian cancer results in any form of survival benefit. The Europeans just completed a trial looking at this exact question. Now closed, results are expected in 2008 and will provide important information as to the benefit of chemotherapy in patients whose only evidence of recurrence is a rising CA 125.

While investigators continue to make improvements with IP chemotherapy, agents that take advantage of the specific biology of tumor cells have been introduced into the arsenal of drugs that fight ovarian cancer. A number of biological agents that target specific molecular pathways have been developed and are currently undergoing active clinical testing. CTI-2103 (Xyotax™) is a large molecule that changes the structure of paclitaxel, a drug known to be highly effective against ovarian cancer, by combining it with a large sugar molecule. Being larger than regular paclitaxel, CT-2103 becomes trapped preferentially in the tumor by leaky blood vessels, and can thus minimize exposure and side effects in normal tissues in the body. In a Phase III trial by the Gynecologic Oncology Group, CT-2013 is being compared to standard paclitaxel to compare the two drug's ability to keep ovarian cancer from coming back in women who are in remission after primary surgery and chemotherapy.

Biologic agents that block angiogenesis, or the growth of new blood vessels in tumor tissue, are the focus of other recent studies in ovarian cancer. As most of these agents are in the early stages of transition from the laboratory to the bedside, most information about the anti-angiogenesis agents in ovarian cancer comes from Phase I and Phase II clinical trials. One of the keys to blocking the angiogenesis pathway in cancer cells is interfering with vascular endothelial growth factor (VEGF), the substance that signals new blood vessels to grow. VEGF Trap is a new and promising potent angiogenesis blocker currently in development that works as a decoy receptor, soaking up much of the VEGF in the tumor tissue and preventing it from binding to its intended target. Preliminary results of a Phase II trial, reported at the recent ASCO meeting, showed that VEGF Trap has activity against ovarian cancer in some women whose cancer recurred after they had received 2 or 3 different types of chemotherapy. The results of this small study are promising and will hopefully lead to continued development of agents that target the angiogenesis pathway. Bevacizumab was the first anti-angiogenic agent approved by the Food and Drug Administration for use in oncology patients. Bevacizumab is an antibody that binds to VEGF, thus inactivating its blood vessel growing capacities and inhibiting tumor growth. In 2005, the GOG initiated trial 218; a Phase III randomized trial of carboplatin and paclitaxel with and without bevacizumab in patients with advanced ovarian

cancer. This trial is based on at least four positive Phase III trials in non-gynecologic cancers as well as a Phase II ovarian cancer trial that was sponsored by the GOG. The results showed that bevacizumab was able to shrink ovarian cancer in 20 percent of patients and keep the cancer from progressing in 40 percent of patients with recurrent disease. Results of clinical trials with agents such as CT-2103, VEGF Trap and bevacizumab will be important steps towards establishing the role of biologic agents in developing better treatments for ovarian cancer.

This review summarizes a number of the new and exciting agents now under development in the struggle to overcome ovarian cancer, a debilitating and deadly disease. The Women's Cancer Network (www.wcn.org) offers detailed information about current GOG clinical trials and the National Cancer Institute Clinical Trials Web site (www.cancer.gov) details over 250 clinical trials worldwide related to ovarian cancer. Overall, women with ovarian cancer now live longer and with better qualities of life. This is thanks to the many women who have volunteered their time to participate in clinical trials thus helping pioneer the current standards of care. It is now up to the next generation of physicians and patients to pioneer the next generation of agents that will set the standards of care for this disease.

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 in the cells that produce female hormones and hold the ovarian tissues together.

Symptoms: Stromal cell and germ 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 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 stromal cell and germ 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

In 2007, investigators reported a detailed description of germ cell tumor and stromal cell tumor occurrences in the United States by analyzing data in the Surveillance, Epidemiology, and End Results (SEER) national cancer database. Findings from the stromal cell review are discussed in the following section. Using data from 1988–2001, it was reported that patients diagnosed with germ cell cancers later in life fared worse than those diagnosed at a younger age. As expected, patients with advanced stage tumors and tumors that resembled the yolk sac, a structure seen in the early stages of a developing embryo, had a worse outcome than those patients diagnosed at an earlier stage and without yolk sac appearance of their tumor. Importantly, in those patients in whom the uterus and normal ovary were not removed, survival was identical to girls and women who had more extensive surgery, including removal of the uterus, and both tubes and ovaries. Thus, in girls and women with early stage germ cell cancer who want to have children in the future, conservative surgery that preserves their ability to become pregnant is an appropriate and reasonable option.

