

# **CGC Update Provider Newsletter**

## **Fall 2001**

We are pleased to bring you the latest edition of the CGC Newsletter, with many updates in the area of Cancer Genetics. We look forward to working with you and your patients as this area continues to expand and progress.

Sincerely,

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## **Prophylactic Bilateral Salpingo-Oophorectomy (BSO) +/- Total Abdominal Hysterectomy (TAH) for BRCA1 and BRCA2 Carriers**

It has been well established that BRCA carriers have between a 15-60% lifetime risk to develop ovarian cancer, as opposed to the 1-2% lifetime risk of this disease observed in the general population<sup>1-2</sup>. Surveillance for ovarian cancer via transvaginal ultrasound and/or CA-125 is available, but there are no conclusive data that demonstrate that these surveillance techniques detect ovarian cancer at an early, more treatable stage. While clinicians have been hopeful that oral contraceptives will reduce the risk of ovarian cancer in BRCA carriers - as proven in women in the general population - a recent study calls this into question (see Journal Clips in this newsletter). For these reasons and due to the poor prognosis associated with ovarian cancer, prophylactic BSO should be considered in BRCA carriers who are >35 years of age and are finished with childbearing<sup>3</sup>.

Studies have demonstrated that prophylactic BSO, like most prophylactic surgeries, does not reduce the risk of ovarian cancer to zero. The majority of this residual risk lies in the risk of developing a primary peritoneal carcinoma<sup>4</sup>. However, recent data suggest that prophylactic BSO in BRCA carriers reduces the risk of ovarian cancer by approximately 95%, and significantly reduces the risk of breast cancer in premenopausal BRCA carriers<sup>5</sup>.

Should healthy BRCA carriers considering prophylactic BSO have this procedure alone, or as part of a complete hysterectomy? A few case studies report uterine serous papillary carcinomas in BRCA carriers, raising the question of whether carriers are at increased risk for these aggressive uterine tumors<sup>6</sup>. Researchers from Memorial Sloan-Kettering approached this question by testing 199 Jewish women diagnosed with endometrial cancer for the common Jewish BRCA mutations<sup>7</sup>. They did not find an excess of carriers in this population. This finding, combined with the fact that uterine cancer was not reported in excess in the original BRCA linkage analyses, provides evidence that endometrial cancer is not increased in BRCA carriers.

In addition, women who carry BRCA mutations are also at increased risk to develop breast cancer, and therefore may also be candidates for prophylactic tamoxifen use. Some clinicians have argued that because the incidence of endometrial cancer is increased in tamoxifen users, these women should have TAH in addition to BSO. However, when we compare the low risk of endometrial cancer associated with tamoxifen use and the high early-detection and cure rate of this disease with the risks/benefits of the procedure, it is not clear that such additional surgery is advisable or necessary in this population based on carrier status alone.

### **References**

1. *Am J Hum Genet* 1995; 56:265-71.
2. *Am J Hum Genet* 1997; 61:120-28.
3. *Am J Obstet Gynecol* 1996; 176:1.

4. *JNCI Monographs* 1995; 17:33-35.
5. *J Natl Cancer Inst* 1999; 91:1475-79.
6. *Gyne Oncol* 1999; 75:300-4.
7. *Gyne Oncol* 2001; 80:395-98.



and his or her physician should consider both the age-specific risks of gastric cancer and the high morbidity of the surgery (estimated 100% long term morbidity even in young, healthy patients). Mutation carriers who decide not to have prophylactic gastrectomy should have intensive surveillance including detailed endoscopy every 6 to 12 months and multiple biopsies of any suspicious lesions.

