Only 5-10% of ovarian cancers are due to mutations within inherited cancer susceptibility genes and the use of several well-established risk factors can help clinicians decipher which patients are at greatest risk for hereditary cancer (see Table 1, page 2 for hereditary breast and ovarian cancer risk factors). It now appears that ovarian cancer histopathology also plays an important role in risk assessment, patient selection, and result interpretation.

Results from a new study, published in Clinical Genetics, illustrate the impact of confirming ovarian cancer pathology on risk assessment and mutation detection. Researchers performed BRCA testing in 442 families with a significant family history of ovarian cancer (1). A total of 166 (38%) mutations were identified. When families with pathologically confirmed ovarian cancers were selected (108 families), the frequency of mutations increased to 80%. The increase in detection rate may be due to the elimination of uterine cancers originally reported as ovarian cancer, which has been documented as a common misreport (2). Although these differences may seem subtle to the patient, it has a tremendous impact on the likelihood that the cancers in the family are hereditary and thus whether genetic testing is appropriate for the family.

Ovarian cancer pathology must also be considered when determining the most appropriate family member to begin testing. Ideally, this is an affected family member. However, this study did not reveal ANY mutations in individuals with mucinous or borderline ovarian cancers. While the possibility of a BRCA mutation cannot be dismissed solely on the presence of mucinous or borderline tumors, it does not appear that they add to the likelihood of identifying a BRCA mutation. Therefore, it is better to begin testing in a family member with breast cancer or invasive, non-mucinous, non-borderline (~80% of all cases) ovarian cancer. In high-risk families a borderline (~10% of all cases) or malignant mucinous (~1% of all cases) ovarian cancer may represent a sporadic case within a hereditary family.

Histopathology can also provide valuable data to help interpret the results from genetic testing. Patients with a negative result or BRCA variant of uncertain significance are of greatest concern because these

RENAL CELL CARCINOMA (RCC)

RCC accounts for approximately 3% of all malignancies and its incidence appears to be increasing. It is estimated that ~2-4% of renal cell carcinomas have a hereditary basis. RCC can be divided into several histological subtypes: clear cell (~75%), papillary (~10-15%), chromophobe (~5%), and oncocytomas (~5%). Sporadic and hereditary forms of each subtype exist. The hereditary forms often present at an earlier age and are more often bilateral and multifocal than sporadic disease. Hereditary forms can involve RCC only, or additional malignancies or clinical manifestations in other organ systems. RCC is a major feature of at least 6 known hereditary cancer syndromes all of which are
Welcome to a new year, a new administration, and a sense of renewed hope and enthusiasm in the field of Cancer Genetic Counseling.

All signs point to the fact that our new President will support science & technology. This includes a greater investment in scientific research, which will hopefully translate into more monies available for scientific grants and research. This is critical in a young field like Cancer Genetics in order to fund the discovery of new genes, laboratory technology, chemoprevention medications, cancer markers, and surveillance techniques. We are hopeful that a renewed commitment to medical and scientific research will rea more testing, prevention, and surveillance options for our patients in the next decade, and an even better understanding of the genes that have already been discovered.

This administration also plans to advance medical education and training in health-related fields. An increase in professional education and training will be critical as human genomics continues to expand, and as more testing options become available through medical offices and online.

There is also a pledge to invest in electronic information technology systems, which could be critical in sharing patient information between providers in an efficient and timely manner. This will be extremely helpful in managing our patients, who often see many specialists. Such systems will allow us to optimize a multidisciplinary approach in the care of our families.

An increase in stem cell research may also help scientists use novel approaches to treat and prevent cancer. We are excited to see what new treatments unfold over the next decade and look forward to sharing each new advance with you.

Sincerely,

Ellen T. Matloff, MS
Director, Cancer Genetic Counseling

Editor's Letter

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Vist Our Blog on Cancer Genetics

This innovative resource will help keep patients and providers updated on the newest research, announcements, and events at the Yale Cancer Center Genetic Counseling Program.