A vital area of investigation relates to the quality of life experienced by patients following diagnosis and treatment for germ cell tumors, particularly since this cancer is often diagnosed in women and girls at a young age. Important data regarding the quality of life experienced by survivors of ovarian germ cell cancers was reported in 2007. Patients from four previous Gynecologic Oncology Group (GOG) trials, along with patients enrolled in similar trials through The University of Texas M.D. Anderson Cancer Center, were contacted to participate in this study. At a median of 10 years following their chemotherapy, 132 patients were evaluated for their physical, psychosocial, sexual and spiritual function. In this group of patients, all of whom completed chemotherapy for ovarian germ cell cancers, function in all categories was better in patients who reported better self-confidence and social support. Sexual function was better in younger and married survivors. Neurologic toxicity was common in all patients requiring chemotherapy with platinum drugs, and was the strongest factor affecting physical function in the women participating in this study. These data suggest that clinicians caring for patients with ovarian germ cell cancers should be sensitive to social support and self-confidence in order to promote the highest quality of life following cancer treatment. In a study comparing these women with a matched set of women without ovarian germ cell cancers matched for age, race and education, of those women who remained potentially fertile after surgery, the majority (88 percent) had menstrual cycles. Compared with those women without cancer, cancer survivors experienced greater reproductive concerns, less sexual pleasure, but had a better ability to establish and maintain close relationships.

Currently, researchers are investigating novel approaches to the treatment of patients with ovarian germ cell cancers. Along with the investigation of high-dose chemotherapy with stem cell transplantation, other agents such as those that target specific cancer-causing changes are being investigated in clinical trials. Two such agents are sunitinib and bevacizumab, which block the formation of new blood vessels (angiogenesis), thereby limiting tumor growth and spread. These agents are currently being studied in patients with ovarian germ cell cancers.

Most women with ovarian germ cell cancer are treated with chemotherapy after surgery has removed the primary tumor. Since many patients with this cancer are diagnosed at a young age, side effects of chemotherapy can have a lasting impact on many aspects of their lives. In an effort to improve the quality of life of patients with germ cell cancer, the Children's Oncology Group (COG) has an ongoing study of the safety and effectiveness of giving fewer patients chemotherapy after surgery that will soon be supported by the GOG. In this trial, patients 21 years old and younger with early stage germ cell cancers of the ovary are closely monitored after surgery using blood tests, physical examinations, and imaging studies to look for signs that their cancer has recurred. Instead of all patients getting chemotherapy, only those with evidence of recurrence based on these tests receive treatment. In a related effort to reduce chemotherapy related side effects, carefully selected patients who are treated with chemotherapy as part of this trial get a shorter three-day course of a three-drug combination called BEP, rather than the traditional standard of five days of treatment with each cycle.

Advances in Stromal Ovarian Cancer

Stromal cell cancers of the ovary are rare, accounting for only about five percent of all ovarian cancers. Stromal cancers tend to be slow growing tumors and, although they are less likely to recur, they display less sensitivity to chemotherapy when recurrences are detected. These tumors can recur 10 to 15 years or more after first diagnosis. The most common type of stromal cell cancer is granulosa cell tumor. A special subtype, the juvenile granulosa cell tumor, principally occurs in girls, whereas the more common adult type may occur at any age, most commonly in the postmenopausal age group.

