In 2012, ovarian cancer, the eighth most common cancer and fifth most common cause of cancer-related deaths in the United States, will affect more than 22,000 women, and in excess of 15,000 will die from the disease. It is the most lethal of all female reproductive cancers. Although the term suggests the ovary as the site of origin, recent analyses suggest the fallopian tube and the peritoneal cavity are also likely sources of this disease’s process. The chance a woman will develop this disease during her lifetime is 1 in 70. The majority of patients are Caucasian, and more than half are 65 years or older at diagnosis. More often than not the disease is diagnosed at an advanced stage (III/IV).

Risk factors for the disease include deleterious mutations of the BRCA1 and BRCA2 genes, family history, increased age, early menarche, late menopause, and nulliparity.

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The disease has previously been described as silent, but studies have indicated clusters of symptoms are more common in women with this disease process. In 2007, the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society issued a consensus statement on symptoms of ovarian cancer. Women and their health care providers were advised to consider symptoms that were new and persistent to include bloating, early satiety, abdominal pain, and urinary frequency and urgency as possible indicators of the disease. Comprehensive gynecological examination and directed imaging were recommended for these individuals.

The majority of ovarian cancers are epithelial in nature and include serous, mucinous, endometrioid, clear cell, and transitional cell tumors. Sex-cord and germ-cell tumors are less common, as are borderline tumors, also known as atypical proliferative tumors, or tumors of low malignant potential. Extensive pathological sampling is required to establish diagnosis.

Previously considered to be a low-grade and non-aggressive lesion, heterogeneity of this group has helped identify subsets of patients who may benefit from additional therapy. Consideration of the cell type, stage, implant type (invasive vs. noninvasive), micropapillary features (for serous tumors), and presence of microinvasion can help identify patients at risk for recurrence. Overall, serous and mucinous borderline tumors have survival rates ranging from 75% to 95%.

Surgical approaches for a patient with suspected ovarian cancer include an adequate abdominal incision to view and palpate all the abdominal organs and surfaces. In patients who have completed childbirth, a hysterectomy and bilateral salpingo-oophorectomy is advised. Staging is performed for disease that appears to be confined to the ovary or ovaries, and includes removal of the omentum, extensive sampling of the peritoneal surfaces in the pelvis and abdomen, removal of both pelvic and para-aortic lymph nodes, and directed biopsies of any suspicious lesions. In women of childbearing age who have disease that appears to be confined to one ovary, the preservation of the uterus and contra-lateral ovary is often feasible. Careful inspection of this ovary is required, and providing that the ovary and uterus appear to be normal, there is no role for a biopsy or bivalving this structure.

In patients with spread of disease, an effort is made to optimally remove or debulk all visible disease, or if not possible, all remaining disease to less than 1 cm.

**Case Report**

N.K. is a 28-year-old woman who presented to her gynecologist after experiencing several weeks of abdominal pain. During examination, a 10 cm left side mass was palpitated. N.K. underwent radiographic imaging, which demonstrated the mass to be solid and rising in the region of the left adnexa. There was no evidence of ascites, adenopathy, or intra-abdominal metastases. A left adnexal mass was confirmed on ultrasound and CT scan. The mass was located in the left ovary and was noted to be fixed to the omentum, indicating possible ovarian malignancy. Due to the size of the mass, it was felt that the ovaries could not be removed at this time. The case was presented to the Magee-Womens Gynecologic Cancer Program’s multidisciplinary tumor board, where her situation was reviewed and deliberated with a final recommendation for cytotoxic chemotherapy for three cycles utilizing carboplatin and taxol. The basis of the recommendation was the serious nature of the tumor, along with evidence of disease on the surface of the ovary.

The Gynecologic Cancer Program performed a randomized Phase III trial comparing three to six cycles of carboplatin and taxol in early stage high-risk ovarian cancer. High risk was defined as Stage IA grade 3, Stage IB grade 3, and Stage IC all grades, as well as completely resected Stage II disease. There were 457 patients with median age of 55 and majority (69%) with Stage I disease. Median follow-up was 6.4 years, and while both groups had similar recurrence rates, the cohort treated with six cycles of therapy had higher rates of grade 3 and 4 toxicities.

