

Cancer Genetic Counseling Program

Diffuse Gastric Cancer and Lobular Breast Cancer

Ellen Matloff, MS

The gene CDH1 is known for its association with Hereditary Diffuse Gastric Cancer (HDGC). However, we now know that mutations in this gene are also responsible for an increased risk of lobular breast cancer. CDH1 is located on chromosome 16q22.1 and encodes the cell-cell adhesion molecule E-cadherin.

More than half of HDGC families (defined as at least 2 cases of diffuse gastric cancer, one diagnosed before the age of 50) carry a detectable mutation in CDH1. The lifetime risks associated with these mutations are:

GASTRIC CANCER, DIFFUSE

40-60% for men
60-80% for women

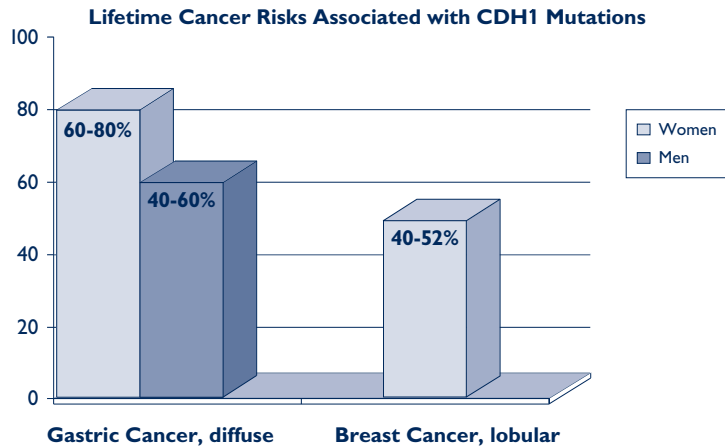
BREAST CANCER, LOBULAR

40-52% for women

The risk of gastric cancer by age 30 is approximately 4%, and the risk by age 50 is 21% for men and 46% for women (1). However, gastric cancers have been reported from age 16 to 82 years, with the youngest reported fatality from gastric cancer in a CDH1 family at age 16 years (2). The option of choice for surveillance in CDH1 carriers is upper endoscopy with random biopsies (1). However, of

concern, 21 of 22 CDH1 mutation carriers who had negative endoscopies and chose to have prophylactic gastrectomies were found to have early diffuse gastric cancer in their tissue specimens (2). Not all early lesions proceed to lethal carcinomas, but this finding calls into question the efficacy of surveillance in this population. For this reason, prophylactic gastrectomy is an option that warrants consideration in known carriers with a strong family history of gastric cancer. This surgery is obviously associated with significant morbidity and potential mortality (<1%) and should be performed after counseling about the pros/cons by a team of experts (2).

The risk of lobular breast cancer in this continued on page 2 >



Sexual Functioning After Cancer or Prophylactic Surgery for Women

Rachel E. Barnett, MS

Sexual functioning is often impacted by cancer treatments such as chemotherapy or radiation to the pelvis. It is estimated that approximately 50% of women diagnosed with a breast cancer or gynecological cancer have serious concerns regarding sexual functioning (1). Women may also experience a change in sexual functioning after prophylactic bilateral salpingo-

oophorectomy (BSO) because of the reduction in estrogen following surgery. We became aware of these issues because they are some of the most popular issues discussed on our patient listserv and at the Yale Cancer Center Connecticut Challenge Survivorship Clinic. However, this important side effect is not routinely discussed in the oncology setting.

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Editor's Letter

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Happy New Year and welcome to the new home of our Provider newsletter. The Yale Cancer Genetic Counseling Program Provider newsletter will now be replaced by a biannual cancer genetic counseling issue of the Yale Cancer Center Advances newsletter.

We have been busy branching out into new areas: sexuality in cancer survivors and previvors, legislation regarding genetic testing and direct-to-consumer (DTC) advertising, and providing long-term counseling services for patients carrying a germline mutation. In this issue you will find an article on sexuality in cancer survivors, which we hope will be of use to you in your practice. We held one Discussion Group for women carrying BRCA mutations on this topic, and plan to have additional events on this important issue.

