National Ovarian Cancer Early Detection Program

A National Cancer Institute-Supported Ovarian Cancer Program

Mount Sinai School of Medicine
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David A. Fishman, MD, is Professor of Obstetrics and Gynecology at Mount Sinai School of Medicine and the Director of Gynecologic Oncology Research within the Cancer Center. Dr. Fishman is an internationally recognized gynecologic oncologist, especially noted for his innovative research on the regulation of ovarian metastasis and in developing new methods for the detection of early stage ovarian carcinoma. He established The National Ovarian Cancer Dearly Detection Program in 1999 with a grant from the National Cancer Institute and philanthropic support. Dr. Fishman received his medical degree from Texas Tech School of Medicine and completed his residency and fellowship in Obstetrics and Gynecology and Gynecologic Oncology at the Yale University School of Medicine. Dr. Fishman has authored over 230 scientific papers, abstracts, book chapters and several books on gynecologic malignancies. His research has received awards from the National Institutes of Health, National Cancer Institute, Society of Gynecologic Oncologists, Gynecologic Cancer Foundation, American Cancer Society, Society of Gynecologic Investigation, and the Berlex Foundation. He serves as an editor for three journals and ad hoc reviewer for 43 medical and scientific journals and is a member of national and international cancer institute study sections from the National Cancer Institute and Centers for Disease Control to the Royal College of Obstetricians and Gynecologists. He is a member of many medical and honor societies and patient advocacy groups including the American Gynecologic and Obstetrical Society, Society for Gynecologic Investigation, AOA, the Society of Gynecologic Oncologists and the National Ovarian Cancer Coalition.
Introduction

The National Ovarian Cancer Early Detection Program (NOCEDP) provides focused, high quality, innovative care and services for asymptomatic women at increased risk of developing ovarian cancer. The hallmark of the program is the coordinated, multidisciplinary services provided during each comprehensive clinic visit. These clinical services include evaluations by board certified specialists in cancer genetics, gynecologic oncology, ultrasound, and psychology. The NOCEDP is a state-of-the-art ovarian cancer program that combines clinical expertise with our NCI-funded cancer research programs. We are committed to optimizing women’s healthcare related to ovarian cancer.

While all cancer patients can potentially benefit from early detection, the development of new screening methods for epithelial ovarian cancer (EOC) is unique. The National Ovarian Cancer Early Detection Program (NOCEDP), under the direction of David A. Fishman, MD, is an international clinical and scientific effort to develop methods that accurately detect early stage ovarian cancer. In collaboration with physicians and scientists at the National Cancer Institute, Food and Drug Administration, and other centers of academic excellence, the NOCEDP is committed to developing effective means for the accurate detection of early stage EOC. Within the NOCEDP we have identified clinically relevant serum/plasma markers based on the latest understanding of ovarian carcinogenesis, invasion, and metastasis, which are combined with newly developed diagnostic technologies (ovarian Pap test, contrast sonography, artificial intelligence) and clinical genetics to achieve this goal. The NOCEDP represents a world-wide integrated, multidisciplinary collaboration of experts working together to facilitate the detection of early stage EOC in asymptomatic high-risk women.

