

Fall 2004

Our program has grown significantly since the last edition of this newsletter. We have added two new counselors to our team (one replacement, one new position) and have moved into larger space within the same building. We hope that these changes will allow us to serve you and your patients more efficiently! Please contact us with any comments, suggestions, or questions at karina.brierley@yale.edu.

Sincerely,

Karina L. Brierley, MS

Rachel E. Barnett, MS

Danielle Campfield, MS

Ellen T. Matloff, MS

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Should BRCA1/2 Carriers take HRT After Prophylactic Oophorectomy?

Armstrong K, et al. *J Clinical Oncology* 2004; 22(6).

Garber, JE, et al. *J Clinical Oncology* 2004; 22(6).

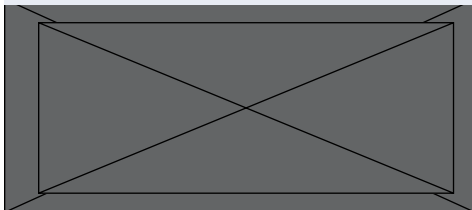
Women who carry a BRCA1 or BRCA2 mutation have a high (15-60%) lifetime risk of developing ovarian cancer. Ovarian cancer surveillance is difficult and rarely detects disease at an early, treatable stage. For this reason, it is recommended that women who carry a BRCA1/2 mutation undergo prophylactic salpingo-oophorectomy before age 40. This procedure obviously causes a surgical menopause.

The side effects of surgical menopause can be severe and can affect quality-of-life and future disease risks. For these reasons it has been suggested that young, healthy women who undergo prophylactic salpingo-oophorectomy should consider taking short-term, low-dose hormone replacement therapy (HRT) to help them transition through premature menopause.

This decision analysis by Armstrong, et al. compared life expectancy in female BRCA carriers who had a prophylactic oophorectomy and used short-term HRT to those who did not use HRT post-surgery. The model considered risk for five different diseases: breast cancer, ovarian cancer, heart disease, osteoporosis and venous thrombosis. The model suggests that in BRCA1/2 carriers the decreased risk of ovarian cancer and breast cancer achieved from prophylactic oophorectomy more than offsets the increased risk of heart disease and osteoporosis (if they don't use HRT) or the increased risk of breast cancer (if they do use HRT). *It appears that women who have a prophylactic oophorectomy reduce their future risk of developing breast cancer, even if they do use short-term HRT.*

The authors state that the decision about whether or not to use short-term HRT after prophylactic oophorectomy should be based on quality-of-life issues, such as symptom relief and cancer-related anxiety. If women do experience menopausal symptoms after this surgery, they can then consider HRT. However, women who have never had cancer and have both a prophylactic oophorectomy and a bilateral prophylactic mastectomy have a breast cancer risk that is so low that short-term HRT should be considered to increase life expectancy, alone.

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Should BRCA1/2 Carriers take HRT After Prophylactic Oophorectomy?

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This paper concludes that BRCA1/2 carriers should not postpone oophorectomy because of concerns about HRT. This is an important issue in that some female BRCA carriers postpone oophorectomy for fear that their providers will discourage use of HRT after surgery, and they will experience severe surgical menopause. Postponing oophorectomy increases risk for both ovarian and breast cancer and is not recommended for these women.

HRT use in high-risk women who experience an early, surgical menopause cannot be compared to data from the recent large studies of HRT in older women who go through a natural menopause and then choose to extend their estrogen exposure by taking hormones. These are two different populations with different risks and different issues.

Announcements

The Cancer Genetic Counseling program has moved to larger space on the 4th floor of the same building on 55 Church Street. Our phone/fax/e-mail all remain the same, but our suite number is now #402.

Christina M. Chimera, MS left the program after two years of outstanding service to join her fiancé, Keith, in Pittsburgh, PA. We wish Christina & Keith all the best!

We are pleased to announce that **Rachel E. Barnett, MS** joined our program on July 1, 2004. Rachel received her Bachelor's degree from Washington and Jefferson College, and her Master's degree in Genetic Counseling from the University of North Carolina at Greensboro.

Danielle Campfield, MS joined our program on August 16, 2004. Danielle received her Bachelor's degree from Case Western Reserve and her Master's degree in Genetic Counseling from Sarah Lawrence College in Bronxville, NY. Danielle completed a summer fellowship in Cancer Genetic Counseling at our program last year and we are excited to have her rejoin our team.