Earlier this year investigators reported data regarding the factors that impact survival of women diagnosed with stromal cell ovarian cancer. Using data from the SEER database, it was recognized that patients diagnosed with stromal cell cancers at an earlier age and with earlier stage disease had a better survival than those patients diagnosed after the age of 50. The age difference was most apparent in patients with early stage tumors. As with germ cell tumors, the investigators found that in those patients in whom the uterus and unaffected ovary were not removed, survival was identical to that of patients who had more extensive surgery, including hysterectomy and removal of both ovaries. This is important and good news for girls and women with stromal cell tumors who wish to maintain the option of future pregnancy.

In patients with ovarian granulosa cell tumors, response to therapy has been evaluated using a blood test called inhibin. Rising inhibin levels offer a clue that a granulosa cell tumor may be growing or may have recurred after a period of remission. Scientists have described two different but related inhibin component parts referred to as inhibin A and inhibin B. Recently, investigators have demonstrated that inhibin B may be a better indicator for granulosa cell tumor. In blood samples obtained at the time of first diagnosis, inhibin B levels were elevated in 89 percent of patients while inhibin A levels were elevated in 67 percent. Though this is a small study, it may lead to better diagnostic testing for this rare tumor.

Recent advances in the basic science investigations of ovarian stromal cell cancers include studies of novel genetic changes in these tumors that could aid in their early detection, diagnosis and treatment. One gene of interest is FOXL2. Preliminary data shows that FOXL2 has reduced expression in many ovarian granulosa cell tumors, and that in more advanced cancers, expression is reduced compared with early stage cancers. These data suggest that FOXL2 may be a tumor suppressor gene for granulosa cell tumors, meaning it functions to block the growth of this type of cancer cell. Clues such as this may someday provide researchers with new strategies to treat granulosa cell tumors and other ovarian stromal cancers.

Uterine Cancer: Endometrial

State of Endometrial Cancer

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

Symptoms: Most cases of endometrial cancer occur in women after menopause. The most common warning sign is any bleeding after menopause. Younger women may develop endometrial cancer and may notice irregular or heavy vaginal bleeding.

Risk Factors: Risk factors for endometrial cancer include obesity, hypertension, diabetes, use of estrogen without progesterone, tamoxifen use and late menopause. Women who have not been pregnant also have a slightly higher risk for endometrial cancer.

Screening/Prevention: Currently, there are no screening tests for endometrial cancer that are recommended on a routine basis. The Pap test is designed to find cervical cancers and its precursors, not endometrial cancer. A woman may lower her risk for developing endometrial cancer by exercising regularly, eating a healthy diet and maintaining a healthy weight. Keeping blood sugar and blood pressure under control also helps lower the risk. Women with unexpected postmenopausal bleeding or heavy, prolonged or unexpected bleeding during the menstruating years should have an endometrial biopsy to check for endometrial cancer.

Incidence: Cancer of the endometrium is the most common reproductive cancer. It is estimated that there will be about 39,080 new cases diagnosed and approximately 7,400 deaths from endometrial cancer in the United States during 2007.⁴

Advances in Endometrial Cancer

Endometrial cancer is the second most common gynecologic cancer in the world, and is the most common in developed countries. Nearly 50 percent of all gynecologic cancers diagnosed in the United States will be from the uterus. Because of this, there is a continued interest in improving the understanding of endometrial cancer and in developing better treatments.

In November 2006, a meeting jointly sponsored by the National Cancer Institute, the National Cancer Research Institute and the Gynecologic Cancer Intergroup was held in the United Kingdom to define the “State of the Science” in endometrial cancer and discuss important research objectives. A multi-disciplinary group of 75 physicians and research scientists from 18 countries met to review the current knowledge about endometrial cancer and its treatments, and to work together to develop key research questions that clinical trials should address in the immediate future. This meeting resulted in the first-ever international collaborative effort dedicated to advancing the care of women with endometrial cancer.

⁴ American Cancer Society. Cancer Facts & Figures, 2007. Available at: http://www.cancer.org/docroot/stt/stt_0.asp. Accessed April 19, 2007.

