

2005 ONCOLOGY ANNUAL REPORT
REPORTING 2004 CANCER REGISTRY DATA



FOCUS: HEREDITARY CANCERS

CENTRAL BAPTIST HOSPITAL
CANCER CARE CENTER

CHAIRMAN'S INTRODUCTION

ELVIS DONALDSON, MD, CHAIRPERSON, GYNECOLOGIC ONCOLOGIST

I appreciate your interest and attention to this, the 2005 Annual Report of the Cancer Care Center at Central Baptist Hospital. This year the emphasis of the report is the diagnosis, prevention and treatment of genetically associated malignancies. As knowledge about the cellular mechanisms that cause cancer expands, it is clear that improvement in the prevention and management of cancer requires an ongoing diligence to learn how growing information from basic cellular biology can be used clinically in the care of our patients.

With this in mind, one of the programs that Central Baptist and the staff have initiated is a full-service genetics program. Patients at potential risk may be referred for counseling, advice and appropriate prevention, treatment and follow-up. A registry of patients has been established so that they may be followed and informed of new information regarding their situation on an ongoing basis.

In this report the current status of genetically related cancers is reviewed. I urge you to keep this as a reference and guide for the appropriate referral of patients and their families.

The Central Baptist cancer program is designated by the American College of Surgeons Commission on Cancer as a Community Hospital Comprehensive Cancer program. This recognizes our commitment to the highest standard of patient care. This includes ongoing surveillance, comparison of outcomes data with regional and national benchmarks, and clinical research, while maintaining a holistic caring environment for patients and their families. In addition we are also committed to offering the cutting edge in technology. Examples include: digital radiology, MRI mammography, various minimally invasive and microsurgical techniques and the recent acquisition of the Cyber Knife radiosurgical instrument – the only one in the region.

For inquires regarding the Cancer Care Center, referrals to the Hereditary Cancer Program, oncology physicians, the multidisciplinary clinic, or diagnostics and treatment, please feel free to contact Peggy Wheeler, RN; Susan Yackzan, RN, MSN, AOCN®; or Rachel Kelleher, MS, CGC at 859-260-4270.

Again, thank you. I hope this information is helpful in your decisions regarding cancer management and prevention.

AN INTRODUCTION TO THE HEREDITARY CANCER PROGRAM

RACHEL KELLEHER, MS, CERTIFIED GENETIC COUNSELOR

Genetic counseling and cancer risk assessment is a relatively new field that is rapidly growing as advances in our understanding of the causes and prevention of cancer expand. With the establishment of the **Hereditary Cancer Program** in November of 2004, Central Baptist Hospital once again demonstrated a drive to provide high-quality comprehensive cancer care. The program was established to provide cancer risk assessment and genetic testing to patients and their families with a history of cancer in the Central Kentucky region.

GENETIC COUNSELING

Genetic counseling is a process of risk assessment, education and coordination of genetic testing and results. A detailed three-generation pedigree is first obtained from the patient. Medical records on other family members may be collected. Not only is the risk of a hereditary cancer syndrome in the family assessed, but also the patient's individual risk of cancer. In some instances, the family has a relatively low risk for a hereditary cancer syndrome, but the patient has a high risk of cancer due to a combination of family history and personal risk factors. Screening recommendations are then provided for the patient AND his or her family based on the risk assessment and/or results of genetic testing. If there is a risk of a hereditary cancer syndrome, genetic testing is offered. Coordination of the testing and interpretation and delivery of the results is provided by the genetic counselor. Genetic testing can take anywhere from three to eight weeks to be completed once a blood sample is received by the laboratory. Results are always given to the patient at a pre-scheduled follow-up genetic counseling visit.

GENETIC TESTING & INTERPRETATION OF RESULTS

It is preferable to begin genetic testing on a family member who has been affected with cancer. If a mutation is identified in the affected family member, other individuals within the family can then be offered testing. Family members who test negative for known familial mutations are then considered to be at population risk for cancer despite the family history. Informed consent for genetic testing is obtained prior to any testing being performed. This consent process involves reviewing the potential outcomes of the test results, as well as the pros and cons of genetic testing. Genetic test results for hereditary cancer syndromes are not always clear. The identification of a known mutation, or "positive" result, is the most straightforward, as the cancer risks are frequently known and various management options are available. The meaning of a "negative" test result must be interpreted in light of the family history. If a significant family history of cancer is present, a negative result may not impact the cancer risk assessment due to the existence of other cancer susceptibility genes that have yet to be discovered. Finally, genetic testing sometimes reveals a "variant of uncertain significance" (VUS). These variants may or may not be associated with an increased cancer risk and are anxiety-provoking for the family. In some cases, additional research studies are able to determine if a VUS does pose an increased risk for cancer. Due to the complexity in interpreting the three types of test results, patients should be well-informed on the potential outcomes prior to making a decision to test.

Hallmarks of a Hereditary Cancer Syndrome

- Multiple family members with the same or related cancers (i.e., breast and ovarian cancer, colon and uterine cancer)
- Early age of diagnosis
- Multiple primary tumors in the same individual
- Bilateral or multiple rare cancers

To make a referral, contact:
Rachel S. Kelleher, MS, CGC
Certified Genetic Counselor
859-260-4419

Facilitation of the testing process is an integral part of the genetic counselor's job. Genetic testing can be expensive, ranging in cost from several hundred dollars to several thousand dollars. Frequently, insurance companies will cover all or part of the cost of testing. Preauthorization is often required and can take several weeks to obtain, as education of the insurer is often necessary.