Evidence suggests that early detection and inhibition of metastases will require the development of strategies based on the molecular, genetic, and biochemical events that regulate carcinogenesis, invasion, and metastatic dissemination. We continue to investigate many novel blood markers such as lysophospholipids, autotaxin, proteinases (matrix metalloproteinases and kallikreins), adhesion molecules, extracellular matrix proteins, and specific growth factors (EGF, VEGF) which have significant roles in the regulation of ovarian metastasis and may serve as markers for early stage disease as well as targets for new therapeutics. Additionally, new powerful technologies employing genomics and proteomics (the study of how genes and proteins work within the host environment) are also evaluated to identify early stage ovarian cancer. Genetic evaluation of specimens obtained using the ovarian Pap test allow for the genetic identification of malignant cells prior to the development of physical change and may allow the detection of pre-malignant cells or ovarian dysplasia. Similarly, new diagnostic imaging technologies such as our use of contrast sonography appear to be promising in detecting cancer early in otherwise normal appearing ovaries.
Ovarian Cancer Statistics
Currently, the American Cancer Society estimates that annually approximately 21,650 women are diagnosed with ovarian cancer and more than 15,520 women die from this disease. Ovarian cancer is the fifth leading cause of cancer death among U.S. women and has the highest mortality rate of all gynecologic cancers. More women die from ovarian cancer than from all other gynecologic cancers combined. The majority of women (approximately 75%) continue to be diagnosed when the disease has reached an advanced stage (stage III or IV) and spread throughout or beyond the abdominal cavity. Despite aggressive surgical intervention and new chemotherapeutic regimens, the overall five-year survival rate for women with advanced stage epithelial ovarian cancer (Stage III and IV) remains poor (<30%). However, if EOC is detected when confined to the ovary (stage I), the 5-year survival is more than 90%, requires less radical and morbid operations, and may not require adjuvant chemotherapy. Clearly, detection of early stage ovarian cancer is the best way to improve survival.

Ovarian Cancer
Early stage epithelial ovarian cancer is extremely difficult to detect as evidenced by the fact that the majority of women continue to be diagnosed with advanced stage disease. This is partly due to the fact that each ovary is a small (2x3 cm), oval-shaped organ embedded deep within the abdominal cavity on each side of the uterus. In addition, the signs and symptoms are generally non-specific and may include:

- gastrointestinal upset such as gas, indigestion or nausea
- pelvic and/or abdominal pain or discomfort
- pelvic and/or abdominal bloating or swelling
- a constant feeling of fullness
- unexplained change in bowel and/or bladder habits
- fatigue
- unexplained weight loss or gain
- abnormal or postmenopausal bleeding

Because these potential symptoms and signs of ovarian cancer are vague, only about 25% of ovarian cancers are found in the early stages. Symptoms typically become more prominent in advanced stages when tumor growth creates pressure on the bladder and rectum and ascites (fluid in the abdomen causing abdominal distension) begins to form.
Risk Reduction for Ovarian Cancer

Although there is no known method to prevent ovarian cancer, there are ways to significantly reduce the risk of developing this disease. They include:

- Oral contraception: One non-contraceptive benefit of oral contraceptives may be protection against ovarian cancer. The use of oral contraceptives for a total of at least five years can significantly decrease a woman's risk of developing ovarian cancer by up to 60%. This includes women with an inherited BRCA mutation that places them at greater risk of ovarian cancer. The use of oral contraception need not be for five years consecutively, but rather for a total of five years.
- Pregnancy and breast-feeding: The risk of developing ovarian cancer decreases if a woman has had at least one child prior to the age of 30. Also, breast-feeding each child for at least three months may decrease the risk of developing ovarian cancer.
- Tubal ligation: Although this procedure seems to reduce the risk of developing ovarian cancer, the reason for the decreased risk is unknown. Tubal ligation should be performed for valid medical reasons and not solely to reduce the risk of developing ovarian cancer.
- Prophylactic bilateral salpingo-oophorectomy (BSO): Removal of both ovaries and fallopian tubes eliminates the risk of developing ovarian and fallopian tube cancer. Among women who have undergone a BSO, 1-3%, may develop primary peritoneal carcinoma, which is a distinct malignancy from ovarian cancer.
- Oophorectomy in conjunction with hysterectomy: A hysterectomy alone will slightly reduce a woman's risk of developing ovarian cancer. A BSO during a hysterectomy eliminates the risk of developing ovarian cancer. Women over age 50 who are having a hysterectomy should discuss the option of a simultaneous BSO.

