

Cancer Genetic Counseling

Screening for Breast Cancer: Making Sense of the Recommendations for Average and High-Risk Women

By Karina Brierley, MS

In November 2009, the United States Preventive Services Task Force (USPSTF) released new breast cancer screening guidelines. Unfortunately, this ill-timed release coincided with debate over health-care reform leading to strong emotional reactions, misinformation, and controversy. Hopefully, with some time and distance, we can focus on the facts and the commonalities expressed in expert opinions to better understand these guidelines and how to use them to guide screening recommendations for women at average risk. We will also examine new data on the breast cancer screening options for women at high-risk.

First, it is important to address some of the questions that surround this discussion:

WHAT IS THE UNITED STATES PREVENTIVE SERVICES TASK FORCE (USPSTF)?

The USPSTF is an independent panel of primary and preventive care experts established in 1984 to conduct systematic, unbiased reviews of the available scientific evidence regarding the effectiveness of various preventive medical services (1). They make recommendations based on a rigorous review of the data on the risks and benefits to patients (1). They are not a political group, do not consider the cost or coverage issues, and do not set federal policies or determine which services will be covered by federal programs (1).

WHAT RISKS, BENEFITS, AND LIMITATIONS ARE CONSIDERED IN MAKING RECOMMENDATIONS ABOUT BREAST CANCER SCREENING?

The benefit of a breast cancer screening method is often measured by its ability to reduce breast cancer mortality. However, other measures of benefits are sometimes used including the number of cancers detected, the stage at which the cancers are detected, and number of life-years gained.

A number of potential risks are considered including:

- **False negative results**, which may lead to false reassurance and cause a woman to delay seeking treatment for symptoms.
- **False positive results**, which can lead to anxiety, distress, additional screening tests, and unnecessary biopsies.
- **Overdiagnosis** - This is a more recently recognized and poorly understood risk but may prove to be one of the more serious risks. It refers to the fact that some cancers detected by screening may never have caused symptoms or death and may have actually regressed without treatment (2). Overdiagnosis may occur when an early-stage cancer is detected in an older woman who has a higher risk of dying from a competing cause before the breast cancer became clinically significant (3). It may also occur if the screening-detected early-stage lesion is one that would never progress to an invasive cancer (3). A more familiar example of overdiagnosis is the detection of indolent

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Featured Clinical Topic: Lynch Syndrome/Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

By Danielle Campfield, MS

A recent study showed that fewer providers were aware of clinical genetic testing for hereditary colon-uterine cancer than for hereditary breast-ovarian cancer(1). Although BRCA testing has been heavily advertised, clinical genetic testing is available for several of the most common genes involved in Hereditary Non-Polyposis Colorectal Cancer (HNPCC), including MLH1, MSH2, and MSH6. In fact, some providers have become so familiar with BRCA testing that it is often the only test that it offered to families with ovarian cancer, even when their family history is more suggestive of HNPCC.

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Editor's Letter

Ellen T. Matloff, MS
(203) 764-8400
ellen.matloff@yale.edu

Welcome to a new year, a new decade, and continued advances in the field of cancer genetic counseling and testing.

It is impressive to glance back ten short years ago to the year 2000, when cancer genetic counseling and testing was a relatively new phenomenon. We were making surveillance, prevention, and treatment decisions in this area based on best clinical judgment, often with little guidance from long-term, clinical studies. As you will see in this issue of *Advances*, our knowledge base in cancer genetics continues to grow exponentially.

Healthcare reform is one of the big topics on America's agenda this year. We are trending toward smarter, more effective and efficient personalized medicine. This will allow us to care for our patients in a manner that is both cost-effective and tailored toward their actual risks. Genetic counseling and testing will play a major role in that process in the next decade as more testing becomes available for more conditions.

On that note, in this issue you will read our take on the mammography guidelines that caused a nationwide commotion, and much confusion, amongst patients, providers, and the general public in the past few months. Are we basing cancer screening guidelines on emotion and public interest, or on clinical data and knowledge? How should we decide which patients need what screening, when, and how often?