CONCERNS OF GENETIC DISCRIMINATION

Many patients have concerns regarding the possibility of health insurance discrimination if they decide to proceed with genetic testing. Despite federal and state laws to prevent genetic discrimination, fear of discrimination continues to be a barrier for patients and physicians who would otherwise pursue genetic counseling and testing. The state of Kentucky has laws that offer more protection against genetic discrimination by health insurers than the laws at the federal level. In summary, these laws state that genetic information, including genetic test results, cannot be used by group and individual health insurers to deny, cancel or refuse to renew health insurance benefits and coverage. Genetic information cannot be considered a pre-existing condition. Genetic tests results cannot be used to make

Primary Reason for Referral: Personal/Family History of:			
TABLE 1	Breast Cancer	60	58.8%
	Colon Cancer	31	30.4%
	Colon and Breast Cancer	5	4.9%
	Other (melanoma, question of Cowden Syndrome)	6	5.9%

an individual pay a higher premium and insurers cannot legally require the results of genetic testing. A bill to strengthen the laws at the federal level has passed in the Senate and has been forwarded to the House of Representatives. At this point in time, there are no laws regarding the use of genetic test results in obtaining life insurance.

CBH EXPERIENCE

Since the first patient was counseled in early December of 2004, the Hereditary Cancer Program has evaluated 102 patients from 91 families for a total of 145 patient encounters. Table 1 outlines the primary reason patients were referred to the Hereditary Cancer Program. After evaluation, approximately 32.8% of the breast cancer referrals and 42% of the colon cancer referrals were found to be at high-risk for a hereditary cancer syndrome (Tables 2 and 3). BRCA mutations

Risk Assessment of the 64* Patients Referred for Personal/Family History of Breast Cancer					
TABLE 2	Risk Assessment After Evaluation	# of Patients	# That Pursued Genetic Testing	# of BRCA+ Results	# With Results Pending
	High Risk of BRCA Mutation	21 (32.8%)	12	4/8 (50%)	4
	Moderate Risk of BRCA Mutation	16 (25%)	11	0/9, 1 VUS	2
	Low Risk of Hereditary Cancer Syndrome	16 (25%)	0		
	High Risk of Breast Cancer, but Low Risk of Hereditary Cancer Syndrome	5 (7.8%)	0		
	More Information Needed to Assess Risk	6 (9.4%)	0		

*Includes four of the breast/colon families who had high or moderate risks for BRCA 1/2

were identified in half of the high-risk breast cancer patients who underwent genetic testing and for whom results are available. Of those with a moderate risk of a hereditary breast/ovarian cancer syndrome, half were reclassified to low risk after negative genetic testing.

According to data obtained from the Cancer Registry, 220 new breast cancers, 22 new ovarian cancers and 115 new colorectal cancers were diagnosed at CBH in 2004. Genetic mutations can be expected in 5% of those breast cancer patients, 10% of those ovarian cancer patients and 3-5% of those colorectal cancer patients. In order to identify these patients through genetic

Risk Assessment of the 31 Patients Referred for Personal/Family History of Colon Cancer		
TABLE 3	High Risk/Clinical Diagnosis of a Colon Cancer Syndrome	13 (42%)
	HNPCC [†] (Amsterdam Criteria)	9 (4 families)
	AFAP/FAP*	4
	Moderate Risk (Bethesda Criteria)	14 (45%)
	Familial Colon Cancer	2 (6%)
	More Information Needed	2 (6%)

[†]Hereditary Nonpolyposis Colorectal Cancer

*Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP)

TABLE 4		Average # of New Cancers Diagnosed at CBH in 9 Months	Expected # of Patients with Genetic Mutations	Actual # of Patients Identified with Genetic Mutations	Expected # of High-Risk Patients Evaluated	Actual # of High-Risk Patients Seen for Genetic Counseling	Actual # of High-Risk Patients who had Genetic Testing
	Breast & Ovarian Cancer (BRCA)	165-Breast 16.5 - Ovarian	9.9	4*	29.7	21	12 (4 pending)
	Colorectal Cancer (HNPCC/FAP)	86	4.3	4 (1 family)	12.6	13	9 (3 pending)

*Only 57% of high risk patients pursued testing.

testing, a hereditary cancer program would need to evaluate at least three times that many high-risk patients. Table 4 compares the expected number of referrals and mutation-positive patients identified with the actual numbers obtained by the Hereditary Cancer Program over its first nine months. Table 5 provides an overview of all of the testing that has been pursued through the Hereditary Cancer Program.

While these numbers seem to indicate that the Hereditary Cancer Program is evaluating and identifying approximately the expected number of patients, more program growth is possible. Many of the above referrals represent individuals diagnosed in previous years and at other facilities. In the future, we will expect to see more patients than is reflected in the CBH cancer registry data. As physicians become aware of our services, identification and referral of suspicious patients and family histories will continue to add to the development and growth of the Hereditary Cancer Program.

Testing Overview						
TABLE 5	Test Ordered	Positive Result	Negative Result	VUS	Pending (Preauth. or Results)	Total
	BRCA 1/2 Genetic Testing	4	12	1	6	23
	HNPCC Genetic Testing	4	1	0	3	8
	AFAP/FAP Genetic Testing	0	1	0	0	1
	MSI/IHC* Screening	0	4	0	2	6
	TOTAL	8	18	1	11	38

*Microsatellite Instability (MSI)/Immunohistochemistry (IHC)

HEREDITARY BREAST AND OVARIAN CANCER: A REVIEW OF BRCA1 AND BRCA2

RACHEL KELLEHER, MS, CERTIFIED GENETIC COUNSELOR

Breast cancer susceptibility genes are thought to cause approximately 5-7% of all cases of breast cancer. Approximately 85% of hereditary breast cancer can be attributed to mutations in the BRCA1 and BRCA2 genes. Men and women with mutations in these genes are at greatly increased risk for cancer.

Mutations in BRCA1 and BRCA2 confer a 56-87% risk of breast cancer by age 70 and a 40-60% lifetime risk of a second breast primary. The risk of ovarian cancer is also increased: BRCA1 mutations carry a 44% lifetime risk and BRCA2 mutations carry a 10-27% lifetime risk. Additionally, the risk is as high as 6% for male breast cancer and 34% for prostate cancer. BRCA2 mutations have also been associated with increased risks for other types of cancer, including pancreatic cancer, cutaneous and ocular melanoma, gallbladder cancer and gastric cancer. The absolute risk for these cancers is low.

