The Genetic Etiology of Familial and Nonfamilial Colorectal Cancer

About Colorectal Cancer

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in the US and the second leading cause of cancer death. CRCs arise from a multistep carcinogenic process, beginning with early changes from normal to hyperproliferative epithelium, then to the development of adenomas, which in turn are believed to be precursors of carcinomas. These histological changes are associated with the accumulation of genetic and epigenetic changes involving the activation of oncogenes and the inactivation of tumor suppressor genes.

Approximately two thirds of new cases of CRC appear to be sporadic (i.e., occur without a family history of the disease), and the necessary genetic changes seem to arise de novo, fueled by etiologic agents that can include age, environmental exposures, and lifestyle factors. Nearly one third of cases, however, tend to cluster in families, so that first-degree relatives of patients with newly diagnosed adenomas or invasive CRCs are at increased risk. While many of these familial clusters may be linked to shared behaviors or environmental exposures among family members, some are associated with germline mutations in specific genes.

(Continued on page 3)
Inheritance: the acquisition of a possession, condition, or trait from past generations.

Genetic: of, relating to, caused by, or controlled by genes <a genetic disease> <genetic variation>

“I have Mom’s curly hair, Dad’s blue eyes, and Grandpa’s sense of humor.” We can all easily relate to those things that we have inherited from our family. Yet, not all of the characteristics that are carried on our genes are as noticeable as hair and eyes. It has long been known that some things run within families. There were clearly defined genetic diseases like hemophilia, sickle cell disease (SCD), and Huntington’s disease. The inheritance of these diseases can be clearly worked out by examining family trees, and the likelihood of an offspring being affected can be predicted.

It is only recently that we have begun to understand the complex genetic alterations that impact our risk of developing cancer. The relationships are not as simple as in hemophilia or SCD, where the genetic changes are manifested early in life, or as with Huntington’s disease, where there is a predictable age of onset. “Knowledge is power.” Regarding genetic risk of cancer, this is very true. By knowing their risk, in many cases individuals may be able to take action to alter the predetermined course.

This issue of CancerUpdate describes some of the programs at Baylor Charles A. Sammons Cancer Center aimed at research and education in genetic risk of cancer. From the laboratory to the clinic, there is a focus on understanding the issues and educating the individual.

“I have also seen children successfully surmounting the effects of an evil inheritance. That is due to purity being an inherent attribute of the soul.”—Mahatma Gandhi
Although specific genetic mutations have been identified for a wide variety of syndromes that may involve CRC, screening is normally directed at the most common of these: hereditary nonpolyposis CRC (HNPCC), also known as Lynch syndrome, and familial adenomatous polyposis (FAP). Lynch syndrome is the most common hereditary cancer syndrome predisposing to CRC, accounting for approximately 3% of all cases. It is associated with mutations in four DNA mismatch repair (MMR) genes: MSH2, MLH1, MSH6, and PMS2. Individuals with a germline mutation in any of these genes have a significant lifetime risk of developing CRC (70% for men, 40% for women), as well as a heightened risk for the development of cancers at other sites, including the endometrium, ovary, stomach, small bowel, urinary tract, and pancreas. FAP, about one tenth as common as Lynch syndrome, is associated with mutations in the APC gene, which is classified as a tumor suppressor gene. Individuals with FAP may have hundreds of adenomas, making this syndrome relatively straightforward to detect. Because so many adenomas develop at an early age, classic FAP carries a lifetime risk of nearly 100% for the development of CRC. Additional hereditary CRC syndromes that are not routinely tested for include Peutz-Jeghers syndrome, familial juvenile polyposis, Cowden’s disease, Bannayan-Ruvalcaba-Riley syndrome, and Li-Fraumeni syndrome.

For both sporadic and familial CRC, a key early change is the development of genetic and epigenetic instability, which increases the rate at which further changes can be accumulated. At least three patterns of instability can contribute to the development of CRC; typically, one type will predominate in a specific cancer.

- One common pattern, prominent in at least 50% of CRCs, is chromosome instability (CIN), which can result in genetic deletions, duplications, and rearrangements. CRCs with CIN are characterized by aneuploid tumor cells.

- A second pattern is microsatellite instability, or MSI, which occurs in about 15% of CRCs. Microsatellites are simple repeat sequences 1 to 6 base pairs in length that occur thousands of times across the genome. MSI occurs through the inactivation of the DNA mismatch repair (MMR) system, resulting in sequences that accumulate errors and become abnormally long or short. In some instances, this creates a frameshift mutation in a gene, such as a tumor suppressor gene. Unlike CIN, most CRCs with MSI are diploid or near diploid. More than 90% of the CRCs attributable to Lynch syndrome are associated with MSI.