Today, one of the key research issues in endometrial cancer relates to developing a more comprehensive and detailed understanding of cancers at a genetic and molecular level. One such large research effort involves a 3,500 patient trial conducted by the Gynecologic Oncology Group (GOG), of patients with endometrial cancer who are scheduled to undergo surgery. These patients donate samples of their blood, urine and cancer tissue to create a large tumor bank. Researchers will analyze the samples to determine what biologic, molecular and genetic changes are responsible for endometrial cancer spread (metastases), and which changes predict response to particular treatments (radiation, chemotherapy, hormonal therapy). Information about each patient's exposures to risk factors for developing endometrial cancer including estrogen use, family history and obesity will be linked to the patient's history as well as to particular molecular changes in the tumors. Through this unprecedented detailed study of endometrial cancer patients, researchers hope to foster new understanding of this cancer that will lead to promising avenues for treatment and prevention. This trial is near completion of collection of specimens for analysis, but will require several years of follow-up before conclusions may be reached.

An example of using knowledge of the tumor biology to develop new treatments for endometrial cancer is seen in two recent studies that tested drugs which target important steps in a cancer cell's life. One particular genetic change frequently seen in endometrial cancer is a mutation of the PTEN gene. Damage to the PTEN gene may lead to loss of control of signals in the cancer cell and lead to uncontrolled growth. One class of agents which may block the uncontrolled growth resulting from the PTEN gene mutation is called an mTOR inhibitor (The abbreviated name stands for "mammalian target of rapamycin"). mTOR inhibitor drugs are quite recent developments in cancer fighting agents. Like most newly introduced cancer drugs, they have been studied primarily in patients with advanced disease. In one study of an mTOR inhibitor, 25 percent of patients had shrinkage of their tumor and 57 percent had no growth of their tumor for a long period of time. At the 2007 the American Society of Clinical Oncologists (ASCO) meeting, preliminary results of a different mTOR inhibitor showed that 1/3 of treated patients had shrinkage, or no growth, of their cancer. Because these drugs interact with a signal that is absent from most normal cells, they have far fewer side effects than most chemotherapy drugs.

Although most women who develop endometrial cancer are past the age of menopause, about 1/4 of cases are found in women younger than 50 at the time of diagnosis. Recently investigators, using the SEER national cancer database, reported results from a study of over 900 women who were age 35 years or younger when their endometrial cancer was found. Younger women were more likely to be diagnosed with early-stage, low-grade cancers than women over 35, and had better survival than older women, including women with the same stage of cancer. Responding to what appears to be an increasing incidence of endometrial cancer in young women, researchers are searching for treatments that will preserve the option for future childbearing in this group of patients. Investigators from 16 institutions in Japan recently published results of a prospective clinical trial of six months of daily hormonal treatment with medroxyprogesterone acetate (MPA) in young women (age less than 40 years) with endometrial cancer, or a form of endometrial pre-cancer called atypical hyperplasia. Treatment with daily MPA destroyed the hyperplasia and cancer cells in 2/3 of patients, and 15 percent had a pregnancy and normal delivery. However, almost half had recurrence of pre-cancer changes, reminding all that women who are treated in this manner must be monitored closely.

Following surgery, some patients with endometrial cancer can be categorized as low risk for recurrence and do not require additional treatment. For patients with higher-risk tumors, controversy exists as to which patients should receive additional therapy and what type of treatment is best. In one study from Canada and the United Kingdom, 906 patients with endometrial cancer factors that placed them at higher risk for recurrence were assigned to receive either pelvic radiation therapy or no treatment following surgery. Preliminary results showed that although patients who got radiation had fewer recurrences of cancer in the pelvis (the radiated field), they had the same survival rates as patients who got no treatment. Another trial evaluated a similar patient population and compared pelvic radiation to radiation plus chemotherapy. In this trial, the addition of chemotherapy improved outcomes. It remains to be determined whether chemotherapy by itself is sufficient therapy and what chemotherapy regimen should be used.