BRCA1 and BRCA2 mutations are inherited in an autosomal dominant manner, meaning that the parents, siblings and children of a mutation carrier are at 50% risk to also have the mutation. Genetic testing is available on a clinical basis to identify individuals with these mutations and should be offered to individuals and their families in the context of pre- and post-test genetic counseling. Genetic testing can be utilized to influence decisions regarding screening and prevention in unaffected individuals and may be used by others to aid in surgical decision-making at the time of diagnosis (i.e., lumpectomy vs. mastectomy, unilateral vs. bilateral mastectomy). A negative genetic testing result can also aid in assessing the risk for ovarian cancer in a family with only

a moderate risk of having a BRCA mutation (i.e., a woman with a negative family history but young-onset breast cancer).

The medical management options for individuals with BRCA mutations include increased surveillance, chemoprevention and prophylactic surgery. Screening for individuals with BRCA mutations includes: monthly breast self-examinations beginning at age 20-25, semi-annual clinical breast exam beginning at age 25-35, and a yearly mammogram beginning at age 25-35.

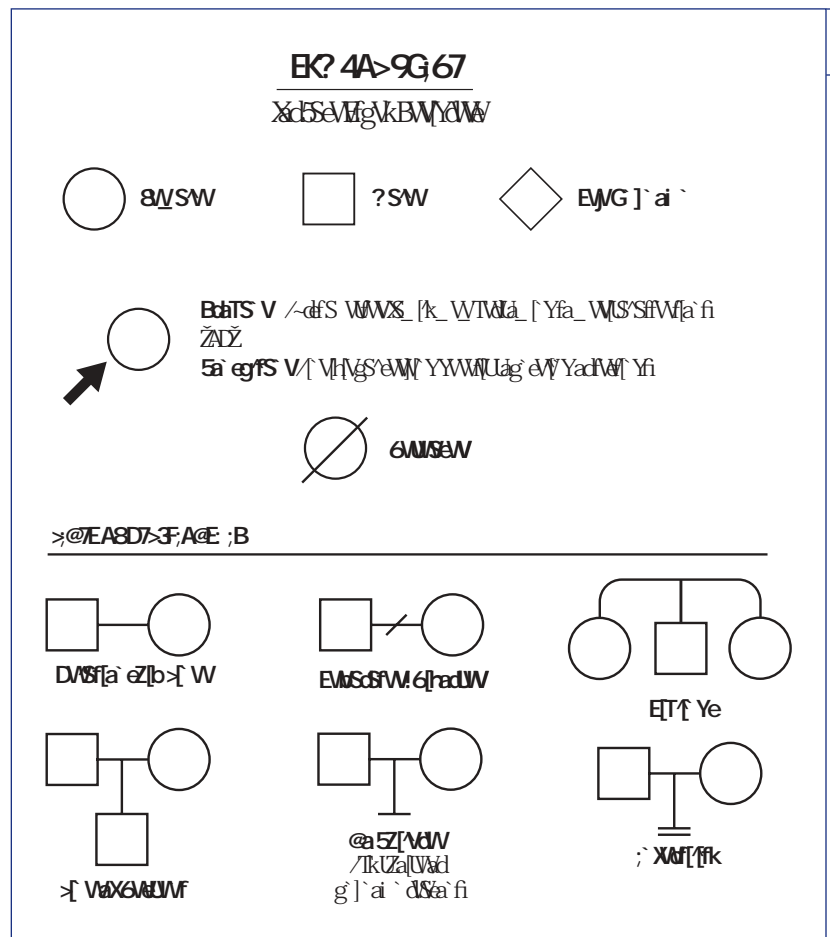
In families with younger ages of cancer diagnoses, screening may need to start at a lower age limit. Typically, screening should start at least ten years before the youngest age of diagnosis in a family. Additional screening modalities, such as breast MRI and breast ultrasound, should be considered (see Spotlight on Breast MRI, p. 9). Ovarian cancer screening is also recommended (See Spotlight on Ovarian Cancer Screening). Screening for males with BRCA mutations should include prostate cancer screening beginning at age 40 and self-breast exam. Mammography can be considered in males with gynecomastia. Given the risk for melanoma, annual skin and eye examinations should be considered for both males and females with BRCA2 mutations.

Chemoprevention is not only available for breast cancer prevention (see Spotlight on Chemoprevention, p. 11), but also ovarian cancer prevention. Oral contraceptives have been shown to reduce the risk of ovarian cancer by as much as 60% in BRCA-positive patients when taken for 6 or more years. Although lower, risk reductions are still obtained when you shorten the length of



time the oral contraceptives are taken. It is controversial whether oral contraceptives slightly increase the risk of breast cancer in these patients. Weighing the impact on overall cancer risk, the short-term use (5 years or less) of oral contraceptives to reduce the risk of ovarian cancer is generally supported.

Finally, women with BRCA mutations can obtain the greatest reduction in risk by undergoing prophylactic surgery (see Spotlight on Prophylactic Surgery, p. 10). Prophylactic bilateral mastectomy has been shown to reduce the relative risk of breast cancer in BRCA mutation-positive patients by approximately 90%. Prophylactic bilateral salpingo-oophorectomy (BSO) has been shown to reduce the risk of ovarian cancer by as much as 96%. Prophylactic BSO has also been shown to reduce the risk of breast cancer by as much as 50%. Careful removal of the fallopian tubes is essential, due to the risk for fallopian tube cancer in BRCA-positive patients; therefore it has been suggested that a surgeon experienced with high-risk patients, such as a gynecologic



oncologist, perform the prophylactic BSO. Additionally, 2-3% of BRCA mutation-positive patients are found to have ovarian cancer at the time of BSO; therefore, careful pathologic exam of the ovaries is recommended.

SPOTLIGHT ON: BREAST MRI

TAMARA PATSEY, MD, RADIOLOGIST

Breast cancer screening in patients at high risk is controversial. Genetically-predisposed women tend to develop aggressive, rapidly growing tumors at a young age, when breast parenchymal density limits diagnosis mammographically. Recent studies have compared accuracy of yearly MRI with mammography in high-risk patients. The sensitivity of MRI has been reported in most studies as greater than 90%. Specificity is much lower. Thus, there is the potential for false positive results. There is significant interindividual normal breast tissue enhancement and significant intraindividual enhancement of normal tissue depending on the phase of the woman's menstrual cycle. Enhancing normally on MRI are fibrocystic changes, fibroadenomata, and even normal parenchyma.