You will also read an update on Lynch Syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC). Lynch syndrome encompasses not only risk for colon cancers, but for ovarian and uterine cancers, as well as several other malignancies and skin findings. There have been multiple local and national reports of HNPCC families erroneously being offered BRCA testing --- sometimes with devastating results.

We've also provided a summary of some of the journal articles that were noteworthy in the last six months. The good news is that we are so inundated with journal articles in the field of Cancer Genetics that it is hard to choose the top three articles to present to you in this forum. It is exciting to think of the thousands of articles that will be published in the next decade, and how those findings will influence and improve our treatment of high-risk patients and their families. We look forward to sorting through those data with you in the future.

Sincerely,

Ellen T. Matloff, MS
Director, Cancer Genetic Counseling

Genetic Testing Company Discourages Doctors From Referring to Genetics Experts: Get the Facts

By Rachel Barnett, MS

Commercial genetic testing companies are aggressively targeting provider's offices and encouraging them to order testing directly and without consultation from a genetics expert. The testing companies argue that their sales forces are "providing doctors with the tools they need to do counseling in-house" (1,2). However, few clinicians have the infrastructure in their office to provide long-term follow-up for patients who carry a mutation, coordination of testing for family members, and methods of re-contacting patients when new laboratory techniques and additional testing become available. The ordering provider must be responsible for these tasks if he/she takes on the role of ordering genetic testing. In addition, the testing companies are not educating doctors about other hereditary cancer syndromes and genetic tests that may be offered by different testing companies, and, therefore, may be providing unbalanced and biased information to physicians, which may result in the wrong test being ordered.

Testing companies are claiming that there are too few genetic counselors to provide genetic counseling services; thus, doctors should provide this service directly to their patients. They argue that referring to an outside genetic counseling center delays testing and cancer treatment. However, there are many genetic counselors in the Northeast, including Connecticut, and accommodations are made for urgent cases to prevent delays in treatment. There are also options for accessing genetic counseling by certified providers through phone- and/or internet-based telemedicine services (e.g. www.informeddna.com).

These marketing tools have led to an increasing number of claims nationwide that patients are receiving "either too little or the wrong information about their genetic risk of developing cancer from companies marketing the tests," said Sue Friedman, Director of Facing Our Risk of Cancer Empowered (FORCE) (3). This has also led, in some cases, to unnecessary surgery, anxiety, and misuse of insurance money (Yale Cancer Genetic Counseling, unpublished data).

We recommend that all patients considering genetic testing be offered genetic counseling by a genetics expert prior to having their blood drawn for testing. To find a list of cancer genetic counselors in Connecticut, go to www.nsgc.org.

References:

1. Myriad Avoids Genetic Counseling 'Bottleneck' for BRCA Testing By Helping Docs Do It Themselves. *Pharmacogenomics Reporter*, September 23, 2009.
2. Myriad Defends Policy of Urging Docs to Genetically Counsel BRCA Analysis Customers. *Pharmacogenomics Reporter*, February 10, 2010.
3. More Patients Experience Inadequate Genetic Testing, Advocacy Official Says. *Pharmacogenomics Reporter*, January 14, 2009.

Patients with any of the following risk factors in their personal or family history should be considered for genetic counseling:

- Colon or uterine cancer diagnosed before the age of 50.
- Related cancers on the same side of the family (colon/uterine/ovarian/urinary tract cancers/sebaceous carcinomas).
- Multiple primary cancers in one individual (e.g. colon and uterine, synchronous/metachronous colon cancers, or colon and ovarian).
- Rare or unusual tumors or physical findings (even one sebaceous carcinoma/adenoma).
- Any HNPCC-related cancer/tumor that demonstrates an MSI (microsatellite instability) or IHC (immunohistochemistry) abnormality.
- A known HNPCC related mutation in the family.