Patients with the most advanced tumors continue to present a treatment challenge. For patients whose cancer has spread outside of the uterus at the time of diagnosis (Stage III-IV), chemotherapy has been increasingly used as a treatment option. Many oncologists are treating patients with endometrial cancer using chemotherapy drugs commonly utilized in ovarian cancer, such as paclitaxel and carboplatin. The GOG is currently comparing a 3-drug regimen (doxorubicin, cisplatin and paclitaxel) to a 2-drug regimen (paclitaxel and carboplatin) in patients with advanced stage or recurrent endometrial cancer. Following the international “State of the Science” meeting mentioned earlier in this report, research groups, such as the GOG, have been charged with conducting studies evaluating the best combinations of chemotherapy with and without radiation therapy.

Each year studies show continued progress in the understanding of the prevention, diagnosis and treatment of endometrial cancer. Moving toward a better understanding of the specific biologic changes that occur in endometrial cancer cells will accelerate these gains. Advances will be made by the continued commitment patients and their physicians make to research efforts such as the studies discussed in this review.

Uterine Cancer: Uterine Sarcomas

State of Uterine Sarcomas

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). Endometrial adenocarcinoma (see prior section) is the most common type of uterine malignancy. However, uterine sarcomas, which account for fewer than five percent of all uterine cancers, are associated with a much more aggressive clinical behavior.

Symptoms: Abnormal vaginal bleeding, especially after menopause, is the most common symptom in women with uterine sarcomas. Sarcomas can also produce pelvic pain or pressure. In addition, a rapidly-growing fibroid, especially during the post-menopausal period, should raise the suspicion of a leiomyosarcoma.

Risk Factors: Sarcomas have been reported to occur more frequently in women after pelvic radiation therapy. National statistics show that the incidence of these rare malignancies is twice as high in black women as in other racial groups.

Screening/Prevention: Due to their rarity, there is no proven effective screening method for these cancers. In addition, there are no known methods of prevention available for this disease.

Incidence: There are approximately 39,080 cases of uterine cancer annually, and sarcomas comprise two percent to four percent of these cases.⁵

Advances in Uterine Sarcomas

Uterine sarcomas represent a mixed group of cancers with varied clinical behaviors. Effective treatment for one type of sarcoma may not be valid for another. Therefore, readers should be cautioned against making generalizations based on investigations directed at a specific type of uterine sarcoma.

Surgery continues to be the most important initial treatment for uterine sarcomas of all types. As in endometrial cancer, lymph node metastases occur in significant number of patients with apparent early carcinosarcomas and endometrial stromal sarcomas. Women with these diagnoses should have comprehensive surgery, including removal of the uterus, fallopian tubes and ovaries, and regional lymph nodes. The role for removal of lymph nodes and for removal of apparently normal ovaries in uterine leiomyosarcoma is less clear.

Radiation therapy is often recommended in the postoperative treatment of uterine sarcomas. The European Organization for Research and Treatment of Cancer (EORTC) performed a study that compared pelvic radiation after surgery to observation with no additional treatment in patients with early stage uterine sarcoma. Although the final results are not yet available, a preliminary report suggests that pelvic radiation does not improve overall survival for any of the

⁵ American Cancer Society. Detailed Guide: Uterine Sarcoma. What Are the Key Statistics for Uterine Sarcoma? Available at: http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=63. Accessed April 29, 2007.

uterine sarcomas. However, radiation appears to decrease the risk of pelvic recurrences in patients with carcinosarcomas. Although improvements in survival are not seen, the decrease in pelvic recurrence may offer benefit in quality of life, and needs to be considered carefully by patients with carcinosarcoma and their cancer treatment team. No radiation benefit was noted for patients with uterine leiomyosarcoma. Conclusions for women with endometrial stromal sarcoma are difficult as only a small number of patients with this type of sarcoma were included in this study.

Ifosfamide is an active agent in the treatment of uterine carcinosarcoma. In a randomized Gynecologic Oncology Group investigation of patients with advanced uterine carcinosarcoma, the combination of paclitaxel (Taxol) and ifosfamide was associated with significantly improved overall survival compared with ifosfamide alone. However, the survival rate with this combination treatment is not yet optimal and new therapeutic agents are needed.

Other than surgery, effective therapies for uterine leiomyosarcoma are limited. A clinical trial of extreme interest for patients with leiomyosarcoma is underway that evaluates a novel postoperative sequential chemotherapy treatment plan and is being conducted by the Sarcoma Alliance for Research through Collaboration (SARC) clinical trials group.