Ovarian Cancer Research

As a state-of-the art clinical research program, the NOCEDP has achieved international recognition for scientific insights regarding the genetics, biology and mechanisms of ovarian cancer. It is our goal to translate this information into new methods for both the identification of at-risk individuals as well as early detection of early stage disease and treatment of ovarian cancer.

Blood Tests

Overview of Serum/Plasma Biomarker Assays

The goal of cancer screening is to detect precancerous lesions or early stage malignancies in the asymptomatic preclinical phase of disease so that subsequent diagnosis and treatment will significantly reduce disease morbidity and mortality. Ideally the screening tool should be noninvasive and inexpensive.
to achieve widespread acceptance and applicability. Thus, biological molecules found in circulatory fluids (eg, blood, urine, and saliva) represent ideal markers for cancer screening. Unlike symptomatic and abnormal clinical findings that may lead to definitive surgical and histopathological diagnostic tests, serum biomarkers promise to provide information to assess cancer risk, to detect precancerous or cancerous lesions, and to formulate a precise diagnosis before invasive procedures are required to diagnose ovarian cancer. Hence, the development of serum biomarkers for the assessment of cancer risk, screening, early detection, and diagnosis of malignancy has become a national priority.

The ability to detect human malignancy by a simple blood test has long been an objective in medical screening. A suitable test or examination to screen for a disease should have both high sensitivity (the probability of the test being positive in individuals with disease) and high specificity (the probability of the test being negative in those without the disease). Developing a highly specific screening test is a major concern for ovarian cancer because the majority of women who test positive on screening will require surgical intervention to confirm the diagnosis. A screening test with low specificity requires a large number of operations to detect one case of ovarian cancer, which is not acceptable to patients or clinicians. For example, in postmenopausal women, even a screening test with 98% specificity would result in operations on 50 women who do not have cancer for every one case of ovarian cancer found during surgery.

In fact, a screening test in postmenopausal women requires 99.6% specificity to yield a positive predictive value (PPV) of 10% (10 operations for each case of ovarian cancer detected). The generally acceptable PPV for a screening test in ovarian cancer is a minimum of 10%. However, because the incidence of ovarian cancer in the general population is low, approximately 1.8%, the specificity of the CA-125 blood test (a test currently used for ovarian cancer) is unacceptably low for screening for ovarian cancer in the general population.

The age of the population screened is also a factor in the usefulness and specificity of screening tests for EOC. Less than 15% of ovarian cancers occur in women younger than 50 years of age and many malignancies in women less than 25 years are non-epithelial, usually germ cell malignancies. The incidence of ovarian cancer rapidly increases after the age of 50. For example, the rate in women 60 to 64 years of age is more than double the rate in women 45 to 49 years of age. The incidence peaks between 70 to 74 years of age. However, in women with inherited BRCA mutations ovarian cancer typically occurs earlier than in the general population and the incidence approaches 40%. Thus, although these women may comprise a younger population to screen, a screening test becomes practical in such women. In BRCA carriers a test with 90% specificity would yield a PPV of 10% because the incidence of ovarian cancer in this population is so high.
Problems With Currently Available Tests

The advantage of a relatively noninvasive, operator-independent screening test is self-evident. Several ovarian tumor markers have been studied. The most commonly utilized in clinical practice is CA-125, an antigen expressed by various epithelial cells. The CA-125 tumor marker was first used in 1981 in an experimental model. CA-125 was initially detected using the monoclonal antibody OC125. This antibody was found to bind the CA-125 antigen that is expressed by approximately 80% of serous epithelial ovarian cancers. Overall, more than 80% of women with advanced stage EOC have an elevated CA-125 level. (The normal value is typically <35 U/ml.) However, levels are elevated in many different physiologic situations that are not always cancer. Moreover, the test is not useful to detect asymptomatic early stage ovarian cancer because it is only elevated in approximately 47% of women who have surgical confirmation that they have early stage disease (Stage I).