Research Opportunity: Ovarian Cancer Prevention and Surveillance Study

The National Cancer Institute (NCI), in collaboration with the Gynecologic Oncology Group, is sponsoring an ovarian cancer study that focuses on prevention and screening in **high-risk women**. One clinic site of this study is Yale School of Medicine. The two groups of high-risk women being studied are those who choose:

1. prophylactic bilateral salpingo-oophorectomy;
2. surveillance only.

Both groups will complete a series of questionnaires, receive an ultrasound examination, and provide blood samples for screening.

Patients may be eligible for this study if they are at least 30 years old and:

- a. carry a BRCA1/2 mutation or have a family history of a BRCA1/2 mutation, but have not been tested, **and/or**
- b. have a very strong family history of breast and/or ovarian cancer (patients with ovarian cancer are ineligible).

Please contact Linda Rink, RN at (203) 785-6128 to learn more about this study.

Journal Clips

Interval Breast Cancer in Women with BRCA Mutations

Cancer (2004) 100(10):2079-2083.

This study retrospectively reviewed the medical charts of 13 female BRCA carriers who chose to have breast cancer surveillance rather than prophylactic mastectomy. The authors found that 46% (6/13) of these BRCA positive women were diagnosed with a palpable interval breast cancer within an average of 5.1 months from their last mammogram. Four of these patients had invasive breast cancer and three had positive lymph nodes. Although these findings are based on a very small sample at one center, they suggest that BRCA+ patients who choose not to have prophylactic mastectomy should consider more frequent breast cancer screening using additional imaging techniques (ultrasound and/or MRI). These events should be spaced out around the calendar year.

Prophylactic Mastectomy Reduces Breast Cancer Risk in BRCA Mutation Carriers

JCO (2004) 22(6):1-8.

This prospective matched case-control study obtained data via self-administered questionnaires (confirmed with medical records when possible) from BRCA positive women from 11 North American and European centers (including the Yale Cancer Genetic Counseling Program). This data showed that bilateral mastectomy reduces the risk of breast cancer by ~90% in BRCA carriers. Only 1.9% (2/105) women who had bilateral mastectomy were diagnosed with breast cancer as compared to 48.7% (184/378) of controls. Cases and controls were matched based on gene, study center, and age and the analysis was adjusted for endogenous estrogen exposure (including age at bilateral prophylactic oophorectomy). Both women who were diagnosed with breast cancer post-bilateral mastectomy had had subcutaneous mastectomies. Therefore, this study suggests that bilateral prophylactic mastectomy provides a significant reduction in breast cancer risk in BRCA carriers and that total mastectomy (as compared to subcutaneous mastectomy) is the procedure of choice for BRCA carriers.

Biology of Ovarian Cancer: Implications for Screening High-Risk Women

JCO (2004) 22:1315-1327.

This review of the published literature on ovarian cancer screening suggests that current screening methods (CA125 and ultrasound) are unlikely to reduce mortality in high-risk women. In order for screening to reduce mortality in this population, it must detect early-stage invasive epithelial (particularly high-grade serous) ovarian cancer and this review found that these types of tumors are rarely detected with screening. The authors suggest that the biology and natural history of serous ovarian cancer may make it difficult to detect. Therefore, they suggest that the most effective means of reducing ovarian cancer risk and mortality in high-risk women (including BRCA carriers) is prophylactic bilateral salpingo-oophorectomy and that women who chose screening should be informed of the lack of a proven benefit of the available screening methods and the low likelihood of detecting early-stage serous ovarian cancers. The timing of such surgery is obviously dependent upon child-bearing status and age.

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) 852-2148

Danbury, CT

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

Featured Syndrome

Hereditary Pancreatic Cancer

Pancreatic cancer accounts for approximately 2% of all cancer diagnoses worldwide. **It is estimated that up to 10% of pancreatic cancers are due to a hereditary cause.**

Hereditary pancreatic cancer can be characterized into two distinct clinical settings.

1. **Hereditary Cancer Syndromes** (All are autosomal dominant)

a. **Hereditary Breast and Ovarian Cancer (HBOC)**

- BRCA2 is the most common inherited predisposition to familial pancreatic cancer.
- ~4-5% lifetime risk for pancreatic cancer.
- Families with hereditary pancreatic cancer do not necessarily include a significant history of breast and ovarian cancer and may have no other family history of cancer.
- Age of onset does not differ from sporadic cases of pancreatic cancer.

b. **Familial Multiple Mole and Melanoma syndrome (FAMMM)**

- Due to mutations in the p16 protein (CDKN2A) involved in tumor suppression.
- ~17% lifetime risk for pancreatic cancer.
- Clinical features may include a personal and/or family history of: multiple nevi, melanoma (skin findings must be present for a diagnosis), and pancreatic cancer
- Genetic testing is clinically available.