Recently, the Gynecologic Oncology Group evaluated the effect of thalidomide in patients with persistent or recurrent uterine leiomyosarcoma. A small percentage of patients had disease that did not grow while they were treated with this well-tolerated drug, but none of the patients had meaningful shrinkage of their tumor. This clinical trial provides solid data upon which to make the recommendation that thalidomide is not indicated for most patients with uterine leiomyosarcoma.

Hormonal therapy has not been comprehensively evaluated for the treatment of women uterine sarcomas. Endometrial stromal sarcomas are divided into low grade (slow to grow and spread) and high grade (aggressive clinical behavior). The low-grade lesions are often sensitive to hormone treatment. Megace (a potent progestin agent) is commonly recommended for recurrent or advanced low-grade disease. Individual reports of treatment success with newer anti-estrogen medications, such as anastrozole, offer interesting, but relatively untested, options for hormone treatment of low-grade endometrial stromal sarcomas.

Uterine sarcomas are very rare tumors. When a woman is diagnosed with or suspected to have uterine sarcoma, expert consultation with a gynecologic oncologist should be considered. To increase knowledge and continue advancements in treatment, clinical trial participation for women with uterine sarcoma should be encouraged whenever such investigations are available.

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.

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 the commercially available cervical cancer vaccine offers protection against HPV types that are also associated with many vaginal cancers, vaccination may reduce the risk of vaginal cancer.

Incidence: Vaginal cancer is very rare. It is estimated that there will be about 2,140 new cases diagnosed and 790 deaths from vaginal cancer in the United States during 2007.⁶ Vaginal cancer accounts for about 3 percent of reproductive cancers.

Advances in Vaginal Cancer

Because of its rarity, it is not possible to conduct large clinical studies in patients with vaginal cancer, comparing one form of treatment with another. Therefore, much of what is understood in vaginal cancer treatment is borrowed from clinical trials in related other cancers including 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 percent of the tumors, and correctly demonstrated disease

⁶ American Cancer Society. Detailed Guide: Vaginal Cancer. What are the key statistics for vaginal cancer? Available at: http://www.cancer.org/docroot/cr/cr_2_3x.asp?dt=55. Accessed April 19, 2007.

that involved tissues beyond the vagina in 88 percent 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.

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 percent in detecting sites of cancer beyond the pelvis with 73 percent specificity. 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 cancers, if chemotherapy is given along with radiation therapy, cancer control rates and survival significantly improve. Similar to results seen in large clinical trials of women with cervical cancer, a recent study shows that by giving chemotherapy at the same time as radiation to women with vaginal cancer, cancer control rates and survival are improved with an acceptable level of side-effects.

It is hoped that the integration of PET with other novel imaging methods may improve the accuracy of surgery or radiation treatment planning, resulting in improved survival and reduced treatment-related side effects for women with vaginal cancer. 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 rare 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.

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, may reduce the risk of vulvar cancer. Examination of the vulva for changes by a woman at home or by her gynecologist during her yearly pelvic exam may lead to early detection of vulvar cancer. Suspicious or unexplained changes on the vulva should be biopsied by a health care professional.

Incidence: Vulvar cancer is uncommon. It is estimated that there will be about 3,490 new cases diagnosed and approximately 880 deaths from vulvar cancer in the United States during 2007.⁷ 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 which results from having the majority of regional lymph nodes removed just to find one or two that contain cancer cells. One of the most significant advances in surgical oncology, sentinel lymph node biopsy, offers the potential to address both of these issues. The sentinel lymph node is the node that is most directly connected to the 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

⁷ American Cancer Society. Detailed Guide:Vulvar Cancer. What are the key statistics for vulvar cancer? Available at: http://www.cancer.org/docroot/cr/cr_2_3x.asp?dt=45. Accessed April 29, 2007.