Many of you may have now seen the DTC advertising for BRCA1 and BRCA2 carriers, and a few of you report that more patients have begun requesting this test. We've also heard from many of you that you've been approached by representatives of this company and have been encouraged to provide your own genetic counseling and testing. We are examining this issue and would very much like to hear your experiences. Please feel free to contact us via e-mail at ellen.matloff@yale.edu

We welcome all of our new readers and look forward to your suggestions for upcoming editions.

Sincerely,

Ellen T. Matloff, MS

► GASTRIC AND BREAST CANCER continued from page 1

syndrome is often overlooked and can be an important factor in calculating risk. Female carriers of a CDH1 mutation can be offered surveillance in the form of earlier mammograms, breast MRI, and clinical breast exams. Risk reduction in the form of tamoxifen or prophylactic mastectomy (particularly because these cancers are most often lobular) is also an option. One study done on women with either early-onset (<45 years) lobular breast cancer and/or a family history of lobular breast cancer without gastric cancer found that 1/23 (4%) women carried a CDH1 mutation (3). While this is certainly not suggestive that every woman with breast cancer should be offered CDH1 testing, we now know:

1. The type of breast cancer (ductal vs. lobular) is an important component of every family history.
2. In every family history of breast can-

cer, we need to elicit a history of diffuse gastric cancer.

3. Family histories of lobular breast cancer and diffuse gastric cancer are more suggestive of CDH1 than of BRCA1 or BRCA2.

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FDA issues warning about Pharmacy Compounded "Bio-Identical" Hormone Therapy

In January, The FDA sent letters to seven pharmacies warning them to stop making false and misleading statements about the safety and efficacy of their "bio-identical hormone replacement therapy products." The FDA is also cautioning physicians and consumers to be aware that many of the claims about the safety, efficacy, and superiority of these products are deceptive. There is no evidence to suggest that the risks and benefits of these drugs are any different from the risks and benefits of FDA-approved hormone therapy drugs (including increased risks of breast cancer, blood clots, and stroke). In fact, these drugs may be less safe as there are fewer regulations to ensure their quality, purity, and dosage. For more information about these warnings and the myths and facts about "bio-identicals," please visit the following FDA webpage: <http://www.fda.gov/consumer/updates/bioidenticals010908.html>

Connecticut Medicaid Now Covering Genetic Testing at Myriad Labs

Myriad Genetic Laboratories, Inc. will now accept Connecticut Medicaid for the tests that they perform. In the past, most Connecticut Medicaid policies did not cover testing at Myriad because the lab is located out of state. If you have patients with Connecticut Medicaid who were denied coverage in the past, please have them contact our office if they are interested in pursuing preauthorization to determine their current coverage.

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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Therefore, here we propose a sample approach for speaking to patients about these side effects.

1. ASK YOUR PATIENT WHETHER SHE HAS HAD SEXUAL CHANGES AFTER TREATMENT OR SURGERY.

Many patients will not initiate this conversation with their health care provider. The most important thing is to initiate this discussion and identify that this is a topic that your patients can discuss with you.

2. SUGGEST THAT YOUR PATIENT GET FAMILIAR WITH HER BODY AGAIN AFTER SURGERY AND/OR TREATMENT AND HOW IT HAS CHANGED.

Ask your patient to make some time alone to look in the mirror or to feel how her body has changed, clothed and unclothed. What, if anything, has changed about her physical appearance? What is the same prior to her surgery and/or treatment? It is important for a woman to take time to feel comfortable with her body before approaching intimacy after surgery or a cancer diagnosis.

3. ENCOURAGE YOUR PATIENT TO APPROACH HER SEXUALITY BY HERSELF, FIRST.

Have your patient ask herself: Are there areas that are more or less sensitive after surgery? This process is important so that your patient can communicate with her partner about what she likes and what to avoid.

