

## FALL 2003

Welcome to our second e-mail based newsletter! If you would like to be added to our e-mail notification list, please contact us at karina.brierley@yale.edu with your e-mail address. We also welcome your comments and suggestions for future articles that would be of interest.

Sincerely,

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## Gynecologic Cancer and Surgical Decision-Making in BRCA1 and BRCA2 Carriers

It has been well established that women who carry mutations in BRCA1 or BRCA2 have a high lifetime risk of developing ovarian cancer. The lifetime risk for a mutation carrier to develop ovarian cancer ranges from 15-60%, depending on the population studied; however, even the lowest end of this range is much greater than the population risk of 1-2%. Due to the limitations in detecting ovarian cancer at an early, treatable stage, prophylactic surgery is recommended for BRCA carriers who are >35 years of age and have completed childbearing<sup>1</sup>.

This lifetime risk of 'ovarian' cancer includes a risk to develop primary cancers of the fallopian tube and the peritoneum<sup>2</sup>. Therefore, the minimum prophylactic surgery in BRCA carriers is bilateral salpingo-oophorectomy (BSO). This surgery reduces the risk of ovarian and fallopian tube cancers in BRCA carriers by >90%. BSO also significantly reduces the future risk of breast cancer, particularly in women who have this surgery prior to menopause<sup>3-4</sup>.

There has been debate about whether BRCA carriers are also at risk for endometrial cancer, and should therefore be offered total abdominal hysterectomies (TAH) as the minimum prophylactic procedure. The risk of Uterine Serous Papillary Carcinoma (USPC) is of special concern because it is pathologically similar to both peritoneal and ovarian serous malignancies and is very aggressive. A few case reports have shown that BRCA1 carriers have had USPC<sup>5</sup>. However, a study of Jewish women with endometrial cancer (including 17 cases of USPC) did not show an excess of BRCA mutations<sup>6</sup>.

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# Gynecologic Cancer and Surgical Decision-Making in BRCA1 and BRCA2 Carriers

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In a separate study of 56 non-Jewish women diagnosed with USPC, none (0/56) were found to carry a BRCA mutation<sup>7</sup>. If a causal relationship does exist between BRCA mutations and endometrial cancer, the penetrance for endometrial cancer appears to be low and is not significantly elevated over that of the general population<sup>8</sup>. Some have argued that BSO alone may leave at-risk stumps of fallopian tube that retract into the uterine wall; however, the prophylactic effect of BSO alone (as demonstrated in the large studies discussed above) appears to be high. *It is therefore premature to offer total abdominal hysterectomy as the **only** prophylactic surgical choice for BRCA carriers.*

Ultimately, the decision between TAH-BSO and BSO alone must be made by the patient. Discussion points include:

- Whether the patient has some other indication for TAH (e.g. fibroids, endometriosis).
- If the patient chooses TAH-BSO, she can take unopposed estrogen which may be associated with a lower risk of subsequent breast cancer.
- If the patient chooses TAH-BSO, she can take tamoxifen in the future without the small increased risk of endometrial cancer.
- BSO is a laparoscopic surgery associated with fewer complications and a shorter recovery time than TAH-BSO. Studies have shown that BSO, alone, significantly reduces the risk of ovarian and breast cancer in BRCA carriers.

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| 1. Rebbeck TR J Clin Oncol 2000; 18(21):100s-3s.     | 5. Hornreich G et al. Gyn Oncol 1999;75:300-4. |
| 2. Aziz S et al. Gyn Oncol 2001; 80:341-5.           | 6. Levine DA et al. Gyn Oncol 2001;80:395-8.   |
| 3. Rebbeck TR. et al. N Engl J Med; 346(21):1616-22. | 7. Goshen R. et al. Gyn Oncol 2000;79: 477-81. |
| 4. Kauff ND et al. N Engl J Med; 346(21):1609-15.    | 8. Boyd J. Gyn Oncol 2001; 80:337-40.          |

## ***Yale Cancer Genetic Counseling Clinics***

### ***Yale***

Mondays at 55 Church Street, Suite 800B (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

## *Skin Findings Associated with Hereditary Cancer Syndromes*

Although typically a clustering of specific types of cancers in a family history prompts clinicians to consider genetic counseling/testing for a hereditary cancer syndrome, skin findings can also be associated and unique to some hereditary cancer syndromes. The following listing summarizes some of the distinct skin findings found in hereditary cancer syndromes.