HNPCC is passed down in families in an autosomal dominant pattern of inheritance. Therefore, the siblings and children of a mutation carrier have a 50% risk to carry the familial mutation and genetic counseling is generally recommended by age 25. The following summarizes the current data regarding cancer risks for HNPCC mutation carriers and their options for surveillance and risk reduction:

Colorectal Cancer:

- Lifetime risk ~65-80% with an increased risk of second primary colon cancers.
- **Screening:** Colonoscopy every 1-2 years starting at age 20-25 (or earlier if warranted by family history) (2).
- **Risk Reduction:** Consider total colectomy with ileorectal anastomosis upon a diagnosis of colon cancer. *Prophylactic* colectomy is usually not recommended as regular screening and polypectomy is generally effective (3).

Gynecologic Cancer:

- **Endometrial Cancer:** Lifetime risk ~20-60%
- **Ovarian Cancer:** Lifetime risk ~9-12%
- **Screening:** Educate patients about the symptoms of endometrial cancer and encourage them to seek prompt medical care for any symptoms. Consider annual transvaginal ultrasound, endometrial biopsy, and CA-125 tumor marker blood test starting by age 30 (or earlier if warranted by family history). This screening should preferably take place between day 1-10 of the menstrual cycle (4). *The efficacy of these screening options for women with HNPCC is unclear at this time.*
- **Risk Reduction:** Consider oral contraceptives for risk reduction, although the efficacy is not known specifically among women with HNPCC (2). Consider prophylactic total hysterectomy and bilateral salpingo-oophorectomy by age 35 (or earlier if warranted by family history) (4).

Upper Gastrointestinal and Urinary Tract Cancers:

- **Stomach Cancer** (intestinal type adenocarcinoma): Lifetime risk ~6-19%

- **Small Bowel Cancer** (mainly in duodenum and jejunum): Lifetime risk ~1-7%

- **Urinary Tract Cancer:** Lifetime risk ~4-12%

- **Screening:** Consider upper endoscopy every 1-3 years beginning by age 25-30. Consider annual urinalysis with cytology and imaging of renal collecting system beginning at age 30-35 (4).

Dermatologic Findings:

- Increased risk for sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratoacanthomas. When present in HNPCC, also called Muir-Torre syndrome (4).
- **Screening:** Consider annual dermatologic examination

Cancers of the central nervous system and hepatobiliary tract can also be seen in HNPCC families; however the risks are relatively low (2). The data regarding the efficacy of screening for these cancers are limited and thus there are few, if any, standard screening recommendations. Some suggest an annual physical exam to screen for CNS tumors and endoscopic ultrasound for hepatobiliary cancers (4). The benefits, limitations, risks, and costs of the screening options must be weighed carefully for each individual.

Breast cancer is commonly misperceived as part of the spectrum of cancers seen in HNPCC. Although it is a common cancer, and can be seen with colon cancers in other rare syndromes (e.g., Peutz-Jeghers), the rate of breast cancer is not increased in HNPCC mutation positive families (5).

In the past 15 years, clinically-based genetic testing has evolved from an uncommon analysis ordered for the rare hereditary cancer family to a widely available tool ordered on a routine basis. As the technology of genetic testing continues to grow at expansive rates, it is paramount to ensure that patients are being offered the appropriate genetic test and receiving interpretation of accurate results. Although widespread advertising by commercial testing laboratories has increased the demand for testing, in some instances it has led to testing of the wrong gene, even in families where an HNPCC mutation has already been identified (6). We recommend that all patients considering genetic testing be offered genetic counseling by a genetics expert prior to having their blood drawn for testing. We encourage providers to continue to elicit detailed histories and choose appropriate candidates for genetic counseling. It is quite possible that the results from genetic counseling and testing will be one of a patients' most valuable pieces of medical information.