4. ASK YOUR PATIENT TO IDENTIFY WHAT HAS CHANGED.

a. Does she report a decrease in vaginal moisture?

Estrogen is important for maintaining vaginal health, but has little influence on sexual desire. Decreased estrogen levels can lead to decreased blood flow to vaginal tissue and thinning of the vaginal wall resulting in vaginal dryness or tightness and/or pain during sex. Some types of hormonal therapy (i.e. Evista and Tamoxifen) may also cause vaginal dryness. Studies have shown that short-term hormone replacement therapy (HRT) is an option for young women with no previous history of cancer who carry BRCA mutations and have their ovaries removed before natural menopause (2). HRT may temporarily alleviate the side effects of surgical menopause (i.e. hot flashes) and maintain vaginal health.

Decreased estrogen levels may be more difficult to address in cancer survivors because systemic HRT is often not an option. Internal lubrication, including vaginal moisturizers (i.e. Replens) and water-based lubricants (KY or Good Clean Love) used during intercourse, may help to alleviate vaginal dryness and tightness. Vaginal hormone replacement (i.e. low-dose Estring or Vagifem) provide localized hormones to the vagina and can promote vaginal health (1). Cancer survivors should always speak to their oncologists before initiating any form of hormonal therapy. Gentle massage to the vaginal walls can also increase blood flow to the area.

Bioidentical hormones can have the same adverse side effects as tradi-

tional hormonal therapies. Bioidentical hormones may be compounded to create formulas that are not commercially available and are individually customized based on saliva tests. These compounded bioidentical hormones have been promoted as safer and as more natural than conventional hormonal therapy; however, there are limited scientific data to support these claims. Compounded preparations are not regulated by the FDA and may vary in potency and efficacy. Customized preparations based on saliva tests have shown to be unreliable (3). Until more data are available we should proceed with caution in this area.

Remind your patient to take it slowly.

b. Is there a decrease in size or elasticity of her vagina?

Surgery and/or cancer treatment may affect the size and elasticity of the vagina which can result in pain during intercourse. Pain may also be caused by adhesions from pelvic surgery, radiation therapy, or not enough lubrication. Relaxation training/behavior therapy, Kegel exercises, and pelvic floor rehabilitation are tools that can be used to reduce painful intercourse and enhance pleasure.

Vaginal dilators, when used in combination with lubrication, can be used in gradual steps to keep the vaginal walls open and flexible and to promote vaginal muscle relaxation, thus reducing pain (4). Vaginal dilators may be recommended after radiation treatment. Dilators are recommended only for patients who do not have a medical problem or allergy that a dilator could aggravate.

Remind your patient to take it slow and that she may need to experiment with other forms of intimacy before moving on to intercourse.

c. Does she report sensations on her surgical sites?

Recommend that your patient avoid touching uncomfortable or sensitive areas during intimacy and communicate this to her partner before becoming intimate again. Suggest that your patient create a code-word to let her partner know when something doesn't feel right.

d. Is there a decrease in libido?

This is a complex issue which may be due to a combination of causes. Cancer treatments and medications (i.e. antidepressants and narcotic pain relievers) may alter libido or just make your patient feel plain lousy. Determine whether a change in libido is a side-effect associated with any of her treatments and/or medication. Emotional and psychological changes can also affect libido. If your patient feels good about herself, her relationship, and sets aside time for intimacy, her libido may return.

Testosterone therapy has been touted as an effective treatment for low sexual desire; however, limited long-term data are available and there exist concerns that testosterone supplementation may increase breast cancer risk and risk of recurrence (5).

5. DISCUSS THE IMPORTANCE OF ESTABLISHING AN OPEN DIALOGUE WITH HER PARTNER.

Communication is key. Your patient should ask herself how she feels. Is she scared or nervous? How does her partner feel? Changes in sexual functioning can be due to psychological or emotional issues. A cancer diagnosis may take a significant toll on the way a woman feels about her sexuality and can affect sexual relations with her partner. Issues of mortality may arise. Prophylactic surgeries may alter arousal and/or body image.

