

Fall 2007

We hope you've enjoyed a wonderful summer! In this issue we present updates on a direct-to-consumer marketing campaign for genetic testing that is slated to hit CT this fall, and conclude our series focused on hormones and hormonal therapy use by BRCA mutation carriers. As always, we are looking for comments and suggestions for future newsletters and are interested in hearing from you.

Sincerely,
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Yale CANCER CENTER

A Comprehensive Cancer Center Designated
by the National Cancer Institute

Hormone use in *BRCA1* and *BRCA2* Mutation Carriers-Part 2

This section is a continuation of our last newsletter's review of exogenous hormone use in *BRCA1* and *BRCA2* mutation carriers. (Please see the "fact sheets" section of our website at www.yalecancercenter.org/genetics.) This summary will focus on the use of Tamoxifen to reduce breast cancer risks.

Tamoxifen and BRCA Mutation Carriers

The majority of (~65-70%) *BRCA2* carriers develop ER+ tumors, while the majority (~80-90%) of *BRCA1* carriers develop ER-tumors.^{1,2,3} Chemopreventative medications, such as Tamoxifen, reduce the development of ER+ breast cancers in women at high-risk for the disease. However, Tamoxifen is associated with a small, but increased risk of uterine cancer (<1%) (not ovarian cancer) amongst other side effects.

It is well-known that Tamoxifen can reduce the risk of breast cancer in women at increased risk for the disease due to age, family history, or high-risk findings on breast biopsy. Several studies have examined whether Tamoxifen also decreases the risk for breast cancer in BRCA mutation carriers, although this area needs to be thoroughly examined via other study designs (e.g. a controlled study).

In one study of 491 BRCA mutation carriers who were diagnosed with stage I or stage II breast cancer, Tamoxifen reduced the risk of future ipsilateral and contralateral breast cancers.⁴

Another study compared 209 female BRCA mutation carriers with bilateral breast cancer to 384 female BRCA mutation carriers with unilateral breast cancer. This study demonstrated that the risk of a contralateral breast cancer was 50% lower in *BRCA1* mutation carriers who used Tamoxifen as treatment for their initial breast cancer.⁴ A recent follow-up to this study, which included a larger sample size, found Tamoxifen equally effective in reducing the risk of a future breast cancer in both *BRCA1* and *BRCA2* positive breast cancer survivors who were pre-menopausal or had reached natural menopause.⁵

(continued on page 3)

The Lesser-Known Risk of Genetic Testing

The greatest fear cited by patients considering genetic testing is whether their health insurance company will discriminate against them based on their test results. We now have laws, both state and federal, that help protect patients against genetic discrimination. Luckily, we have not seen the discrimination we feared when this technology began.

Surprisingly, we have found that one of the greatest risks of genetic testing is more subtle--it is the risk that the patient's test results will be misinterpreted. In fact, we have now seen several patients who have either had prophylactic surgery or considered it, based on result misinterpretation. Why? One of the main issues is that genetic testing companies are aggressively targeting provider offices and encouraging them to order their own genetic testing. In fact, many testing companies offer their employees financial incentives for the *number of test kits sold*, and the *number of kits ordered* by new providers. These employees have been known to discourage ordering physicians from referring their patients to graduate-trained cancer genetic specialists (even in areas like Connecticut, where these services are widely available), and encourage them to order the testing themselves after little or no training in genetics. This likely presents a medical-legal liability for busy providers who are not well-versed in genetics, and do not have time in their busy practices to provide detailed genetic counseling and testing.

One genetic testing company is planning to launch a direct-to-consumer campaign via television and magazine ads that is slated to hit Connecticut, Massachusetts and New York City this fall. Unlike ads for prescription medications, these ads are currently not regulated by the federal government.¹⁻⁵ As a result, they include no information about the risk factors for hereditary cancer. Furthermore, they have been described in several publications as inaccurate, misleading, and utilizing scare tactics.^{2,3,6} These ads end by encouraging consumers to contact the company directly, where company employees will provide phone counseling. The conflict of interest is clear.

We have joined with other professionals across the country to counter this campaign and others like it. You can help. Go to:

www.responsiblegenetictesting.org

to learn more and to sign a petition asking for federal oversight before this campaign can launch. Please spread the word.

References:

1. JCO 2003; 21(17):3191-3193.
2. New Genetics and Society 2006; 25(1):89-107.
3. JAMA 2002; 288(14):1762-1767.
4. Issues in Science and Technology 2006; 22(3):59-66.
5. Science 2006; 313:1853.
6. Hastings Center Report 2001; 31(3):33-35.

Additional references:

Williams S and Javitt G. (7/25/2006, update 6/15/2007). Direct-to-consumer genetic testing: Empowering or endangering the public? In Policy and Public Opinion: Issue Briefs. Retrieved May 22, 2007, from <http://www.dnapolicy.org/policy.issue.php> .