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4. J Natl Compr Canc Netw (2010) 8(1):8-61.
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6. Yale Unpublished Data (2009).

prostate cancers with PSA screening. Since it is not currently possible to discriminate between breast cancers that are likely to be indolent and pose minimal risk and those that are likely to be more aggressive, all cancers are considered potentially life-threatening and treated with some combination of surgery, chemotherapy, radiation, or hormonal therapy (2). Therefore, some patients are unnecessarily exposed to the harms of these treatments and the emotional consequences of being diagnosed with cancer (2). Although population-level estimates of overdiagnosis are somewhat uncertain, data from randomized controlled trials of screening mammography suggest that the rate of overdiagnosis is between 1% and 30% with most estimates falling in the 1-10% range (4).

- **Radiation exposure** - Mammograms expose the breast tissue to low levels of radiation (4). High doses of radiation (e.g. chest wall radiation for treatment of lymphoma) have been shown to increase the risk of breast cancer (4). However, there are no data regarding a direct association between radiation exposure from mammograms and breast cancer risk and the amount of radiation exposure from mammograms is generally considered safe (4).

WHAT BREAST CANCER SCREENING RECOMMENDATIONS WERE MADE BY THE USPSTF AND WHAT DO THEY REALLY MEAN?

Keep in mind that these recommendations are intended for women at average risk for breast cancer.

The USPSTF:

- **Recommends biennial screening mammography for women aged 50-74 years** (3).

This is based on data which show that the benefits of mammography outweigh the risks in this age group. This extends previous screening recommendations from age 70 to age 74 and changes the recommended screening interval from every 1-2 years to every 2 years. This change was based on data, which show a better balance of benefits and risks with screening every two years due to a significant reduction in the risks (~50% fewer false positive results) while maintaining most of the benefit (71-99%) seen with annual screening (3,5).

- **Recommends against routine screening mammography in women aged 40-49 years. The decision to start regular, biennial screening mammography before the age of 50 should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms** (3).

This recommendation met with the most controversy. However, some of this was due to misinterpretation of the intent of the recommendation and unclear wording (1). It does not mean that mammograms are of no value to women in their forties or that no woman in her forties should have mammograms (1,6). In fact, screening mammography does reduce breast cancer mortality in women in their forties (3,4,6).

However, the risks associated with screening mammograms (false

positive results) are higher at younger ages and thus the absolute benefit is smaller (1,3,4,6). The first sentence of this recommendation has now been removed to clarify the intent which is that screening in this age group should not be automatic but instead involve an individual, informed decision by a woman and her healthcare provider based on a weighing of her personal risks, benefits, and values (1, 3).

- **Recommends against teaching breast self-examination** (3).

The available data about BSE, although somewhat limited, show an association with an increase in unnecessary biopsies and no reduction in breast cancer mortality (4). This recommendation is in agreement with previous recommendations by other organizations. *However, experts agree that women should still be encouraged to promptly bring any concerns about lumps or changes in their breasts to the attention of their physician* (1,5).

- **Concludes that there is insufficient evidence to assess the benefits and harms of several screening options including: screening mammography in women aged 75 and older, clinical breast exam (CBE), and digital mammography or MRI instead of film mammography** (3).

IS THERE ANY NEW DATA ABOUT BREAST CANCER SCREENING OPTIONS FOR WOMEN AT HIGH RISK?

Although it did not receive the same attention as the USPSTF guidelines, another article published in November addressed breast cancer screening options for women at high-risk. This study compared the effectiveness of several additional breast cancer screening methods (digital mammograms, whole breast ultrasounds, and MRI) in 609 high-risk women who had a normal mammogram within 6 months of enrolling in the study (7). A total of 20 cancers (9 DCIS and 11 invasive) were diagnosed in 18 patients. They concluded that MRI was more sensitive than mammograms and ultrasounds (7). However, the specificity of MRI was lower than other modalities. Based on their data, Weinstein, et al., conclude that the addition of MRI to standard mammography screening is the most effective option for detecting additional cancers in high-risk women and thus support the American Cancer Society recommendation of MRI screening for women with a >20-25% lifetime risk of breast cancer (7). They also conclude that digital mammograms are not a good replacement for MRI but may be an alternative to film mammograms in high-risk patients and that whole breast ultrasound should be reserved for patients who cannot undergo MRI (7).