Some of these issues can be addressed through counseling with a professionally trained psychologist or social worker. Certified Sex Therapists can help to discuss these concerns and also address the physical barriers to intercourse (as described above) and discuss methods to learn to use the body in a different way after a cancer diagnosis or prophylactic surgery. A growing number of cancer centers are developing sexual health programs to address the needs of cancer survivors.

Remind your patient to take it slowly. She may not be ready for intercourse right away after surgery and can rely on touch, massage, music, etc to maintain intimacy with her partner and work up to intercourse over time. Rediscovering her body and sexuality can be an exciting and positive experience for your patient.

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Journal Clips

BREAST CANCER RISKS AMONG MALE BRCA1 AND BRCA2 MUTATION CARRIERS *JNCI* 2007; 99:1811-4.

This study, by Tai et al., evaluated 1939 families with a significant history of breast and ovarian cancer for the presence of a BRCA mutation. The sample included 97 men diagnosed with breast cancer and 35 (36%) were found to carry a BRCA mutation (6 BRCA1 and 29 BRCA2). Researchers retrospectively studied the risk of developing male breast cancer and estimated that male BRCA2 mutation carriers have an 8.3% lifetime risk to develop breast cancer and that male BRCA1 mutation carriers have a 1.8% lifetime risk to develop breast cancer. These estimates are higher than the 0.1% general population risk of male breast cancer. In addition, male carriers in their 30-40s may have the greatest risk to develop breast cancer when compared to non-carriers. Therefore, males from a family with a known BRCA mutation should consider genetic counseling and testing. Men who carry a BRCA mutation should speak with their physicians regarding their options for breast screening including annual clinical breast exams and careful monthly self breast exams.

PREVALENCE OF PATHOGENIC BRCA1 MUTATION CARRIERS IN 5 UNITED STATES RACIAL/ETHNIC GROUPS *JAMA* 2007;298(24)2869-2876.

This study estimated the prevalence of BRCA1 mutations in several racial/ethnic minorities by offering genetic testing to women diagnosed with invasive breast cancer under age 65. BRCA1 mutation testing was completed for 548 non-Hispanic whites, 444 Asian-Americans, 393 Hispanics and 341 African-Americans. Mutations were identified in women from all ethnic backgrounds. Of note, ~17% of African-American women diagnosed under age 35 with a family history of breast or ovarian cancer were found to carry a mutation. This mutation rate was higher among African-Americans than those of other ethnic backgrounds with similar histories. This finding may help to explain why African-American women are more likely to be diagnosed at younger ages and are more likely to have higher grade, estrogen-receptor negative tumors, since these features are also over-represented in BRCA1-associated breast cancers.

PROSPECTIVE DETERMINATION OF PREVALENCE OF LYNCH SYNDROME IN YOUNG WOMEN WITH ENDOMETRIAL CANCER *JCO* 2007;25(33)5158-5164.

Individuals who carry mutations associated with Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC) are at increased risk for cancers of the colon, uterus and ovary. This study examined 100 women diagnosed with endometrial cancer under the age of 50 and found that 9 (9%) women carried a germline mutation in MLH1, MSH2 or MSH6 associated with HNPCC. All mutation carriers had a first degree relative with an HNPCC-related cancer and 7 (77%) met Amsterdam criteria for HNPCC. The mean body mass index for mutation carriers was significantly lower than non-carriers as BMI is a risk factor for the development of endometrial cancer. In addition, 21 women from the entire cohort had a first degree relative with an HNPCC-related cancer and 43% of these women were found to carry a mutation. Therefore, women diagnosed with endometrial cancer under the age of 50 should be referred to genetic counseling to expand their family history and discuss their options for testing.

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Cancer Genetic Counseling Program

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Please visit our new website to learn the facts about genetic testing and to refer a patient for counseling at yalecancercenter.org/genetics.