- The third pattern seen in CRC is an epigenetic change that involves the methylation of promoters of human genes. This can lead to the silencing of certain tumor suppressor genes in CRC. About half of the promoters of human genes are embedded in CpG islands, so this phenotype in tumor DNA is called the CpG island methylator phenotype, or CIMP. Overlap between MSI and CIMP occurs in about 12% of CRCs when the promoter of the MMR gene MLH1 is methylated (and inactivated), leading to MSI.

**Colon Cancer Screening at Baylor Dallas**

C. Richard Boland, MD, a gastroenterologist on the medical staff and chief of the Division of Gastroenterology at Baylor University Medical Center at Dallas, oversees the testing of patients with suspected hereditary CRC syndromes. These patients are referred by other gastroenterologists, oncologists, and surgeons. A sample of patients’ DNA is taken and used to determine if there is a familial aspect to their cancer or some other feature that would allow their oncologists to personalize their care. After testing, most patients opt to be put into a registry so that they can be alerted to new treatments...
or invited to join clinical studies. These patients are also reassessed in light of new research that may provide information about their cancer. “In some cases,” commented Dr. Boland, “a new genetic variation is reported somewhere that fits a patient we looked at 2 or 3 years earlier, and we are able to contact the individuals and their physicians to provide them with useful information. We see patients one time for genetic screening; then they become research subjects.”

**Research in Colon Cancer Genetics at Baylor Dallas**

Dr. Boland has been studying the genetics of CRC for over 25 years. His work studying the relationship of MSI to CRC led to the unexpected discovery that, in addition to genetic mutations in MMR genes, epigenetic changes involving DNA methylation in promoter genes could lead to MMR gene inactivation, resulting in MSI in cases of sporadic CRC.

---

*Two molecular pathways to the development of colorectal cancer with microsatellite instability. (Reprinted with permission from Boland & Goel, Gastroenterology 2010;138:2073-2087.)*
Currently, Dr. Boland and his colleagues, Ajay Goel, PhD, and Minoru Koi, PhD, are engaged in exciting research aimed at developing new genetic-based screening tests for CRC, identifying genes associated with the metastatic phenotype, and investigating a ubiquitous virus that may be involved in the etiology of CRC. Dr. Goel is an investigator and Dr. Koi is a senior research associate at Baylor Research Institute on the Baylor Dallas campus.

New Screening Tests for CRC
One of the most effective ways to prevent CRC is to find and remove polyps and other areas of abnormal cell growth before they develop into malignancies. The current gold standard for screening is colonoscopy, which can provide detection and treatment in one procedure. However, as few as 25% of people older than 50 get colonoscopies. A combination of cost, an unpleasant colon-cleansing preparation required prior to the screening, and fears about potential mishaps during the procedure discourage most eligible adults from having this screening test.

To overcome this difficulty, researchers have worked for many years on developing a noninvasive screening test using stool samples that could be collected at home. The earliest tests looked for blood in the stool as an indication of cancerous tissue or polyps. Subsequent tests looked at gene mutations in cells shed from the colonic lumen. The lumen continually sheds cells to renew the colonic epithelium. If a cancer is present, normal cell-to-cell contact breaks down, and more cells are shed.

These early assays based on the detection of occult blood or a small number of gene mutations proved to be highly inaccurate. About 5 years ago, Drs. Goel and Boland postulated that the tests based on gene mutations did not work because CRCs are heterogeneous genetically, and not all cancers carried the mutations that were used in the screening panel.

Instead, they opted to look at DNA methylation; it is much more common, with a measurable frequency even in healthy individuals. They selected tumor suppressor genes (e.g., those that regulate and restrain cell growth) that are frequent targets for methylation in CRC and demonstrated that a screening test based on these markers could detect abnormal cell growth in the colon with a high degree of sensitivity. The test could distinguish polyps from carcinomas, and small polyps from larger polyps, based on the degree of methylation. By adding additional markers, a single stool sample could be used to look for gastric and pancreatic cancers, in addition to CRC. Because a screening test based on methylation is both noninvasive and less expensive than colonoscopy, it could be performed more frequently in high-risk individuals. Methylation is a reversible phenomenon, so the test may also be of use to monitor treatment effects over time.

Now, Dr. Goel is looking at another type of genetic marker for use in CRC screening tests. MicroRNAs (miRNAs) are short RNA molecules that bind to messenger RNA transcripts (mRNAs), resulting in gene silencing. Each miRNA may regulate up to several hundred genes. MiRNAs are involved in multiple types of cancer, and it appears that there are specific patterns of miRNA expression associated with different cancers. In comparison to mRNA, miRNAs, perhaps because of their small size, are resistant to endogenous degradation and thus remain stable during the process necessary to isolate them from stool samples. Preliminary work recently published by Dr. Goel and colleagues has demonstrated that miRNAs can be successfully isolated from stool samples and may be useful as biomarkers for the early detection of CRC.