Because N.K. had one remaining ovary and was in need of chemotherapy, she consulted her gynecologic oncologist for fertility preservation options. (Both the American Society of Clinical Oncology and the American Society for Reproductive Medicine have issued guidelines that cancer patients should be informed of their options for fertility preservation and future reproduction before cancer treatment.) After medical clearance was obtained, N.K. decided to do an in vitro fertilization (IVF) cycle and freeze her embryos prior to chemotherapy. IVF and embryo cryopreservation, as well as semen cryopreservation, are the current standards-of-care most likely to enable a patient to start a family in the future. The patient had a great response to the medication and was able to cryopreserve 15 embryos. In addition, she opted to use Lupron Depot® during her chemotherapy. Lupron Depot use is controversial and still being studied, but the mechanism of Lupron Depot suppresses the estrogen levels and, therefore, decreases activity and blood flow to the ovaries. N.K.’s menses resumed within two months of discontinuing chemotherapy. She was followed with clinical exams and computed tomography scans for one-year period without evidence of recurrence. N.K. was fortunate in that she conceived shortly after receiving oncology clearance. She did not require embryo transfer. She delivered a healthy baby boy and is without evidence of disease two years out from her diagnosis.

**References**


As cancer therapies become more successful and patient survival improves, quality of life issues such as fertility, following cancer therapy, become more significant. Unfortunately, many cancer therapies can impair fertility due to their non-specific toxicity. However, both oncologists and reproductive endocrinologists are now more aware of the risk of infertility following cancer treatment, and methods to preserve fertility prior to cancer therapy are being explored. Thanks to the Fertility Preservation Program of Pittsburgh at the Center for Fertility and Reproductive Endocrinology (CFRE) at Magee-Womens Hospital of UPMC, fertility preservation options are available for women, men, boys, and girls in the western Pennsylvania region and beyond.

### Options for Women and Girls
Women and girls who have reached menarche are able to undergo ovarian stimulation with follicle stimulating hormone (FSH). Eggs from these follicles are then removed and frozen either as eggs (oocyte cryopreservation), or fertilized with sperm and then frozen as embryos (embryo cryopreservation). It generally takes about two to three weeks to prepare for and complete an ovarian stimulation cycle. Embryo cryopreservation is the only fertility preservation procedure for women considered to be standard-of-care, as embryos have been successfully frozen and thawed for years.

After cancer treatment is complete and remission is achieved, women who previously froze embryos can then use them to attempt pregnancy. Oocyte cryopreservation, in which eggs are frozen prior to fertilization, is still considered to be experimental by the American Society of Reproductive Medicine. While this technology has not been around as long as embryo cryopreservation, more than 1,000 babies have been born from previously frozen oocytes. Oocyte cryopreservation is a good option for women who are single, and wish to retain reproductive freedom by not fertilizing their eggs using donor sperm. Currently, the CFRE performs oocyte cryopreservation under an IRB-approved protocol.

For women who are not able to undergo ovarian stimulation due to time constraints, and for prepubertal girls who cannot undergo ovarian stimulation, ovarian tissue cryopreservation is another experimental fertility preservation option offered by the Fertility Preservation Program of Pittsburgh. In this procedure, ovarian tissue is removed laparoscopically and the cortical tissue where oocytes are located is processed and frozen. Later, this tissue can be transplanted back to the remaining ovary in order to restore ovarian function and achieve pregnancy. Although there are several case reports documenting pregnancy following such transplants, the numbers are still low and the efficiency of the process cannot yet be adequately determined.

### Options for Men and Boys
Men and boys who have reached puberty are able to collect and freeze sperm prior to cancer therapy. This sperm can then be used in the future to achieve pregnancy in a female partner either through intrauterine inseminations or through in vitro fertilization (IVF). Cryopreservation of sperm is the only fertility preservation option in males considered to be non-experimental.