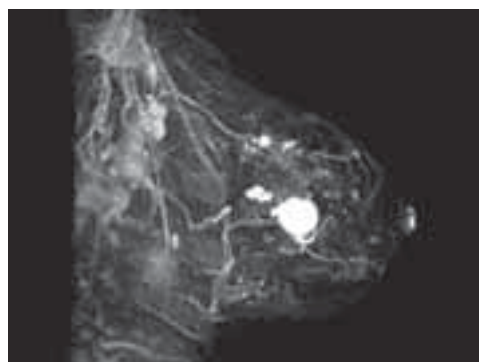
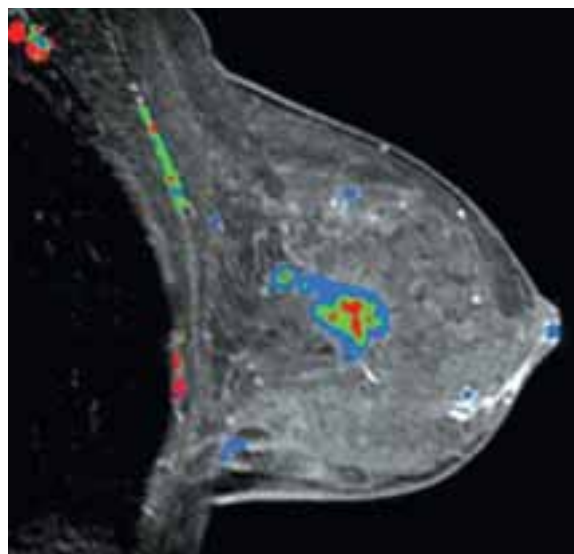
In preparation for beginning a breast MRI screening program for selected high-risk patients, we are planning purchase of new MRI breast software. The program, called CADSTREAM, uses tumor angiogenesis to assign color to enhancing areas of the breast, highlighting the most worrisome areas. It also allows for many manipulations, such as calculation of tumor volumes, aiding in surgical removal, or calculating response to neoadjuvant therapy. We have also begun MRI-directed biopsies and needle localizations of lesions that cannot be visualized with other imaging modalities.

In order to make breast MRI screening as sensitive and specific as possible, breast MRI should be performed between days 7 and 15 of the menstrual cycle to minimize cyclic changes. Ideally, women should be discontinued from hormonal therapy for

four to eight weeks prior to breast MRI.

MRI does not detect calcifications, an early sign of possible cancer by mammography; therefore it must always be correlated with mammographic images.

Ideally, the full potential of all primary breast diagnostic techniques should be utilized with breast MRI (mammography, ultrasound, and percutaneous biopsy), especially in high-risk patients. Sensitivity and specificity are highest when all of these modalities are used in combination. Worrisome findings on mammography and ultrasound should be biopsied regardless of MRI findings.



SPOTLIGHT ON: PROPHYLACTIC SURGERY

PETER TATE, MD, SURGICAL ONCOLOGIST

Of all the components of breast cancer treatment, the least standardized is the management of the contralateral breast. The decision to proceed with a prophylactic removal of a normal organ is often based on non-scientific factors, such as fear of recurrence, emotional stability and/or desire for cosmetic enhancement with third-party coverage. Genetic testing such as BRCA has helped many patients and their physicians make decisions based on scientific data. However, only a minority of breast cancer patients possess the BRCA gene. The same is true for women with a family history of cancer.

The decision for or against prophylactic mastectomy may be further complicated by other factors including:

- 1) Risk assessment, even when based on genetic testing, is at best an extrapolation of data from short-term studies in order to estimate a patient's lifetime risk.
- 2) Though effective, mastectomy does not provide 100% prevention.
- 3) What is the proper threshold of risk above which intervention is recommended?
- 4) What is the role of medical risk reduction, e.g., hormone receptor antagonists?
- 5) Can close surveillance with frequent imaging (e.g., MRI) improve detection and especially survival?
- 6) What is the cost of mastectomy & reconstruction vs. actual life saved?

As these questions are not likely to be answered in the near future, prophylactic mastectomies will continue to be performed based on a little science and a lot of gestalt.



SPOTLIGHT ON: CHEMOPREVENTION

LEE HICKS, MD, MEDICAL ONCOLOGIST

Breast cancer occurs in 12% of women who live to 90 years of age. Models have been developed to predict the risk of developing breast cancer, and measures can be taken to lower these risks. The Gail Breast Cancer Risk Assessment Tool, developed by the National Cancer Institute, based on data from the Breast Cancer Detection Demonstration Project, calculates the risk of developing breast cancer in the next 5 years and until age 90 based on: age, age of menarche, age of first live birth, number of first degree relatives with breast cancer, number of prior breast biopsies, and whether those biopsies showed atypical hyperplasia. For example, a 45-year-old with one first degree relative with breast cancer has a 1.66% risk of breast cancer in the next 5 years. In the NSABP P-1 study of tamoxifen vs. placebo in women with a 1.66% or higher risk of developing breast cancer, tamoxifen cut that risk in half. Tamoxifen increased the relative risk of stroke 1.75%, pulmonary embolus 3%, deep vein clot 1.7% and, in women over 50, endometrial cancer four fold to 3.1 endometrial cancers per 1,000 women on tamoxifen. For every 50 high-risk women who take tamoxifen, one case of breast cancer is prevented. Hence, the benefit of tamoxifen outweighs the risks in women whose 5 year risk of breast cancer is 1.66% or higher, even though the absolute benefit may be small and such non-life threatening side-effects such as hot flashes (46%) and vaginal dryness (12%) can persuade many women to forego the possible benefit. The Gail model is available at <http://bcra.nci.nih.gov/brc/>. Though more intensive screening with mammography every 6 months, transvaginal ultrasonography, breast MRIs, and blood

tumor marker testing may seem reasonable, no study to date has shown these modalities to improve survival.