For more information please visit:
yalecancergeneticcounseling.blogspot.com
RISK FACTORS OF HEREDITARY CANCER SYNDROMES

Risk Factors
Hereditary Breast and Ovarian Cancer

A personal and/or family history of:
• Breast cancer diagnosed before age 45.
• Multiple cases of breast cancer on the same side of the family.
• Ovarian cancer in a family with breast cancer.
• Male breast cancer.
• The combination of pancreatic, breast, and/or ovarian cancer on the same side of the family or in a single individual.
• Jewish ancestry in combination with any of the above.
• Jewish ancestry and even one case of breast or ovarian cancer (even in the absence of additional family history).
• Medullary breast cancer and triple negative breast cancer are over-represented in women with BRCA1 mutations.

Risk Factors
Hereditary Colon Cancer

A personal and/or family history of:
• Colon cancer diagnosed before age 50.
• Multiple cases of colon cancer on the same side of the family.
• The combination of colon, uterine, ovarian, urinary tract, and/or other gastrointestinal cancers on the same side of the family.
• A single individual diagnosed with colon and uterine cancer, synchronous/metachronous colon cancers, or colon and ovarian cancer.
• Even one sebaceous carcinoma.
• Colon cancer that is MSI (microsatellite instability) positive and/or shows the loss of an HNPCC-related protein via immunohistochemistry.
• Multiple adenomatous, hamartomatous, or juvenile polyps.

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inherited in an autosomal dominant pattern:

CLEAR CELL RCC

1. Von Hippel-Lindau (VHL) syndrome
   • VHL tumor-suppressor gene on chromosome 3p25-26
   • ~40-70% develop RCC, often multiple and bilateral, at an average age of 40
   • Other clinical features include:
     – Central nervous system and retinal hemangioblastomas
     – Pheochromocytomas
     – Pancreatic neuroendocrine tumors
     – Renal, hepatic, and pancreatic cysts
     – Endolymphatic sac tumors
     – Papillary cystadenoma of the epididymus or broad ligament

2. Hereditary Paraganglioma type 4 (PGL4)
   • SDHB gene (succinate dehydrogenase subunit B) on chromosome 1p36
   • Main features are paragangliomas and pheochromocytomas (tumors of the autonomic nervous system)
   • A 2004 study showed that ~7% of SDHB carriers had RCC and a recent study of individuals with non-syndromic RCC showed that ~4.4% had SDHB mutations (These individuals had no known personal or family history of paragangliomas or pheochromocytomas).
   • Tumors were early-onset and mainly clear cell type

3. Tuberous Sclerosis (TS)
   • TSC1 gene on chromosome 9q34 and TSC2 gene on 16p13.3
   • Main features include abnormalities of the skin (e.g. facial angiofibromas, hypomelanotic macules, shagreen patches), brain (e.g. subependymal nodules, cortical tubers, subependymal giant cell astrocytomas, seizures, mental retardation, behavioral disturbances), kidney (e.g. angiomyolipomas, cysts, RCC), and heart (e.g. rhabdomyomas, arrhythmias).
   • ~1-5% develop RCC (mainly clear cell type) at an average age of 28

PAPILLARY RCC

1. Hereditary Papillary Renal Cell Carcinoma (HPRC)
   • MET proto-oncogene on chromosome 7q31-34
   • Characterized by multifocal, bilateral papillary type I RCC
   • Earlier average age of onset (majority diagnosed <60 and as early as 20) than sporadic cases, with or without family history of papillary RCC

2. Hereditary Leiomymatosis Renal Cell Carcinoma (HLRCC)
   • Fumarate Hydratase (FH) gene on chromosome 1q42.1
   • ~10-30% develop renal cancer at an average age of ~36-44
   • Usually papillary type II RCC (high grade with large nuclei and prominent eosinophilic nucleoli) but occasionally other types (collecting duct, tubulo-papillary, tubular, and mixed).
   • Often unilateral and solitary lesions but an aggressive course with early metastases even from small primary lesions and a poor prognosis
   • Other clinical features include:
     – Cutaneous leiomyomas appear on average at age 25, increase in number and size with age, and can be quite variable in number (1 to >100 lesions) and presentation pattern (single, clustered, segmental, or disseminated). These skin-colored to light brown benign nodules arise from the smooth muscle fibers associated with hair follicles and are often painful, itchy, and/or sensitive to cold temperatures.
     – Almost all women with HLRCC develop uterine leiomyomas (fibroid tumors) which are more often large, numerous, present at a younger age (<30), and require hysterectomy at a younger age than sporadic cases.