Most gynecologic oncologists utilize CA-125 for surveillance of EOC after the diagnosis has been surgically confirmed because it may be a sensitive indicator of persistent or recurrent disease. Unfortunately CA-125 is even less reliable for the detection of cancer in premenopausal women since it is frequently elevated in noncancerous conditions such as pregnancy, endometriosis, uterine fibroids, liver disease, benign ovarian cysts, and in other malignancies such as colon, uterine, fallopian, gastric, and pancreatic cancer. CA-125 screening for EOC in the general population is problematic; an elevated value accurately detects malignancy in less than 3% of women. Therefore, although it is the best available serum marker, CA-125 does not have sufficient sensitivity to warrant its use as a sole marker to screen for ovarian cancer. In fact, in a study of 110 EOC patients, using a cutoff value of 35 U/ml, the sensitivity was only 57% while the specificity was 100%. Thus, researchers have concluded that although serum CA-125 values alone are highly specific, they are insufficiently sensitive to recommend screening for EOC in the general population. Among all published studies, CA-125 values of >35 U/ml had sensitivities of 51%, 71%, 91%, and 98% for stage I, II, III, and IV EOC, respectively, and 85% for all stages combined. Therefore, more reliable markers for detecting asymptomatic, early-stage EOC are needed to decrease the morbidity and mortality associated with this disease. The major purpose of the NOCEDP is to help develop and validate highly sensitive and specific serum marker(s) for the detection of early stage EOC.
Participants in the NOCEDP have blood samples drawn to test the following identified ovarian and/or breast cancer tumor markers:

- Lipid biomarkers such as lysophospholipids (LPA, LPI and LPC)
- Protein biomarkers such as cytokines, growth factors and their receptors, proteinases, and other proteins which have been identified using proteomic techniques
- Aberrantly methylated genes

Clinical Proteomics

Molecular medicine is rapidly moving beyond the study of the genes involved in cancer to the broader field of proteomics. The protein-protein interactions that drive complex biological processes can be characterized as a fluctuating information flow within the cell, and throughout the organism through protein pathways and the cellular protein “circuity.” The deranged molecular networks in cancer are not confined to the diseased cell, but extend to the microenvironment of the tumor-host interface, the surrounding normal stromal and vascular compartments, and to the circulation macroenvironment. Recognition that cancer is a product of the proteomic tissue microenvironment has important clinical implications in terms of both early detection and therapeutics. The tissue microenvironment can spawn entirely new biomarker cascades that reflect subtle changes at the earliest times of tumor growth and invasion. These changes alter the proteome of the circulation that should be detectable by blood tests.

Because serum is a protein-rich information source that effectively contains what the circulation has encountered on its journey throughout the body, proteomic technologies may have the most impact in biomarker discovery. Unfortunately, past biomarker discovery efforts have centered on laborious approaches looking for one single over-expressed protein in blood that is a marker for ovarian cancer. However, finding that single biomarker is like searching for a needle in a haystack, requiring the separation and identification of each protein biomarker from the myriad of intact, modified, and cleaved protein isoforms in the human serum proteome. Moreover, it is highly likely that a single marker for a specific cancer does not exist, as each organ specific cancer is a disease of normal and abnormal cells existing within a unique microenvironment.

Because the human population is diverse and ovarian cancer is a heterogeneous disease process the clinical application of proteomics is an ideal use of such technology. It seems reasonable that the presence of cancer will be detected by multiplexed panels of clinical tests that measure altered host and tumor-derived proteins produced as a consequence of aberrant cellular function and cellular interactions in cancer.

Current technologic advances have allowed the identification of the proteomic component of serum. Mass spectrometry provides an extremely rapid and potentially high-throughput method for biomarker discovery. Recent
attempts to employ mass spectroscopy to identify biomarkers for cancer have been very promising. Proteomic analysis attempts to identify high and low abundance proteins which may reflect organ specific disease. The mass spectrometer is a powerful tool for discovery reducing the time between identification of the abnormal proteins and their validation as clinically useful markers.