Though breast cancer gene mutations only occur in ~0.1% of the general population, inherited gene mutations occur in 6% of breast cancer patients. Autosomal dominantly inherited BRCA1 and BRCA2 gene mutations occur in 1 to 3% of breast cancer patients. In women who have the BRCA1 or BRCA2 mutation, by age 70 they have a 65 to 85% risk of developing breast cancer. Prophylactic bilateral mastectomies reduce the relative risk of developing breast cancer by 90%. Tamoxifen, which decreases the effect of female hormones on cancers which express hormone-receptors, reduces the risk of developing breast cancer by 50% in BRCA2 patients when taken for five years. BRCA1 patients tend to be hormone-receptor negative, hence their lack of benefit with prophylactic tamoxifen. A risk-assessment incorporating the BRCA data is available at www3.utsouthwestern.edu/cancergene/. The life-time risk of ovarian cancer is 25 to 65% in BRCA1, and 15 to 25% in BRCA2-positive women. Prophylactic bilateral salpingo-oophorectomy (BSO) reduces ovarian cancer risk 96%, while also substantially reducing the risk of breast cancer. Hence, a combination of bilateral prophylactic mastectomy and BSO is rational in BRCA1 or BRCA2-positive women. There is no consensus as to the exact timing of these procedures relative to a woman's desire to conceive or nurse. The impetus for surgery in the BRCA positive woman's mid-20s increases as the age at which the first degree relative developed breast cancer decreases.

SPOTLIGHT ON: OVARIAN CANCER SCREENING

ELVIS S. DONALDSON, JR., MD, GYNECOLOGIC ONCOLOGIST

Ovarian cancer is the second most common gynecologic malignancy in the United States. In 2005, there will be approximately 22,500 new cases. Unfortunately, it is also the most lethal gynecologic malignancy, accounting for approximately 16,500 deaths (the fifth leading cause for death by malignancy in women). The major problem encountered in treatment is that 70% of patients are diagnosed with advanced disease. Overall, the survival for ovarian cancer is about 50%. If the patient is completely staged and diagnosed with stage I disease, the chance of survival is 95%. In contrast, if the patient is diagnosed in stage 3 disease (55% of reported cases), survival is about 25 to 30% (Table 1).

Even though there has been and continues to be active research, no currently effective screening tool for the prevention or early diagnosis of ovarian cancer has been developed.

In the past, it has been reported that patients can develop advanced ovarian malignancies without symptoms. However, retrospective analysis has shown that 95% of women have symptoms for months to a year before the diagnosis of ovarian cancer. These symptoms are not necessarily gynecologic in nature (Table 2). Awareness on the part of the patient, diligence by her primary clinician even though typical symptoms may be vague, a careful history and physical examination, including a pelvic and rectal examination, can play a significant role in early diagnosis. Abnormal findings or suggestive pertinent symptomatology can stimulate further diagnostic studies or referral for evaluation, which could result in earlier diagnosis.

With our current knowledge of molecular and genetic mechanisms within ovarian tissue, 90% of ovarian cancers are considered sporadic occurrences with no predictable background to arouse early suspicion. There are, however, risk factors that can be determined by careful questioning on a medical history. There is, in fact, a very good tool for assessing a woman's cancer risk online at the Women's Cancer Network (www.wcn.org). This site is sponsored by the Society of Gynecologic Oncologists and the Gynecologic Cancer Foundation.

Certain factors affect the risk of ovarian cancer positively (if they are present, the risk is reduced), not the least of which is the utilization of oral contraceptives (Table 3). At a time when all forms of hormone therapy are under the toughest scrutiny, it bears emphasizing that any use of combined oral contraceptives reduces the risk of both ovarian and colon cancer significantly. This occurs with any use (up to one year) and increases directly with time of use. Even though we currently estimate only 10% of ovarian malignancies have known genetic linkage with positive testing, there are factors relating to family history that are known to affect an individual's risk for ovarian cancer in varying degrees. These include cases of ovarian cancer in several family generations, a first-degree relative with ovarian cancer and cancer occurring at a younger age. With combinations of factors such as these, risks may increase exponentially. Many such factors present in a family history should stimulate a conversation regarding ovarian cancer risk and a possible referral for genetic counseling and perhaps testing.

Those patients deemed to be at higher risk for ovarian cancer should enter a program of annual screening that includes the following components:

- Annual pelvic and rectal examination
- A baseline CA-125 and perhaps annual CA-125 screening or subsequent levels should any symptomatology occur
- Transvaginal ultrasound studies with included color Dopplers.

Once increased risk of ovarian cancer has been established, consideration should be given to removing the ovaries, once the patient has completed her childbearing.

As we look to the future for the prevention and early diagnosis of ovarian cancer, the Society of Gynecologic Oncologists has put forth a list of priorities (Table 4). As might be expected, there are certainly challenges and barriers to these endeavors (Table 5), not the least of which, although it is on the bottom line, are the financial resources necessary to carry out this type of basic research because of the vast numbers of patients that need to be involved.

OVARIAN CANCER: STAGE DISTRIBUTION AND SURVIVAL

TABLE 1			
	I	24	95%
	II	6	65%
	III	55	15-30%
	IV	15	0-20%
	Overall		50%

Source: American Cancer Society, 2000

Ovarian Cancer Symptoms	
TABLE 2	<ul style="list-style-type: none"> • Abdominal or pelvic pressure • Abdominal bloating, increased girth • Indigestion, reflux, nausea • Constipation, diarrhea, gas • Pain or cramping • Unusual fatigue • Weight loss or weight gain • Bladder pressure, urinary frequency • Shortness of breath

Ovarian Cancer Risk Reduction & Prevention	
TABLE 3	<ul style="list-style-type: none"> • OCP RR 0.5 after 5 or more years of use, reduction persists for 10 years • First full-term pregnancy < age 25; Multiparity • Breast-feeding • BTL/Hysterectomy RR 0.33/0.67 • Prophylactic Oophorectomy (risk of primary peritoneal cancer remains)