For prepubertal boys who do not yet produce sperm and for men who are unable to collect sperm through ejaculation, a testicular biopsy or orchiectomy can be performed to collect testicular tissue. This testicular tissue contains stem cells from which sperm are derived. The stem cells within this tissue can be frozen and then utilized in the future to be either transplanted back into the testis to regenerate sperm production, or grown and differentiated outside the body (in vitro) to generate sperm. Although these techniques have not yet been performed to achieve pregnancy in humans, researchers are optimistic that this will be possible in the near future. Additionally, for men and boys who have reached adolescence, this tissue also can be examined to see if sperm are present (testicular sperm extraction – TESE), in which case sperm also can be frozen from the testicular tissue. The Fertility Preservation Program of Pittsburgh does currently performs testicular tissue cryopreservation under an IRB-approved protocol.

For further information or patient referrals, call the Fertility Preservation Program at 412-641-7475.
Ms. X is a 63-year-old, para 2, post-menopausal woman with significant medical comorbidities, including obesity (BMI of 38), diabetes mellitus, hypertension, hypothyroidism, hypercholesterolemia, and coronary artery disease, with post-cardiac catheterizations.

At age 38, Ms. X had a total abdominal hysterectomy for fibroid menorrhagia. Both ovaries and tubes were preserved. One month later, Ms. X presented to her gynecologist with a one-month history of pelvic pressure and left iliac fossa discomfort. Following initial evaluation, Ms. X was referred to the Magee-Womens Gynecologic Cancer Program.

Clinical evaluation confirmed the presence of moderate tenderness and fullness in the left iliac fossa, giving an impression of a mass. Her body habitus did not allow for thorough evaluation of the pelvis, but rectal examination did not detect any posterior cul-de-sac nodularity. Pelvic ultrasound showed a complex left adnexal mass measuring 8 x 9 cm, mostly cystic with a small area of solid component, no mural nodules or papillations were seen. The right ovary was normal in size and morphology. Abdominal and pelvic CT scans with contrast confirmed a left adnexal mass without pelvic or peritoneal fluid collection. All other intra-abdominal organs were described as unremarkable. Serum CA 125, CEA, and CA 19-9 were all within normal limits.

Following gynecologic oncology consultation, she opted for a laparoscopic bilateral salpingo-oophorectomy with a plan to proceed with laparotomy if the adnexal mass turned out to be malignant. In addition, Ms. X’s medical team did a comprehensive preoperative evaluation of the pelvic mass to rule out the presence of malignancy and the need to remove the complex mass intact so that peritoneal contamination by malignant cell containing cystic fluid is avoided.

For Ms. X, this approach was chosen for several reasons. Her multiple comorbidities made the patient a high-risk candidate for laparotomy. Surgery would have been difficult with the potential for major bleeding, because of poor access due to obesity. Adjacent organs, such as ureters, bladder, and bowel, could be damaged accidentally. The patient would have required to be admitted for days. Other potential post-operative complications include thrombo-embolism, poor wound healing, and ventral (incisional) hernia. All these potential problems were averted by utilizing the minimal access approach.

A common justification for laparotomy in this type of case is the potential presence of malignancy and the need to remove the complex mass intact so that peritoneal contamination by malignant cell containing cystic fluid is avoided.

The surgical team’s approach in this case gave Ms. X the benefits of minimally invasive surgery, without compromising her safety if the mass turned out to be malignant. In addition, Ms. X’s medical team did a comprehensive preoperative evaluation of the pelvic mass to rule out an obvious malignancy, especially one with extra-ovarian metastasis.

Although malignancy cannot be totally ruled out by any preoperative noninvasive testing, serum CA 125 is commonly elevated in epithelial ovarian cancer(1). When the cancer is in early stages, it can be normal in 50% of cases(2-3). This is the main reason it has failed to become a routine screening test. Its efficacy is particularly low in premenopausal women, where many known benign conditions can cause the level to go up. Regardless of the above facts, an elevated level of serum CA 125 in the presence of a complex pelvic mass in a post-menopausal woman remains a concerning clinical finding. Ms. X’s serum CA 125 level was normal. Emerging data suggest that a combination of serum tumor markers, such as OVARI1 may be more clinically helpful than CA 125 alone(4).