Ovarian Pap Test

The “Ovarian Pap Test” is a developing tool to detect pre-cancerous or early cancerous changes on the ovaries. Utilizing minimally invasive office laparoscopy to directly visualize the ovaries, the ovarian Pap test allows collection of cells from the surface of the ovary and from the peritoneal cavity using a laparoscopic cytologic sampling instrument similar to the cytobrush used in the cervical Pap test. The laparoscopic sampling instrument allows separation and individualization of both the ovarian specimen and the peritoneal specimen. Similar to the cervical Pap smear, collected epithelial cells are analyzed by a cytopathologist to determine whether abnormalities are present.

In the NOCEDP, the ovarian Pap test is performed on women at the time of surgical removal of the ovaries to provide cytological samples for pathologic, genomic, proteomic and biochemical examination, as well as cellular assays using organ culture techniques.

Little is known about the etiology of ovarian cancer at the molecular and genetic level. The ovarian Pap test enables comparison of ovarian epithelium from asymptomatic women at increased risk for the development of ovarian cancer with that from women with ovarian cancer. By comparing these groups, the NOCEDP may be able to develop profiles of the molecular changes relevant to tumor progression for sporadic ovarian cancer. Hopefully, this information will reveal early genomic or proteomic changes that may facilitate detection of early stage epithelial ovarian carcinoma and may identify markers indicative of premalignant changes. Thus far, we have identified increased copies of \textit{EVI1} and \textit{MYC} (gene products associated with ovarian cancer). Such findings may help identify women at increased risk for the development for ovarian cancer, allowing earlier intervention for premalignant changes before ovarian cancer develops.

Contrast-Enhanced Sonographic Microvascular Imaging

At present, sonography is the most effective method for diagnosing ovarian tumors. However, despite rapid technological advances in sonography, the ability to differentiate benign from malignant lesions is severely limited, especially for the detection of early stage EOC. During the last decade three-dimensional transvaginal gray-scale volume imaging (3D TVS) and three-dimensional transvaginal power Doppler imaging (PD3D TVS) have improved upon the diagnostic accuracy of two-dimensional transvaginal gray-scale imaging (2D TVS). This newer technology can better differentiate benign and malignant adnexal pathology. The reported advantages of 3D TVS include improved visualization of the internal architecture of adnexal masses containing cystic components. The addition of PD3D TVS allows thorough examination of the complex adnexal mass for abnormal vascularity in three distinct planes.
We recently compared new 3D techniques with 2D TVS to evaluate the ability of each technique to distinguish benign complex adnexal masses from ovarian carcinoma. Three-dimensional power Doppler imaging better defined the morphologic and vascular characteristics of ovarian lesions. All malignancies were correctly identified by both 2-D and 3-D imaging, however the addition of 3D-power Doppler improved the specificity significantly. This is a significant advance because improving the accuracy of distinguishing complex benign masses from ovarian cancer may improve patient care by facilitating appropriate physician referral.

Recent technical developments involving improved scanning with harmonics and the use of contrast support the need for continued research regarding the sonographic depiction of tumor microvascularity. Such advances in technology may prove to be much more sensitive and specific than traditional ultrasonography. Our recent work with contrast enhanced sonography revealed its significant potential to distinguish benign from malignant ovarian lesions. Presently contrast sonography is limited to those women scheduled for surgical removal of their ovaries as a research tool undergoing clinical validation. It is our hope that the use of relevant serum biomarkers such as the lysophospholipids, EGFRs, kallikreins, and newly identified proteins in combination with sonographic microvascular imaging to detect early stage EOC will soon become a clinical reality.