Greendale K and Pyeritz RE. Empowering primary care health professionals in medical genetics: How soon? How fast? How far? Am J Med Genet 2001;106:223-232.

Hormone use in *BRCA1* and *BRCA2* Mutation Carriers-Part 2

It is unclear whether Tamoxifen further reduces the risk of breast cancer in women who have had a premenopausal bilateral salpingo oophorectomy (BSO). Further studies are needed in this area.^{4,5,6}

There are little data regarding prophylactic Tamoxifen use in *BRCA1* and *BRCA2* mutation carriers who have never been diagnosed with breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) analyzed the effect of Tamoxifen on breast cancer incidence in women never diagnosed with breast cancer; however, this trial did not examine the BRCA status of all of its participants, making conclusions difficult.

Therefore, women who carry either a *BRCA1* or *BRCA2* mutation and have been diagnosed with an ER+ breast cancer may consider taking Tamoxifen or another such medication to reduce their risk of a future breast cancer. *BRCA2* and possibly *BRCA1* mutation carriers who have never had a diagnosis of breast cancer may consider using Tamoxifen (or Raloxifene) prophylactically.

References:

1. Chappuis et al. *Semin Surg Oncol* 2000; 18: 287-295.
2. Lakhani et al. *JCO* 2002; 20(9): 2310-2318.
3. Farshid et al. *Am J Surg Pathol* 2006; 30(11): 1357-1366.
4. Metcalfe et al. *J Clin Oncol* 2004; 22(12): 2328-35.
5. Gronwald J et al. *Int J Cancer* 2006; 118: 2281-84.
6. Narod et al. *Lancet* 2000; 356: 1876-81.

Announcements

Hope Chest Event

The first Hope Chest event was held on May 3, 2007 at the home of Jane Savage and her husband Mark Van Allen. It was a beautiful spring evening and Jane and Mark's young sons, Will (9) and Miles (7), served as waiters for the event, at which about 30 people gathered to learn more about cancer genetics and the Hope Chest. Dr. Kevin Kelly from Yale Cancer Center spoke about the new Cancer Center building, and Jane was generous enough to share her family's story of genetic counseling and testing. Ellen Matloff, MS gave a brief overview of cancer genetics and how counseling and testing can tailor medical management and risk reduction in a family. We have since had several referrals of patients who learned about our program through this event.

Thank you Jane and Mark!

If you are interested in making a contribution to the Hope Chest, or would like additional information, please contact Benita Palmer at (203) 436-8526.

Our website is undergoing an exciting makeover!

Please check for new developments this fall at www.yalecancercenter.org/genetics

Yale Cancer Genetic Counseling Clinics

Yale
55 Church Street, Suite 402 (203) 764-8400

Greenwich, CT
Once a month at the Bendheim Cancer Center, Greenwich Hospital (203) 764-8400

Norwalk, CT
Once a month at the Whittingham Cancer Center, Norwalk Hospital (203) 764-8400

Danbury, CT
Once a month at the Praxair Cancer Center, Danbury Hospital (203) 764-8400

Featured Clinical Issue

Breast Cancer Phenotypes at Greater Risk to be BRCA+

Only ~5-10% of all breast cancers are due to mutations in the *BRCA1* and *BRCA2* genes. Hundreds of mutations distributed throughout the length of these large genes have been identified making the testing process complex and quite expensive. Therefore, one of the key challenges in maximizing the utility of BRCA testing is accurate selection of high-risk patients who are good candidates for testing. Current selection criteria are based on personal and family history risk factors including early age of onset of cancer, multiple affected family members, clustering of related cancers (e.g. breast/ovarian/pancreatic cancer) in a family, multiple primary cancers in one individual, Ashkenazi Jewish ancestry, and male breast cancer. However, use of risk factors which are primarily based on family history may lead to underestimation of risk in some cases, particularly in small families with few female family members. Emerging data suggest that certain distinctive morphologic and immunohistochemical features are over-represented in BRCA-related breast cancers (particularly *BRCA1*-related breast cancers) and that using these features in conjunction with current personal and family history criteria may improve risk assessment and selection of patients for testing.¹ In addition, these distinct features may reflect differences in the underlying biology and behavior of BRCA-related breast cancer and thus may be useful in designing therapies for these patients.² The remainder of this article will outline the morphologic and immunohistochemical features that may increase the likelihood that a patient carries a BRCA mutation. However, it is important to keep in mind that these features should be considered in addition to, and not in place of, current risk factors, particularly since *BRCA2*-related breast cancers have few distinctive features.