References:
Journal Clips


In this retrospective analysis of 35 patients diagnosed with endometrial cancers arising solely in the lower uterine segment (LUS), 10 patients (29%) were found to have Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch syndrome). This is significant when compared to the prevalence of HNPCC in the general endometrial cancer patient population (1.8%) and in women diagnosed with endometrial cancer under the age or 50 (~9%). The diagnosis of HNPCC was made either through genetic testing or by immunohistochemistry (IHC) and microsatellite instability (MSI) results that were highly suspicious for a mismatch repair gene mutation. These patients were more likely to have a first-degree relative with an HNPCC-associated cancer (i.e. endometrial, colon, small bowel, or urinary tract cancer). Due to the fact that HNPCC was over-represented amongst this small cohort, the authors recommend that the possibility of HNPCC be considered in all women diagnosed with LUS tumors.


237 women diagnosed with ovarian cancer were asked to complete a self-administered survey about BRCA genetic testing. Women with all types of ovarian cancer, regardless of family history, were asked to participate. Of this group, 55% indicated that they had not heard about BRCA testing. Eighty-seven percent indicated that they would be willing to have genetic testing to benefit their family and 89% indicated that they would be willing to have testing if it impacted their therapy. Given that the prevalence of BRCA mutations amongst women diagnosed with invasive ovarian cancer is ~12-15%, and the fact that many women are interested in genetic testing, clinicians should discuss the availability of genetic testing with their ovarian cancer patients and refer appropriate patients for genetic counseling.

HORMONE THERAPY AND THE RISK OF BREAST CANCER IN BRCA1 MUTATION CARRIERS J NATL CANCER INST 2008; 100: 1361-1367.

The relationship between hormone therapy (HT) use and the risk of breast cancer was analyzed in this matched case-control study of 472 postmenopausal BRCA1 mutation carriers. These findings suggest that HT use was not associated with an increased risk of breast cancer among BRCA1 mutation carriers. In fact, compared to BRCA1 mutation carriers who never used HT, women in this study who used HT (estrogen alone) had a lower risk of breast cancer. This association appeared to be greater for women who had undergone surgical menopause as opposed to natural menopause. There was no significant difference between the use of estrogen alone and combined therapy overall or the duration of use. These data are preliminary and included small numbers, and thus needs to be studied further before clinical conclusions can be drawn.

ACLU Investigates Gene Patenting

The American Civil Liberties Union (ACLU) is looking into the legality of patenting human genes, including the BRCA1 and BRCA2 genes, and the effects of patenting these genes on research and testing. As we develop our advocacy, we are reaching out to healthcare providers to better understand patients’ experiences with testing.

The ACLU is interested in hearing from you if you have patients who have been advised to get the BRCA test and fall into one of the following categories:

1. They have been advised by their doctor or counselor that they are an appropriate candidate for BRCA testing, but had financial difficulty getting tested (for example, they could not afford the test or they had problems with insurance coverage); or
2. They were tested, and had problems with or concerns about the testing process (for example, their results were unclear or incorrect, or they were advised they might want to be tested a second time due to potential missed rearrangements); or
3. They were tested, and want to be tested again through another lab for verification.

If you have patients who fall into any one of the above categories, please contact Sandra Park, Staff Attorney at the ACLU Women’s Rights Project, at (212) 519-7871 or spark@aclu.org. She will follow up with you individually to ensure patient confidentiality. Your participation is greatly appreciated.

You may also direct patients to the ACLU’s survey on BRCA testing at www.aclu.org/brcasurvey.
We are hopeful that a renewed commitment to medical and scientific research will reap more testing, prevention, and surveillance options for our patients in the next decade, and an even better understanding of the genes that have already been discovered.