Genetic Susceptibility & Prevention Priorities	
TABLE 4	<ul style="list-style-type: none"> • Registry of a cohort of patients at genetically higher risk • Education regarding value & risks of presymptomatic testing • Identify common genetic alterations associated with ovarian cancer • Prevent disease recurrence

Challenges & Barriers to Genetic Research	
TABLE 5	<ul style="list-style-type: none"> • Confidentiality • Obtaining adequate numbers of patients • Financial Resources • Coordination with insurers • Clinical trial support • Financial support for gene identification research

HEREDITARY COLORECTAL CANCER SYNDROMES

STEPHEN C. SCHINDLER, MD, FACP, FACG, GASTROENTEROLOGIST

The etiology of colorectal cancer is varied. Nearly 80% of colorectal cancer patients have sporadic disease. Risk factors include both environmental and genetic factors. Dietary patterns are believed to account for most of the geographic variations in colorectal cancer incidence. A diet high in saturated fat and low in fiber is thought to increase the risk, whereas a high fiber, low fat diet may be protective. Additional risk factors include obesity, diabetes mellitus, smoking, and physical inactivity, all of which have been associated with an increased risk. Increasing age is one of the most important risk factors, with the risk of developing colorectal cancer increasing after age 40 and more than 90% of sporadic cases occurring after the age of 50. In addition, a personal history of colorectal adenomas, of breast, ovarian or uterine cancer or of inflammatory bowel disease places one at risk. The remaining 20% of patients have a definable genetic component which place them at a greatly increased risk. This group includes patients with a family history of colorectal cancer and those with a familial aggregation consistent with an autosomal dominant pattern. The two main types of hereditary colorectal cancer syndromes include: (1) familial adenomatous polyposis (FAP) and (2) hereditary non-polyposis colorectal cancer (HNPCC). A third, less common type of hereditary colorectal cancer is a group of syndromes referred to as the hamartomatous polyposis syndromes. This group includes Peutz-Jeghers syndrome, juvenile polyposis and Cowden syndrome.

FAMILIAL ADENOMATOUS POLYPOSIS

FAP is an autosomal dominant syndrome caused by a germline mutation of the adenomatous polyposis coli gene. It affects males and females equally and clinically is

characterized by the presence of multiple polyps (frequently greater than 100) that develop diffusely throughout the colon. Diagnosis is evident in the teens and progression to colorectal cancer usually occurs by age 40. Polyps may also develop in the stomach, small intestine and biliary ductal system. Desmoid tumors and dental abnormalities are also associated. These patients have an increased risk of extra-colonic malignancies including hepatoblastomas and neoplasms of the small bowel, thyroid gland, biliary tree and brain. Extraintestinal manifestations characterize Gardner's syndrome, whereas CNS lesions are seen in Turcot's syndrome. Although colectomy is protective for colorectal cancer, extra-colonic malignancies are a much greater therapeutic challenge.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

HNPCC is also autosomal dominant and is caused by mutation of one of the DNA mismatch repair genes. Patients with an HNPCC gene mutation have a high lifetime risk for the development of colorectal cancer in the 70 to 80% range. Colorectal cancer occurs much earlier in life (average about 44 years of age) and often involves the right side of the colon. Most people with colorectal cancer who have germline mutations have microsatellite instability (MSI) in their colorectal cancer DNA. Synchronous and metachronous lesions are common, and the cancers are more likely to be flat rather than polypoid. Extra-colonic associated cancers are common, most commonly uterine and ovarian. Stomach, biliary and small bowel lesions do occur, however, as do lesions in the breast, brain and hematopoietic system.

The Amsterdam criteria I and II were established for the diagnosis of HNPCC.

Amsterdam I required all three of the following criteria:

- (1) Three or more family members affected with colorectal cancer, with one of them being a first-degree relative of the other two;
- (2) More than one generation being affected; and
- (3) One or more family members being diagnosed before the age of 50 years.

The Amsterdam II criteria includes extra-colonic tumors that occur commonly in the HNPCC families. The criteria include:

- (1) Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer; cancer of the endometrium, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two; FAP should be excluded;
- (2) Colorectal cancer involving at least two generations;
- (3) One or more cancer cases diagnosed before age 50.

The newer Bethesda Criteria have been developed to help identify individuals for whom genetic testing might be indicated and who should undergo MSI testing. These criteria include:

- (1) Individuals with cancer in families that meet the Amsterdam criteria;
- (2) Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancer or extra-colonic cancers;
- (3) Individuals with colorectal cancer and a first-degree relative with a colorectal cancer and/or a colorectal adenoma;

one of the cancers diagnosed before age 45 years, and the adenoma diagnosed before age 45;

- (4) Individuals with colorectal cancer or endometrial cancer diagnosed before age 45;
- (5) Individuals with right-sided colorectal cancer with an undifferentiated pattern on histology diagnosed before age 45;
- (6) Individuals with signet ring cell-type colorectal cancer diagnosed before the age of 45;
- (7) Individuals with adenomas diagnosed before age 40.

HAMARTOMATOUS POLYPOSIS SYNDROMES

Hamartomatous polyposis syndromes are responsible for less than 0.1% of all colorectal carcinomas diagnosed. Each syndrome is inherited in an autosomal dominant fashion. Unlike the other syndromes, these polyps are hamartomas. Peutz-Jeghers syndrome is characterized by polyps throughout the G.I. tract, mostly in the small bowel. Melanin pigmented papules are present on the lips and peri-oral areas. G.I. tumors occur, although the most common associated malignancies are in the breast, pancreas and ovary. Juvenile polyposis is characterized by the presence of multiple juvenile polyps, commonly in the colon, but scattered throughout the gastrointestinal tract. There is considerable risk for colon cancer in these patients, occurring at an early age (average 34 years). The relevant genes have been identified and genetic testing is available.

CONCLUSION: A thorough understanding of the hereditary colorectal syndromes, combined with current diagnostic testing and genetic counseling, should allow a rational approach to the early detection and eradication of colorectal cancer.