**Several steps should be taken to determine which families should consider genetic counseling and testing for HDGC. They are as follows:**

1. Review histopathology on gastric cancer cases in the family. Only families with tumors that have a diffuse component (either of the isolated cell or mixed types) have been shown to have HDGC.
2. Examine family history in detail to exclude other familial cancer syndromes that can include gastric cancer as a feature. These include hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), Li-Fraumeni syndrome (LFS), Peutz-Jegher syndrome (PJS), and Cowden disease (CD).
3. Determine if the family fits the **current diagnostic criteria** for HDGC:
  - 2 or more documented cases of diffuse gastric cancer in 1<sup>st</sup> or 2<sup>nd</sup> degree relatives with at least one case diagnosed prior to age 50

**OR**

  - 3 or more documented cases of diffuse gastric cancer in 1<sup>st</sup> or 2<sup>nd</sup> degree relatives, regardless of age of onset

**References**

*N Engl J Med* (2001) 344(25): 1904-1909. \*

*J Med Genet* (1999) 36(12): 873-880. \*

*Human Molecular Genetics* (1999) 8(4): 607-610.

*Nature* (1998) 392: 402-404.

\* include screening recommendations

## **Journal Clips**

### **Is Tamoxifen Effective in Reducing the Risk of Breast Cancer in BRCA1 and BRCA2 Carriers?**

*The American Society of Clinical Oncology Meetings, May 2001 [abstract].*

Dr. Mary Claire King and colleagues tested DNA from the 315 women who developed breast cancer during the NSABP Breast Cancer Prevention Trial (BCPT). Eight of these women were BRCA1 carriers [5 on tamoxifen, 3 on placebo], and 11 were BRCA2 carriers [3 on tamoxifen, 8 on placebo]. The design of this study does not allow us to compare the overall percentage of BRCA carriers on tamoxifen vs. placebo who developed breast cancer. Therefore, we are unable to conclude at this time exactly how effective tamoxifen is in reducing the risk of breast cancer in BRCA carriers.

### **The Impact of Prophylactic Bilateral Mastectomy on Breast Cancer Risk in BRCA Carriers**

*NEJM 2001;345(3):159-64.*

This study from the Netherlands followed 139 female, cancer-free BRCA carriers for an average of three years. Of these women, 76 (55%) chose to have prophylactic bilateral total mastectomy (including the nipple) and 63 (45%) chose to be followed by surveillance only. None (0%) of the women who had prophylactic surgery developed breast cancer in this time period, while 8 (12.6%) of the women followed by surveillance developed breast cancer. Of those eight breast cancers, four were associated with at least one positive lymph node and seven were estrogen receptor negative. Two of these tumors were visible by mammogram, six were palpable on clinical breast exam, and one was apparent only on MRI. These data suggest that prophylactic mastectomy reduces the risk of breast cancer in BRCA carriers at three years follow-up.

### **Oral Contraceptive Use and the Risk of Ovarian Cancer**

*NEJM 2001;345(4):235-40.*

This analysis of Jewish women in Israel included 840 ovarian cancer patients and 751 women who had never had cancer. 244/840 (29%) of the women with ovarian cancer carried one of the common Jewish BRCA mutations, while only 13/751 (1.7%) of the control population were BRCA carriers. The authors concluded that oral contraceptive use was less protective, and that increasing parity was more protective, in BRCA carriers. A major limitation of this study, however, is that it included only 13 unaffected BRCA carriers, and therefore cannot draw definitive conclusions regarding the impact of oral contraceptive use on cancer-free women who carry a BRCA mutation.

## **The Yale CGC Program Welcomes a New Genetic Counselor**

The Cancer Genetic Counseling Program is pleased to welcome **Karina L. Brierley, MS** to our team. Karina received her Bachelor's degree in Neuroscience from Bowdoin College and her Master's Degree in Genetic Counseling from Brandeis University. During her graduate training, Karina completed clinical internships at Yale, Boston Children's Hospital, and Dana Farber Cancer Institute. Her thesis research involved surveying obstetricians and gynecologists about their knowledge, interests, and current practices with regard to providing breast and ovarian cancer genetic counseling. Welcome, Kari!

## **Yale Cancer Genetic Counseling Clinics**

### **Yale**

Monday mornings at the Yale Physicians Building

(203) 785-5938

### **Greenwich, CT**

Once a month at the Bendheim Cancer Center

Greenwich Hospital

(203) 785-4253

### **Norwalk, CT**

Once a month at the Whittingham Cancer Center

Norwalk Hospital

(203) 852-2148

### **Danbury, CT**

Once a month at the Praxair Cancer Center

Danbury Hospital

(203) 785-4253

## **CGC Update**

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