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 selected patients. Recently, data from three small studies of patients in Canada, Finland and Spain showed that the sentinel node procedure can be performed safely and can accurately identify spread to the lymph nodes in women with vulvar cancer. Larger clinical trials that investigators hope will prove the value of lymphatic mapping for vulvar cancer are underway in the United States and Europe, including an important prospective study sponsored by the Gynecologic Oncology Group that continues to enroll patients.

Another area of progress in the treatment of vulvar cancer is the use of a combination of types of therapy 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 organ function for patients who might have lost rectal, bladder or sexual function from surgical therapy alone.

Finally, there continue to be efforts on the part of researchers to reduce the damaging side effects of radical surgery and radiation used to treat vulvar cancer. New, less invasive surgical techniques and agents that can protect normal tissue from the side effects of radiation are being tested in clinical trials. To benefit from the growing knowledge about the best treatments for this rare disease gained from these trials, women with known or suspected vulvar cancer should be evaluated by a gynecologic oncologist.

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Medical Editors

Bobbie S. Gostout, MD

Associate Professor
Gynecologic Surgery
Mayo Clinic
Rochester, MN

Carol L. Brown, MD

Assistant Attending Surgeon
Memorial Sloan-Kettering Cancer Center
New York, NY

Editor

Marsha Tanner Wilson, MPH

Director of Communications
Gynecologic Cancer Foundation
Chicago, IL

Contributors

David E. Cohn, MD

Associate Professor
Division of Gynecologic Oncology
The Ohio State University
Columbus, OH

Mark H. Einstein, MD, MS

Assistant Professor
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, NY

Robert L. Giuntoli, II, MD

Assistant Professor
Johns Hopkins Medicine
Kelly Gynecologic Oncology Service
Baltimore, MD

Jean A. Hurteau, MD

Professor, Obstetrics and Gynecology
Northwestern University
Feinberg School of Medicine
Division of Gynecologic Oncology
Evanston Northwestern Healthcare
Evanston, IL

Charles Levenback, MD

Associate Professor
The University of Texas M.D. Anderson
Cancer Center
Houston, TX

D. Scott McMeekin, MD

Associate Professor
Director of Fellowship in
Gynecologic Oncology
Oklahoma University Health Science Center
Oklahoma City, OK

David H. Moore, MD

Gynecologic Oncology of Indiana
Indianapolis, IN

Vivian E. von Gruenigen, MD

Associate Professor
University Hospitals of Cleveland
MacDonald Women's Hospital
Cleveland, OH

Gynecologic Cancer Foundation

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Rochester, MN

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New York, NY

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Deloitte Consulting, LLP
San Francisco, CA

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Columbia University
New York, NY

Communications Committee Chair

Bobbie S. Gostout, MD
Mayo Clinic
Rochester, MN

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Cedars-Sinai Medical Center-UCLA
Los Angeles, CA

Advocacy Committee Chair

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

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Chicago, IL

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Duke University Medical Center
Durham, NC

Jeff Boyd, PhD
Memorial Health University Medical Center
Savannah, GA

Eva Chalas, MD
Long Island Gynecologic Oncologists, PC
Smithtown, NY

Robert L. Coleman, MD
The University of Texas M.D. Anderson
Cancer Center
Houston, TX

Larry J. Copeland, MD
The Ohio State University —
James Cancer Center
Columbus, OH

Mark H. Einstein, MD, MS
Montefiore Medical Center
Bronx, NY

Wesley C. Fowler, Jr., MD
University of North Carolina School
of Medicine
Chapel Hill, NC

Ginger J. Gardner, MD
Memorial Sloan-Kettering Medical Center
New York, NY

Carolyn Muller, MD
University of New Mexico
Albuquerque, NM

Cheryl C. Saenz, MD
Moores UCSD Cancer Center
La Jolla, CA

Vivian E. von Gruenigen, MD
University Hospitals of Cleveland
McDonald Women's Hospital
Cleveland, OH

Awareness. Education. Research.



230 W. Monroe, Suite 2528
Chicago, IL 60606
312.578.1439
info@thegcf.org
www.thegcf.org
www.wcn.org

230 W. Monroe, Suite 710
Chicago, IL 60606
312.235.4060
sgo@sgo.org
www.sgo.org



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