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Despite advances in imaging technology, grayscale transvaginal sonogram remains the gold standard for pelvic mass evaluation\(^5\). In general, the more complex the morphology of the mass, the more suspicious. Features that are considered important on ultrasound morphologically include thickened cyst wall, solid component, papillations, excrescences, and septations. Doppler flow assessment also is used to enhance the pelvic mass evaluation\(^6\). Computed tomography (CT) scans have similar sensitivity and specificity for evaluating an adnexal mass, but ultrasound is generally cheaper. If ultrasound findings are suspicious, CT scanning is recommended for assessment of possible intra-abdominal metastasis and burden of disease assessment. Other modalities of imaging that are occasionally utilized include magnetic resonance imaging (MRI) and positron emission tomography (PET).

In this case, based on clinical assessment, blood tests, and ultrasound findings, there was no evidence to confirm a malignancy prior to surgery. However, considering the inability of any non-invasive test to completely rule out malignancy, Ms. X’s gynecologic oncologist still took all the necessary precautions to protect the patient’s intra-abdominal cavity from any contact with the cystic content.

Lastly, an image-guided biopsy of the pelvic mass could have provided a diagnosis prior to surgery, but this test is to be discouraged, except in very special situations. Such a test could potentially lead to cyst rupture and peritoneal cavity contamination if the mass turned out to be malignant. One special condition for which we utilize this approach is in patients with widely metastatic intra-abdominal cancer suspected to be originating from the ovaries, fallopian tubes, or the peritoneum with disease distribution that favors the neo-adjuvant chemotherapy approach.

**Conclusion**

Laparoscopic resection of adnexal masses is a feasible and safe option with many advantages in carefully selected patients who have been evaluated by gynecologic oncologists.

**Bibliography**


Care for Women at Increased Risk for Breast and Ovarian Cancer

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The BRCA1 and BRCA2 genes were identified in the early 1990s by evaluating families with strong histories of breast and ovarian cancer. While the general population has lifetime risks of approximately 12% for breast cancer and 1.4% for ovarian cancer, BRCA1 and BRCA2 mutations confer a drastically increased lifetime breast cancer risk between 45% and 87%, while the risk of ovarian, fallopian tube, and primary peritoneal cancer ranges from 16% to 44%.

Recent technological advances, such as massively parallel sequencing, have aided in the recognition of additional tumor suppressor genes associated with hereditary breast and/or ovarian cancer, such as RAD51C. These genes have lower penetrance than BRCA1 and BRCA2, but when the various susceptibility genes are taken together, they may account for approximately 25% of breast, ovarian, fallopian tube, and peritoneal cancer cases.

The National Comprehensive Cancer Network established guidelines for BRCA mutation carriers to facilitate clinical management of these high-risk patients based on peer-reviewed, published data (available at www.nccn.org). Screening options include mammography, breast magnetic resonance imaging, transvaginal ultrasonography, and serum, while prevention options include medical therapy with drugs such as tamoxifen and surgery with prophylactic bilateral mastectomy (PBM) and risk-reducing salpingo-oophorectomy (RRSO).

One Site, Many Roles
A multidisciplinary clinic managed by experts familiar with the management of hereditary breast and ovarian cancer can help integrate the strategy for managing risk for multiple cancers. In addition, multidisciplinary clinics consolidate the high-risk population into a single site, making counseling, screening, and research activities more efficient and more convenient for the patient. The Magee-Womens High Risk Breast and Ovarian Cancer Program (HRBOCP), a component of UPMC CancerCenter, was created in 2002 after the need for a more efficient model of providing care for women at increased risk for breast and ovarian cancer was recognized. The main goals of the HRBOCP are:

- To evaluate women at high risk for breast and ovarian cancer and coordinate their clinical care in a multidisciplinary setting staffed by experts in the field.
- To provide updates on new data regarding screening recommendations, prevention options, and risk factors pertinent to an individual’s cancer risk.
- To provide ongoing support to patients and their families, including coordination of genetic testing for family members when appropriate.
- To facilitate enrollment in appropriate research studies and registries.