Features of *BRCA1*-associated breast cancers (vs. sporadic breast cancers):

- An excess of medullary and atypical medullary carcinoma subtypes^{1,2}
- Higher rate of ER, PR, and HER2 negativity (ER/PR/HER2- or “triple negative”)^{1,2,3}
- “Basal-like” subtype on expression microarray analysis^{1,4}
- Higher grade (due to less tubule formation, more nuclear pleomorphism, and higher mitotic count)^{1,2}
- Expression of basal, myoepithelial markers including EGFR (epidermal growth factor receptor), cytokeratins 5/6, cytokeratin 17, cytokeratin 14, and osteonectin^{1,4}
- Higher rate of continuous pushing margins on tumor perimeter²
- Higher proliferative rate²
- More frequent aneuploidy²
- Higher rate of somatic *p53* gene mutations and higher rate of *p53* protein overexpression²
- More often have an important lymphocytic infiltration²

Features of *BRCA2*-associated breast cancers:

- Higher grade due to less tubule formation, only (no difference in nuclear pleomorphism or mitotic count)^{1,2}
- Higher rate of continuous pushing margins on tumor perimeter²
- Higher rate of somatic *p53* gene mutations and higher rate of *p53* protein overexpression²

References:

1. Farshid et al. *Am J Surg Pathol* 2006;30:1357-1366.
2. Chappuis et al. *Seminars in Surgical Oncology* 2000; 18:287-295.
3. Kandel et al. *JCO* 2006; 24(18S):508.
4. Lakhani et al. *Clin Cancer Res* 2005; 11(14):5175-5180.

Journal Clips

Updates and Recommendations on Breast MRI Screening

CA Cancer J Clin 2007;57(2):75-89. and *NEJM* 2007;356(13):1295-303.

The American Cancer Society recently released new recommendations for the use of MRI in women at increased risk for breast cancer. The panel recommends annual breast MRI screening in addition to annual mammography for women who:

- carry a *BRCA1* or *BRCA2* mutation;
- have a first-degree relative with a *BRCA1* or *BRCA2* mutation *and are untested*;
- have an increased lifetime risk of breast cancer of at least 20 to 25% based on their family history;
- have another known genetic susceptibility to breast cancer, or;
- have received radiation treatment to the chest, such as treatment for Hodgkin's Disease.

Furthermore, a study by Lehman et al. screened 969 women who had a recent diagnosis of unilateral breast cancer with clinical breast exam, mammography and MRI to look for contralateral, second primary breast cancers. MRI detected 30 (3.1%) clinically and mammographically occult breast cancers in the contralateral breast. Therefore, MRI should be considered in women with a recent diagnosis of unilateral breast cancer and in women at increased risk.

Prostate Cancer Progression and Survival in BRCA2 Mutation Carriers

JNCI 2007;99:929-35.

This case control study conducted in Iceland screened 527 men with prostate cancer for the common Icelandic *BRCA2* mutation and found 30 carriers (5.7%). Patient records revealed that mutation carriers were 5 years younger at diagnosis, had higher 5 and 10 year mortality rates (79% and 90% vs. 29% and 45%) and had a shorter median survival time (2.1 vs. 12.4 years) than non-carriers. The majority of mutation carriers had metastatic disease at diagnosis (55% vs. 25%), were diagnosed at advanced stages (79% vs. 39%) and had tumors of grade groups G3-4 at diagnosis (84% vs. 53%) when compared to the controls. These results suggest the need for prostate cancer surveillance among carriers of the common Icelandic *BRCA2* mutation. Because previous reports have also tied other BRCA mutations to the development of prostate cancer, males from a family with a known BRCA mutation should consider genetic counseling and testing and speak with their physicians about early prostate screening (including digital rectal exams and PSA blood marker screening) by age 40 if they are found to carry a BRCA mutation.

New Genes Linked to Increased Breast Cancer Risk

Nature 2007;447(7148):1087-93. and *Nature Genetics* 2007;39(7):865-869 and 870-874.

Reports from several studies have identified new genetic markers that may increase the risk of breast cancer. Although *BRCA1* and *BRCA2* are the most commonly known genes associated with an increased lifetime risk for breast and ovarian cancer, these three studies have identified four potentially new breast cancer susceptibility genes, as well as several genetic markers, that are associated with an increased risk for breast cancer and deserve further investigation.

The first study, by Easton, et al., analyzed small genetic variants called single nucleotide polymorphisms or SNPs. Researchers found SNPs in four genes (*FGFR2*, *TNRC9*, *MAP3K1* and *LSP1*) that were more common in women with breast cancer versus female controls. A second study, by Hunter et al., found four SNPs in the *FGFR2* gene that were found more frequent in menopausal women with breast cancer from families with no history of breast cancer than in the control group. The final paper, by Stacey et al., found SNPs on chromosome 2 and on chromosome 16 that increase the risk of estrogen-receptor-positive breast cancer. One of these variants is located near *TNRC9*, which was also identified in the first study.

It is important to note that women in these studies did not receive BRCA mutation testing. At this time it is premature to offer genetic testing for these genes as they are not fully understood yet. However, these results add to our growing knowledge of breast cancer risks and may, someday, lead to clinical testing.

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