CASE STUDY 2 – HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

The patient, a 41-year-old female, was evaluated by genetics in a multidisciplinary clinic, due to a recent diagnosis of ductal carcinoma in situ (DCIS). She underwent a unilateral simple mastectomy and pathology indicated extensive high grade DCIS with multifocal microinvasion, estrogen receptor negative. A family history was obtained during this initial consultation and is seen above.

The patient’s mother died at age 68 after being diagnosed with ovarian cancer at age 50, gastric cancer in her late 50s and colon cancer in her 60s. The patient’s maternal half-sister, age 61, was diagnosed with right-sided colon cancer at age 50, a second carcinoma of the transverse colon just distal to the original anastomosis at age 56, and rectal carcinoma in-situ at age 56. Subsequent colonoscopies have been positive for several flat adenomatous polyps. This half-sister has two daughters and two sons. One daughter, age 42, was diagnosed with ovarian cancer at age 39, and was being treated for two squamous cell carcinomas. One son, age 40, had a history of two to three adenomas identified on colonoscopy at age 37. The second daughter, age 39, had a TAH/BSO for noncancerous reasons and a normal colonoscopy. The patient’s maternal aunt, currently in her late 70s, reported a history of “womb” cancer and squamous cell carcinoma.

After review of the history, it was determined that the family met the Amsterdam II criteria for a clinical diagnosis of HNPCC. Genetic testing was discussed with the patient during the initial consultation. Since breast cancer is not typically associated with HNPCC, it was recommended that genetic testing be initiated on a family member with a definite HNPCC-associated cancer, given the possibility that the patient’s cancer was unrelated to the family history.

The patient’s half-sister was then seen for genetic counseling and testing four months later. Testing was positive for a deleterious deletion of exons 1-6 in the MSH2 gene. This deletion has been associated with the HNPCC variant, Muir-Torre syndrome. Muir-Torre syndrome is a variant of HNPCC in which the typical HNPCC related cancers are observed, as well as sebaceous gland tumors and keratocanthomas. Squamous cell carcinoma is frequently difficult to distinguish from keratocanthomas and is part of the syndrome. Breast cancer has also been observed in some families with Muir-Torre syndrome.

Genetic counseling and testing was then offered to all other family members. At the time of this consultation, the patient reported that she had had a lesion removed from her forehead several years ago. Pathology was not obtained, but her doctor reported at the time that it was likely a benign sebaceous gland tumor. Additionally, the patient had had a TAH/BSO one month after our initial consultation. The patient, her 40-year-old nephew, and 39-year-old niece all underwent genetic testing and all tested positive for the deleterious MSH2 deletion.

Screening recommendations were reviewed with the family, including:

- Colonoscopy annually beginning by age 25
- Annual urinalysis beginning at age 30 to 35
- Upper GI endoscopy every one to two years beginning at age 25 to 35
- Given the history, careful attention for the skin lesions was advised. Annual examination by a dermatologist should be considered.
- Uterine cancer screening (endometrial aspiration and transvaginal ultrasound) every one to two years beginning at age 25 to 35. Consideration of prophylactic TAH/BSO after childbearing.
- Given the patient’s diagnosis of young-onset breast cancer, annual mammograms beginning by age 30. Monthly self-breast exam and annual clinical breast exam is also recommended.
- Ovarian cancer screening (annual pelvic exam, transvaginal ultrasound and consider CA-125 screening) beginning at age 25 to 35.

Additional family members are considering testing.

OTHER HEREDITARY CANCER SYNDROMES

Cancer Syndrome	Associated Cancers/Tumors	Other Features	Genetics
PTEN Hamartoma Tumor Syndrome*	Breast Cancer, Thyroid Cancer, Endometrial Cancer; Less commonly renal cell carcinoma, skin cancer, CNS tumors	Macrocephaly; Lhermitte-Duclos disease; benign thyroid lesions (goiter, etc); Mucocutaneous lesions such as trichilemmomas, papillomas of the lips and mucous membranes, acral keratoses; intestinal polyposis; lipomas; fibrocystic breast disease; GU malformations; mental retardation; epilepsy	Autosomal dominant (AD), Extreme inter and intra-familial variable expressivity, clinical testing available
Von Hippel-Lindau	Renal cell carcinoma; hemangioblastomas of the brain, spinal cord and retina; pheochromocytoma; endolymphatic sac tumors	Multiple renal cysts, pancreatic cysts, epididymal cysts, hypertension, hearing loss	AD, 20% new mutations (no FHx), 99% detection rate w/ genetic testing
Li-Fraumeni syndrome	Soft-tissue sarcoma, breast cancer, brain cancer, leukemia, osteosarcoma, adrenal cortical carcinoma	None	AD, p53 gene mutations. Testing clinically available
MEN2A/2B Familial MTC	Medullary thyroid cancer, pheochromocytoma	Hyperparathyroidism MEN2B – mucosal neuromas of lips and tongue	AD, Account for 25% of cases of MTC; RET proto-oncogene