Ovarian Cancer Genetics

At its most basic level, cancer is a genetic disease, resulting from a step-wise accumulation of mutations in genes that normally control cell growth. The majority of gene mutations involved in cancer are somatic, meaning that they are found only in that individual’s cancer cells. Somatic mutations may occur by chance, as a result of the aging process, or due to environmental and lifestyle exposures. In contrast, germline mutations are inherited from a parent at the time of conception and are present in every cell of the body. Only a small portion of all cancers occur in individuals who carry an inherited mutation that predisposes them to develop cancer. Germline mutations in specific tumor suppressor genes and DNA mismatch repair genes have been associated with numerous hereditary cancer syndromes.

The hereditary cancer susceptibility genes that have been identified to date are highly penetrant, meaning that mutations lead to a risk of developing cancer that is significantly above average. Since cancer is a multi-step process, the presence of a germline mutation makes a person essentially “one step closer” to cancer from the time of birth than the average person, thereby increasing the chance of early-onset cancer and multiple primary cancers. Although a significant risk factor, a germline mutation does not guarantee that cancer will develop. The likelihood that an individual who inherits a mutation will ultimately develop cancer is dependent on other factors that influence the occurrence of subsequent mutations, such as modifier genes and poorly understood diet, lifestyle, and environmental factors.

Epidemiological studies and detailed analysis of familial EOC pedigrees suggest at least three forms of inherited disease: 1) Hereditary, site-specific ovarian carcinoma (ovarian carcinoma without breast cancer); 2) Breast and ovarian cancer syndrome (Lynch type I, including 1st or 2nd degree relatives); and 3) Hereditary nonpolyposis colorectal carcinoma (HNPCC, Lynch type II, ovarian cancers associated with an excess of colorectal, prostate, and endometrial carcinomas).
Approximately only 5-10% of ovarian cancers are due to inherited genetic mutations. EOC most commonly occurs in a sporadic fashion without any antecedent history of familial disease. Epidemiologic factors associated with EOC include nulliparity, personal history of colon or breast cancer, affected 1st degree relatives with EOC, or a family history of a recognized inherited malignancy syndrome.

Research on families with very strong patterns of breast and ovarian cancer led to the discovery of $BRCA1$ on chromosome 17 and $BRCA2$ on chromosome 13. $BRCA1$ and $BRCA2$ are normal genes carried by all men and women. When functioning properly, these genes play a role in tumor suppression through cell cycle regulation and DNA damage repair. Research continues to learn more about the precise role of $BRCA1$ and $BRCA2$ within the cell. About 5-10% of EOC cases are attributable to inheritance of highly penetrant mutations in the breast/ovarian cancer susceptibility genes $BRCA-1$ and -2. The clinical presentation of heritable EOC is similar to sporadic EOC, but tends to occur 10-15 years earlier than in the general population. It is estimated that over 50% of women with $BRCA1$ mutations who develop EOC do so before age 50 and all women with these mutations have about a 30-40% risk of developing EOC by age 70.

Clues suggesting that a $BRCA1$ or $BRCA2$ mutation may be running in a family include: early-onset breast cancer (before menopause) in two or more relatives in different generations, ovarian cancer in addition to breast cancer among relatives, bilateral breast cancer, breast and ovarian cancer in the same woman, and male relatives with breast cancer. Most families with very strong family histories of breast and ovarian cancer have mutations in the $BRCA1$ and $BRCA2$ genes. However, in some high-risk families and many families with more moderate clusters of breast and ovarian cancer, such cancers are not due to $BRCA1$ or $BRCA2$, suggesting the existence of other inherited susceptibility genes yet to be identified.

The importance of identifying families with hereditary cancer susceptibility becomes apparent given the significant cancer risks associated with $BRCA1$ and $BRCA2$ mutations. Women who carry a $BRCA1$ or $BRCA2$ mutation have a 56-85% chance of developing breast cancer by age 70. The associated lifetime risk for ovarian cancer is 20-40% for $BRCA1$ mutations and 10-27% for $BRCA2$ mutations. In addition, $BRCA2$ mutations are associated with an increased risk of male breast cancer, and mutations in both genes may slightly increase the risk of prostate and colon cancer. Research continues to define the cancer spectrum associated with $BRCA1$ and $BRCA2$ mutations, and the magnitude of risk for each type of cancer.