### **Skin Findings:**

**Acrochordons:** Outgrowths of epidermal and dermal fibrovascular tissue. Histological variation of fibrofolliculomas/trichodiscomas.

- Seen in: Birt-Hogg-Dubé syndrome (BHD)

**Epidermoid cysts:** Cysts (also called sebaceous cysts) occurring within the dermis consisting of keratin and sebum and lined with keratin-forming epithelium.

- Seen in: Gardner syndrome

**Fibrofolliculomas/trichodiscomas:** Benign tumors of the hair follicle unit and difficult to distinguish from each other clinically. Fibrofolliculomas are proliferations of the fibrous sheath of the hair follicle while trichodiscomas are fibrovascular proliferations of the hair disc.

- Seen in: BHD

**Keratoacanthomas:** Rapidly growing skin tumors having a central keratin mass, and usually occurring on exposed areas, invading the dermis but remaining localized. Once thought to heal spontaneously, the lesions are considered a variant of well-differentiated squamous cell carcinomas and must be treated accordingly.

- Seen in: Muir-Torre syndrome, Xeroderma Pigmentosum (XP)

**Keratoses:** Excessive growths of horny tissue of the skin. May be actinic and precancerous (sun-induced) or benign (seborrheic).

- Seen in: Cowden syndrome (CS)/Bannayan-Riley-Ruvalcaba syndrome (BRR), XP

**Milia:** Small keratin-filled cysts usually no larger than 1mm.

- Seen in: Nevoid Basal Cell Carcinoma syndrome (NBCC or Gorlin syndrome)

**Mucocutaneous pigmentation:** Distinct freckling (small, flat, tan, dark brown or black) on the lips and/or inner cheeks. Also found on eyelids, hands, and feet.

- Seen in: Peutz-Jeghers syndrome (PJS)

**Palmar/Plantar pits:** Hollows or depressions in the skin on the hands or feet that feel rough on exam. Pits may be a few millimeters deep.

- Seen in: NBCC

**Papillomatosis:** Small raised papules which present projections of the epidermis.

- Seen in: CS/BRR

**Poikilodermas:** Streaks or patches of hyper- or hypopigmentation and telangiectasia of the skin, may be associated with atrophy or thinning of the skin.

- Seen in: XP

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# Skin Findings Associated with Hereditary Cancer Syndromes

(continued from page 3)

## Skin Findings (continued):

**Sebaceous gland tumors:** Includes benign sebaceous adenoma, sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, or sebaceous carcinoma.

- Cancer syndrome: Muir-Torre syndrome

**Trichilemmomas:** Hamartomas derived from the outer root sheath epithelium of the hair follicle.

- Cancer syndrome: CS/BRR

## Cancer Syndromes:

**Birt-Hogg-Dubé syndrome (BHD):** Autosomal dominant and characterized by skin tumors, renal tumors, and spontaneous pneumothorax. Cutaneous skin lesions usually appear in the 3rd or 4th decade and persist indefinitely.

- Skin findings: acrochordons, fibrofolliculomas/trichodiscomas

**Cowden syndrome (CS)/Bannayan-Riley-Ruvalcaba syndrome (BRR):** Both are autosomal dominant and caused by mutations in the PTEN gene. CS is characterized by multiple hamartomas and risks for breast, thyroid, and endometrial cancers. BRR is characterized by macrocephaly, developmental delay, lipomatosis, hemangiomatosis, and penile macules.

- Skin findings: acral/plantar keratoses, cutaneous/oral papillomatosis (in >90% with CS), trichilemmomas

**Gardner syndrome:** Autosomal dominant, a variant of familial adenomatous polyposis (FAP), and characterized by multiple colon polyps, skin findings, desmoid tumors and benign findings of the jaw.

- Skin findings: epidermoid cysts

**Nevoid Basal Cell Carcinoma syndrome (NBCC or Gorlin syndrome):** Autosomal dominant and characterized by basal cell carcinomas of the skin, medulloblastomas, and ovarian fibromas. Skin findings and defects of the brain and skeletal system may be present.