* Also called Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome

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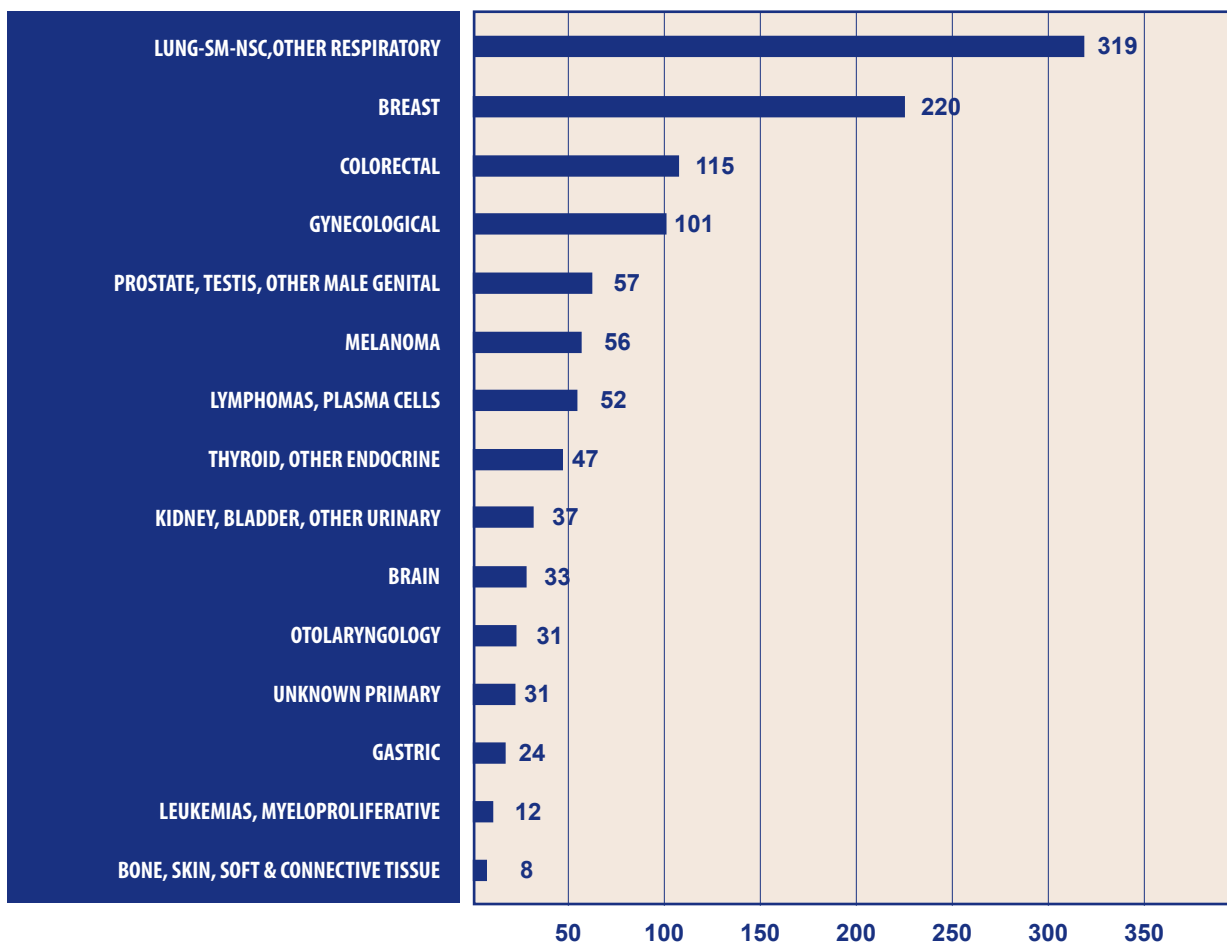
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Dr. Elvis Donaldson is a graduate of Tulane University and the University of Kentucky College of Medicine. He completed an internship in surgery at Medical University of South Carolina Affiliated Hospitals, a residency in obstetrics and gynecology at Southern Illinois University Affiliated Hospitals, and a fellowship in gynecologic oncology at the UK College of Medicine for 14 years, and held various leadership roles, including clinical director of the UK Hospital Center for Women's Health. He has served as a member of several committees of the American College of Surgeons Commission on Cancer, including the Committee on Approvals. Dr. Donaldson has been chair of the Central Baptist Hospital Cancer Committee since 1999.



Dr. Lee G. Hicks received his bachelor's degree from the University of Louisville in 1984. He graduated from the University of Louisville School of Medicine in 1988. He did his medical internship and residency at the Methodist Hospital of Indiana from 1988 to 1991. From 1991 to 1994 Dr. Hicks was a postdoctoral fellow at The Ohio State University, Department of Internal Medicine, Division of Hematology and Oncology. He is a member of the American Medical Association and the American College of Physicians. He is in private practice with Lexington Oncology Associates and is a member of the Multidisciplinary Oncology Team at Central Baptist Hospital.



Rachel Kelleher has been a genetic counselor at Central Baptist Hospital since November of 2004. Rachel received a Bachelor of Science degree in Molecular Genetics and a Bachelor of Arts in Anthropology from the University of Rochester. She received her master's degree in Human Genetics from Sarah Lawrence College in Bronxville, New York. Rachel is a member of the National Society of Genetic Counselors and is certified by the American Board of Genetic Counseling.



Dr. Tamara Patsey received her bachelor's degree in Biology in 1985 from the University of North Carolina at Chapel Hill. She graduated from the University of North Carolina School of Medicine in 1992. In 1993, she completed her general surgery internship at the University of North Carolina Hospital and her radiology residency at the University of Tennessee-Knoxville in 1999. Dr. Patsey joined Central Radiology Associates in 1999 and is currently the Medical Director of Women's Health Central at Central Baptist Hospital.



Dr. Stephen C. Schindler graduated from the University of Notre Dame with a Bachelors of Science degree in Pre-Professional Studies in 1958. In 1961, he graduated from the St. Louis University Medical School. Dr. Schindler completed his internal medicine residency and his fellowship in gastroenterology at The University of Kentucky. He has served as Diplomat on the American Board of Internal Medicine and the American Board of Gastroenterology. Currently he is in private practice in Lexington, Kentucky.



Dr. Peter Tate graduated from Princeton University in 1978, and the University of Kentucky College of Medicine in 1982. He completed his residency in general surgery and a fellowship in surgical oncology at the University of Illinois/Cook County Hospital of Chicago. He has practiced in Lexington since 1990 as a member of Lexington Surgeons/United Surgical Associates. His professional interests include neoplasms of the breast, skin, and soft tissues, GI tract, and endocrine systems. As Medical Director of Oncology Research, he is actively involved in the promotion of clinical cancer research at Central Baptist Hospital, and is the principal investigator of several studies. He also leads a multidisciplinary clinic in the Cancer Care Center and is a member of the Multidisciplinary GI Cancer Team.



Peggy Wheeler is the Cancer Resources Coordinator and Oncology Clinics Coordinator. She oversees the Multidisciplinary Clinic and supervises the Cancer Resource Library. Peggy is responsible for facilitating support groups and educational programs for patients, families, health care professionals and the community. She received her nursing degree from Midway College, Midway, Kentucky, and her bachelor's degree in Business from Mount Vernon College, Washington, D.C.



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