In conclusion, clinicians should recognize and help patients to understand that the mammography controversy is not new and that although mammography is the best available breast cancer screening option for the general population and reduces breast cancer mortality, it is not without its limitations and harms. Mammography fails to detect a large number of cancers, particularly the most aggressive and lethal ones, and it leads to false positives and overdiagnosis too frequently. Therefore, healthcare providers should help women make informed decisions about breast cancer screen-

ing by assessing their risk based on family and personal history, referring high-risk women for further assessment and genetic testing, and discussing the risks, benefits, and limitations of the available options and individual preferences and values.

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Cancer Genetic Counseling Program

yalecancercenter.org/genetics

Ellen Matloff, MS, Director
(203) 764-8400

Allen E. Bale, MD, Medical Director
(203) 785-5749

Rachel E. Barnett, MS
Cancer Genetic Counselor
(203) 764-8400

Karina L. Brierley, MS, Cancer Genetic Counselor and Managing Editor of *Advances*
(203) 764-8400

Danielle Campfield, MS
Cancer Genetic Counselor
(203) 764-8400

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For more information please visit:
yalecancergeneticcounseling.blogspot.com

Journal Clips

CONTRALATERAL BREAST CANCER RISK IN BRCA1 AND BRCA2 MUTATION CARRIERS

J CLIN ONCOL 2009; 27:5887-5892.

We have long suspected that BRCA carriers are at increased risk for contralateral breast cancer, and this study confirms that suspicion. This large, retrospective, multicenter German study comprised 2,020 women with unilateral breast cancer from 978 BRCA families. The cumulative risk for contralateral breast cancer 25 years after the first breast cancer was 47.4%. The risk in BRCA1 families was greater than in BRCA2 families. Younger age at first breast cancer diagnosis was associated with a significantly higher risk of contralateral breast cancer in patients with a BRCA1 mutation, with a trend observed in BRCA2 families. These data confirm that genetic counseling and testing should precede surgical decision-making whenever possible.

ASSOCIATION OF BRCA1 MUTATIONS WITH OCCULT PRIMARY OVARIAN INSUFFICIENCY: A POSSIBLE EXPLANATION FOR THE LINK BETWEEN INFERTILITY AND BREAST/OVARIAN CANCER RISKS

J CLIN ONCOL 2010; 28:240-244.

Eighty-two women with breast cancer were offered ovarian stimulation and embryo or oocyte cryopreservation for the purpose of fertility preservation. Of these women, 57% (47) had undergone BRCA testing and 12 carried true mutations. Compared with controls, BRCA1 carriers produced lower number of eggs and had a higher likelihood of low response. Further studies are needed in this area before conclusions can be drawn regarding BRCA1 mutations and fertility.

SURVIVAL ANALYSIS OF CANCER RISK REDUCTION STRATEGIES FOR BRCA1/2 MUTATION CARRIERS

J CLIN ONCOL 2010; 28:222-231.

This decision analysis estimated and compared survival for BRCA carriers based on several possible intervention strategies. With no intervention, they estimated survival by age 70 to be 53% for BRCA1 and 71% for BRCA2 mutation carriers. They estimated the most effective single intervention to be prophylactic bilateral salpingo-oophorectomy (BSO) at age 40 for BRCA1 carriers, and prophylactic bilateral mastectomy at age 40 for BRCA2 carriers. The combination of both interventions at age 40 would yield a 24% survival gain for BRCA1 and 11% for BRCA2 carriers. There are several limitations in this analysis. First, this is based on a decision analysis and not a randomized clinical trial (which would be impossible, for obvious reasons). Second, it did not consider the impact of prophylactic use of tamoxifen/raloxifene to reduce the risk of breast cancer. Third, it did not consider the impact of hormone replacement therapy after BSO to reduce the risks of fractures and dementia.

333 Cedar Street
P.O. Box 208028
New Haven, CT 06520-8028

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