- Skin findings: milia (can be mixed with basal cell carcinomas on face), palmar (more common) and/or plantar pits

**Muir-Torre syndrome:** Autosomal dominant, variant of hereditary non-polyposis colon cancer syndrome (HNPCC), and characterized by skin findings and an increased risk for colon, uterine, ovarian, stomach, and urinary tract cancers.

- Skin findings: keratoacanthomas, sebaceous gland tumors

**Peutz-Jeghers syndrome (PJS):** Autosomal dominant and characterized by gastrointestinal polyps (hamartomas that typically occur in small intestines) and mucocutaneous pigmentation.

- Skin findings: mucocutaneous pigmentation.

**Xeroderma pigmentosum (XP):** Autosomal recessive and characterized by hypersensitivity to sun exposure, pigmentary alterations and premalignant lesions in sun-exposed areas of the skin, an extremely high incidence of skin cancer, an increase risk for other tumors (brain, lung, stomach, breast, uterus, testes), and neurological abnormalities.

- Skin findings: keratoacanthomas, keratoses, poikilodermas (please see references on page 5)

# Journal Clips

## **Multiple Colorectal Polyps and Mutations in the MYH gene**

*NEJM* 2003; 348(9): 791-799.

In this study, ~4% (6/152) of patients with multiple (3-100) colorectal adenomas and 7.5% (8/107) of APC-mutation-negative patients with classic familial adenomatous polyposis (FAP) (>100 adenomas) had 2 copies of the MYH gene mutation (autosomal recessive pattern). Overall, ~1/3 of patients with 15 or more adenomas had 2 MYH gene mutations. Sieber et al conclude that MYH gene testing may be indicated in patients with 15 or more colorectal adenomas, particularly if the history is consistent with recessive inheritance (i.e. an isolated case or only siblings in one generation affected) and no germ-line APC mutation has been identified. *However, clinical testing is not currently available in the U.S. and we have limited data on the clinical care of patients with MYH gene mutations.*

## **MRI screening for breast cancer in high-risk women**

*Proceedings of the American Society of Clinical Oncology* May 2003, abstracts 4, 5, 362.

These 3 studies examine the efficacy of MRI as a screening tool for breast cancer among BRCA carriers and/or women at high risk to carry a BRCA mutation. All of them found that MRI is very sensitive (sensitivity of 71-100%) and both studies comparing MRI to other screening methods (mammography, clinical breast exam, and ultrasound) found that MRI had the highest sensitivity. However, the specificity of MRI was less consistent. It ranged from 81-95% and was higher than mammography in one study (95% vs. 94%) but lower than mammography in another (88% vs. 95%). Overall, these studies agree that MRI is an appropriate screening tool for women at high risk. However, two of the studies caution that specificity is suboptimal.

## **Familial Pancreatic Cancer and BRCA2**

*JNCI* 2003; 95(3): 214-221.

*Cancer Research* 2002; 62: 3789-3793.

Hahn et al (2003) found that 12% (3/26) of non-Jewish European families with familial pancreatic cancer (2+ first degree relatives with pancreatic cancer) carried a BRCA2 mutation. Murphy et al (2002) found that 17.5% (5/29) of families (Jewish and non-Jewish) with 3+ family members with pancreatic cancer (at least 2 of which were first degree relatives) carried a BRCA2 mutation. None of the families with identifiable BRCA2 mutations in these studies had a history that was classic for hereditary breast-ovarian cancer. Both studies conclude that BRCA2 testing should be considered in families with familial pancreatic cancer.

## **References for “Syndrome of the Month”:**

Counseling About Cancer: Strategies for Genetic Counseling 2nd Edition (2002), Wiley-Liss, Inc  
Mayo Clinical Proceedings (2000) 75 (1): 57-67  
Journal of Medical Genetics (2002) 39: 906-912  
American Journal of Human Genetics (2002) 70: 829-844  
Stedman’s Medical Dictionary (1995), Houghton Mifflin Co

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# CGC UPDATE

*NEWSLETTER OF THE CANCER GENETIC COUNSELING PROGRAM AT YALE*

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