In the general population of the U.S., approximately 1 in 400 individuals carries a $BRCA1$ or $BRCA2$ mutation. To date, several hundred different mutations predisposing to breast and ovarian cancer have been found in the $BRCA1$ and $BRCA2$ genes. However, certain mutations have been identified that are more common in individuals of particular ethnic backgrounds. Three “founder” mutations have been identified in Jewish individuals of Eastern European (Ashkenazi) ancestry. Ashkenazi Jewish women have an unexpectedly high frequency of a specific $BRCA1$ mutation compared with the general population. In the Ashkenazi Jewish population, about 2.5% have $BRCA-1$ or -2 mutations. Approximately 1 in 40 Ashkenazi Jewish individuals carry one of these particular mutations, which is significantly higher than the general population. These mutations may account for 30-50% of all early-onset breast or ovarian cancer cases in this ethnic population. To date, research in which the NOCEDP has participated suggests that up to
40% of Jewish women diagnosed with ovarian cancer and approximately 20% of Jewish women diagnosed with premenopausal breast cancer have a **BRCA1** or **BRCA2** mutation.

A less common cause of hereditary ovarian cancer occurs in association with the Hereditary Non-Polyposis Colon Cancer (HNPCC) syndrome. The most common features of HNPCC are early-onset colorectal cancer and endometrial cancer, although affected women also have a moderately increased risk of developing ovarian cancer (9-12%).

**Genetic Counseling and Genetic Testing**

Participants in the NOCEDP receive a consultation with a board certified genetic counselor, who reviews the family history of cancer in detail and provides an estimate of the likelihood of hereditary susceptibility. Cancer risk assessment is a complicated process that should be performed by a physician or genetic counselor with special training in cancer genetics. While some families will have histories that are clearly suggestive of hereditary cancer susceptibility, the pattern is less than clear in most families. Small family size, the presence of few female relatives, or relatives who have died young due to other causes are factors that may obscure signs of hereditary susceptibility, even if it is present. In addition, reports of cancer diagnoses among more distant relatives are notoriously inaccurate. For example, ovarian cancer may have been referred to as “stomach” cancer, or relatives may be aware of the site of cancer metastasis rather than the site of the original tumor. The genetic counselor in the NOCEDP helps participants obtain medical records on family members and other necessary information that may be crucial to the overall risk assessment.

The genetics consultation that is a standard part of the NOCEDP provides women with an estimate of their cancer risk and identifies individuals who may be appropriate for genetic testing for **BRCA1** and **BRCA2** mutations. Genetic testing is performed only after the potential benefits, risks, and limitations of testing are discussed at length. Whether or not to have genetic testing is ultimately up to each individual.

The most obvious benefit of genetic testing is that it may provide more information about an individual’s cancer risk, thereby facilitating decisions about surveillance and prevention. Women who test positive for a **BRCA1** or **BRCA2** mutation should be offered earlier and more frequent screening for breast and ovarian cancer. These women are also candidates for chemopreventative options and prophylactic surgery. At this point in time, however, there are still many unanswered questions about cancer screening and prevention for high-risk women. For example, what is the remaining risk of cancer after prophylactic mastectomy or prophylactic oophorectomy among women with **BRCA** mutations? How does the use of exogenous estrogen affect cancer risk in this group of women? What is the relationship between hereditary susceptibility and environmental or lifestyle risk factors? While research continues to explore these questions, any woman considering genetic testing deserves the opportunity to discuss the current state of knowledge before making her decision.

There are many benefits, risks, and limitations of genetic testing other than the impact of the results on medical choices. For many individuals, their main reason for pursuing genetic testing may be to provide further information to their family members. An individual’s anticipated emotional reactions to genetic testing results should also be
explored prior to testing. Some may feel that determining the underlying cause of their own cancer or family history of cancer may be a relief, while others may be concerned that they will suffer excessive anxiety, fear, or guilt if they receive a positive result. Still others may be concerned about how the information will affect relationships with their family members.