These goals are addressed by involving several programs within UPMC, including genetic counseling, gynecologic oncology, medical oncology, and radiology. Other providers, such as social workers, surgical oncologists, plastic surgeons, and psychologists, are consulted as needed. The majority of the referrals for the HRBOCP come from primary care physicians, radiologists, surgeons, gynecologists, and oncologists. As awareness of the program has grown, self-referrals and referrals from family members have increased steadily.

Charting the Course
Depending on their personal and family histories, women are scheduled in the breast component of the clinic, the ovarian component of the clinic, or both. Any individual with a personal or family history of a BRCA mutation, a family history of breast and/or ovarian cancer, or a family history suspicious for a hereditary cancer predisposition is eligible for referral to the HRBOCP. However, any woman concerned that she is at increased risk for breast or ovarian cancer also is welcome as part of UPMC’s effort to increase understanding of breast and ovarian cancer risk and their management in our community. For example, a major component of the high-risk breast cancer clinic is prescribing preventive medical therapy to appropriate patients. UPMC’s referral guidelines are deliberately inclusive, as we are attempting to capture not just patients at hereditary risk, but also more moderate-risk patients who are eligible for preventive therapy with medications such as tamoxifen.

The past decade has seen continuous growth in patient visits for the HRBOCP. The first year of the program saw a total of 86 patients; in 2010, more than 850 patients consulted the specialists of the HRBOCP. Other activities sparked by the presence of the HRBOCP include:

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• The Cancer Family Registry (CFR): A research tool that was created in 2002 to collect data on individuals at high risk to develop gynecologic and related cancers based on hereditary and familial predispositions. The CFR recruits men and women with known BRCA or Lynch syndrome mutations, as well as individuals with a strong family history suggestive of genetic susceptibility to develop cancer. Participants provide biologic medical histories and specimens that are de-identified and stored in a tissue bank and database for current and future research. To date, more than 450 individuals have joined the registry.

• The HRBOCP has facilitated accrual to a study of novel screening modalities, including breast tomosynthesis, for breast cancer in high-risk women.

• The Access to Genetic Testing Project: Created to help individuals with suspicious personal and family cancer histories gain access to genetic testing when it is not covered by their insurance.

Components of our high-risk program have been supported by benefactors, such as the Scaife Family Foundation, the Frieda G. and Saul F. Shapira BRCA Cancer Research Program, the Glimmer of Hope Foundation, Hackers for Hope, the Magee-Womens Hospital Volunteer Service Board, PNC Foundation, Mellon Foundation, and Barbara and Herb Shear.

Looking Ahead
While we have made great strides in the prevention of breast and ovarian cancer through prophylactic surgery and the early diagnosis of breast cancer with improved screening, the biggest benefit to the high-risk patient population going forward would be less invasive prevention strategies. Our goal is to see the HRBOCP become a resource for a full spectrum of research to improve the lives of women at high risk for breast and gynecologic cancers while maintaining its current role as a clinical management resource. In particular, we hope that trials for cancer prevention become available as our understanding of the biology underlying women’s cancers improves. This shift would make the HRBOCP increasingly multidisciplinary, offering patients an expanded menu of care services, not just in the sense of the health care providers present, but also with respect to the management options available to patients.

For more information or for patient referrals, call the High Risk Breast and Ovarian Cancer Program at 412-623-3425.
CME OPPORTUNITIES

Peritoneal Therapy in Ovarian Cancer
Robert Edwards, MD, provides an analysis of the pros and cons of peritoneal therapy for ovarian cancer. The presentation includes disease characteristics and patient issues in defining whether peritoneal therapy will be successful.

Cancer Risk Assessment and Genetic Counseling: Hereditary Breast and Ovarian Cancer (HBOC)
Darcy Thull, MD, provides an overview of the causes of hereditary breast and ovarian cancers, the role of a genetic counselor, and the importance of family history. Early detection and prevention strategies are also discussed.

Breast Cancer Risk Assessment and Primary Prevention for High Risk Patients
Rachel Jankowitz, MD, provides an overview of breast cancer risk factors, as well as factors differentiating moderate and high-risk patients. She discusses methods of preventive therapy and the benefits and risks associated with such therapy.