c. **Hereditary Non-Polyposis Colorectal Cancer (HNPCC)**

- Due to mutations in mismatch repair genes (hMSH2, hMLH1, hPMS1, hPMS2, hMSH6).
- Risk for multiple cancers including up to ~65-75% lifetime risk of colorectal cancer, up to ~30-40% lifetime risk of endometrial cancer, and up to an ~10% lifetime risk of ovarian cancer.
- Genetic testing is clinically available.

d. **Peutz-Jeghers syndrome (PJS)**

- Due to mutations in STK11/LKB1.
- Variable penetrance.
- Clinical features may include: hamartomatous polyps in the gastrointestinal tract, pigmented macules of the lips, buccal mucosa, and digits, increased risk of gastrointestinal cancers.
- As high as ~11% lifetime risk of developing pancreatic cancer.
- Genetic testing is clinically available.

2. **Hereditary Pancreatitis**

- Autosomal dominant inheritance due to mutations in PRSS1.
- Clinical features include recurrent pancreatitis, often beginning in the teenage years.
- As high as ~40% lifetime risk of pancreatic cancer.
- Genetic testing is clinically available.

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Featured Syndrome: Hereditary Pancreatic Cancer

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Individuals with pancreatic cancer who should be referred for genetic counseling and genetic testing include those with the following risk factors:

- (1) family history of pancreatic cancer
- (2) family history of melanoma
- (3) family history of colon cancer
- (4) family history of breast and/or ovarian cancer
- (5) Ashkenazi Jewish ancestry
- (6) known family history of any of the above syndromes

References

Am J of Surgery (2003) 186: 279-286
Cancer Journal (2001) 7: 266-273
Cancer Research (2002) 62: 3789-3793
JNCI (2003) 95: 214-221

Which patients should have microsatellite instability (MSI) testing on their colon cancer tumor block?

The Bethesda Guidelines¹ have recently been revised and suggest that colon tumors from individuals meeting any of the following criteria should be tested for MSI:

1. Patients diagnosed with colon cancer at <50 years old (*even in the absence of any additional history*).
2. Patients with synchronous or metachronous colon or other HNPCC-related tumors*, regardless of age.
3. Patients with colon cancer with "MSI-H histology" (i.e. presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed at <60 years old.
4. Patients with colon cancer and 1 or more first degree relatives with an HNPCC-related tumor*, with one of the cancers diagnosed <50 years old.
5. Patients with colon cancer and 2 or more first or second degree relatives with HNPCC-related tumors, regardless of age.

* Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include:

-colorectal, endometrial, stomach, ovarian, pancreatic, ureter and renal pelvis, biliary tract, carcinoma of the small bowel, brain tumors (glioblastoma in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas (seen in Muir-Torre syndrome)

Microsatellite Instability (MSI) is important today because it helps to determine which patients are at high risk for a hereditary form of colon cancer. However, this testing may eventually become a standard of care on all colon cancer tumor blocks as recent data suggests that it may also be important as a prognostic factor and in determining appropriate adjuvant chemotherapy^{2,3}. Some data suggest a significant survival benefit for patients with colon tumors with high microsatellite instability (MSI-H) compared to patients with tumors with low-frequency microsatellite instability (MSI-L) or microsatellite stability^{2,3}. However, several studies have shown that patients with MSI-H tumors do not benefit from 5-fluorouracil-based adjuvant chemotherapy and may actually fare *worse* with this treatment than they would without adjuvant chemotherapy; whereas patients with MSI-L or microsatellite stable colon tumors do benefit from 5-fluorouracil-based adjuvant chemotherapy^{2,3}. More research is needed in this area.

1. *JNCI* (2004) 96(4):261-265.
2. *Gastroenterology* (2004) 126:394-401.
3. *NEJM* (2003) 349(3):247-257.

This newsletter is produced by the:
Yale Cancer Genetic Counseling Program
55 Church Street, Suite 402
New Haven, CT 06510
(203) 764-8400
fax (203) 764-8401
www.yalecancercenter.org/genetics

Written by: Karina L. Brierley, MS
Rachel E. Barnett, MS
Ellen T. Matloff, MS
Edited by: Heidi G. Edmonds
Karina L. Brierley, MS
Layout by: Karina L. Brierley, MS
Nathan Gault

**Yale Cancer Genetic Counseling Program
55 Church Street, Suite 402
New Haven, CT 06510**