Finally, genetic testing for cancer susceptibility is different from other medical tests in many ways. It may be most informative for a family member affected by cancer to have genetic testing first, to determine if a \textit{BRCA1} or \textit{BRCA2} mutation is even present in the family. A DNA alteration may be found through genetic testing that is of uncertain significance and should be interpreted with caution. Genetic tests are expensive and individuals may need guidance about obtaining insurance authorization. Many individuals have questions about the impact of genetic test results on insurability and the current status of legislation protecting against genetic discrimination. The NOCEDP provides the opportunity to discuss the numerous and complicated issues surrounding genetic testing with a board-certified genetic counselor experienced in cancer genetics.

The NOCEDP

The purpose of the NOCEDP is to identify and optimize care for those women who are at increased risk for developing ovarian cancer and to develop new tests to detect ovarian cancer at an early, treatable stage. While the presence of one or more of the following risk factors may increase a woman’s risk for developing ovarian cancer, it does not necessarily mean that she will.

- a personal history of breast, colon, or GU cancer
- one or more first-degree relative (mother, sister, daughter) who has ovarian cancer
- multiple family members with breast and/or ovarian cancer
- uninterrupted ovulation (infertility, never used birth control pills, or nulliparity)
- the use of fertility drugs for more than one year
- age 40 or older (as with most cancers, a woman’s chances of developing ovarian cancer increases with age; the highest risk age group is 70-79 years)

Inclusion Criteria for the NOCEDP

One or more of the following is suggested for participation in the program:

- a personal history of breast, colon, or urinary cancer
- one or more first-degree relative (mother, sister, daughter) with ovarian cancer
- multiple family members with breast and/or ovarian cancer
- a personal history of a positive \textit{BRCA1} or \textit{BRCA2} genetic test result
- a close relative with a positive \textit{BRCA1} or \textit{BRCA2} genetic test result
- the use of fertility drugs for more than one year
The NOCEDP Core Evaluation

Women who enter the program receive an extensive personal and family medical history questionnaire to complete prior to their initial visit. Appointments last one to two hours, with more time allotted as necessary.

This clinical research program is limited to the early detection of early stage ovarian cancer. Therefore, all participants entering the program must have a referring physician who will provide routine gynecologic care, such as internal examinations, Pap tests, and annual examinations. The success of the NOCEDP is contingent upon collaboration and communication among the program participant, the referring physician, and the NOCEDP.

The Core Evaluation includes:

- a consultation with a board certified genetic counselor
- vaginal or abdominal ultrasound using vascular analysis, 3D or 4D image analysis and possibly contrast sonography
- physical examination, including an internal pelvic and rectal examination
- blood work for tumor marker experimental tests
- psychological, social, and physical well-being studies, such as:
  - Impact of Events Scale (IES)
  - Profile of Mood States (POMS)
  - Functional Assessment of Cancer Therapy Scale, General (FACT-G)
  - Medical Outcomes Study, Short Form-36 (SF-36)

Participants are expected to return to the Ovarian Cancer Early Detection Program every six months for ultrasound, physical examination, and experimental blood work. At each visit the participant’s personal and family medical history will be updated if changes have occurred.

Either the participant and/or her insurance company will be billed for the genetic counseling, ultrasound and internal examinations. Participants will not be billed for any experimental studies.
Location
The NOCEDP is located in The Derald H. Ruttenberg Treatment Center in the Department of Obstetrics, Gynecology and Reproductive Science
1190 Fifth Avenue, New York, NY 10029

For more information about the Mount Sinai National Ovarian Cancer Early Detection Program please contact:

David A. Fishman, MD
E-mail address: david.fishman@mssm.edu
NOCEDP Phone number — (212) 427-9898