Dr. Goel believes that, in the end, the best fecal screening assay for CRC will be a cocktail of multiple assays—gene mutation, methylation, miRNA—each with its unique strength. This combined assay will be noninvasive and could be inexpensive, removing the major roadblocks to consumer acceptance of regular colon screening.

Genes Associated with Metastasis in CRC
Dr. Koi's research is focused on the identification of metastasis-specific gene markers associated with CRC. Mutations in the four MMR genes, MSH2, MLH1, MSH6, and PMS2, commonly result in MSI. This leads to mistakes in DNA replication, which in turn lead to mutations in many different genes, enhancing cancer development.

There are many types of microsatellites, based on the number of bases involved in the repeated sequence (i.e., mononucle-
otide, dinucleotide, trinucleotide, etc.). Most Lynch syndrome CRC tumor specimens with *MSH2* or *MLH1* germline mutations as well as sporadic CRCs with the *MLH1* gene silenced by promoter hypermethylation show a high level of MSI at mono-, di-, tri-, and tetranucleotide repeats.

Dr. Koi has directed his attention to larger microsatellites and is looking at instability in tetranucleotide repeats. He has found that 50% to 60% of sporadic primary CRCs show instability in tetranucleotide repeats and that this is associated with loss of the *MSH3* gene. Cells that lose the protein product of this gene show a unique type of MSI profile: the affected repeats are larger (mostly tetranucleotides), and mononucleotides are seldom involved.

Based on published papers indicating a possible association of tetranucleotide repeats and down-regulation of *MSH3* with poor outcome, Dr. Koi is examining primary and liver metastatic tissue from patients with sporadic CRC to more carefully define this relationship. His goal is to determine if specific loci targeted by the *MSH3* deficiency might be good candidates for metastasis-specific gene markers.

The JC Virus and CRC

In the early 1970s, there was keen interest among oncologists in the idea that cancer might be the result of viral infection. Although this idea did not turn out to have the global applicability that many hoped for, viruses are in fact associated with some cancers. As of 2002, Max Park, MD, senior epidemiologist at the Wolfson Institute of Preventive Medicine in London, estimated that approximately 12% of cancers are related to viral infection, with the most noteworthy examples being cervical cancer (human papillomavirus), hepatocellular carcinoma (hepatitis B/C virus), lymphoma (Epstein-Barr virus), and Kaposi sarcoma (human immunodeficiency virus).

Dr. Boland and colleagues are interested in the role of viruses in the etiology of CRC, especially the JC virus (JCV). JCV is a human polyomavirus that is extremely common, affecting up to 90% of the general population. Most people acquire the virus in their childhood or early adolescence. In most cases, the virus appears to be relatively benign, although it can become activated in patients with immunodeficiency or immunosuppression, resulting in fatal encephalopathies.

Dr. Boland’s interest in JCV lies in the fact that, like the closely related SV40 virus, it has a transforming gene that encodes T antigen, which will induce chromosome instability in vitro and make normal cells behave malignantly. However, evidence is missing about whether JCV is sufficient in itself to result in malignancy or whether it is a component of a larger process—that is, whether it is a driver or a passenger. Dr. Boland believes that it is a driver, but one that requires activation. He hypothesizes that JCV is present in almost everyone in a latent state. At some point, another factor (dietary exposure, cell proliferation, etc.) allows the virus to become oncogenic, inducing chromosome instability and making CRC likely to occur.

The idea of a latent virus incubating harmlessly for years before being activated by an environmental factor is consistent with a growing amount of epidemiologic evidence about the relationship between environment and CRC. There is a clear indication of geographic variation in CRC, with incidence rates 20 times greater in north central Europe than in Africa, India, and Southeast Asia. This variation is presumed to be associated with dietary factors. For example, in Japan in the 1970s, the incidence of CRC was very low; the rate has increased in the intervening years with the growing incursion of Western cultural influence. In Japanese nationals who migrated to Hawaii, CRC incidence quickly became equivalent to that seen in the Caucasian population. Unlike

“Probably there are no two colon cancers that are just alike. Most are enormously different from one another.”

C. Richard Boland, MD
Site-Specific Tumor Conferences
Dr. Boland and colleagues present many of their most interesting cases at Baylor Charles A. Sammons Cancer Center’s gastrointestinal (GI) site-specific tumor conferences. These conferences, which are held biweekly for GI, are truly multidisciplinary, attended by gastroenterologists, surgeons, medical oncologists, radiation oncologists, nurses, trainees, and research staff.

The goals of the site-specific conferences are to improve the care of the oncology patient and to establish a background for team learning. On average, four cases are presented at each conference. The cases are presented prospectively, so that suggestions and discussion from the attendees are available to the treating physicians. In 2009, there were 24 GI conferences, each with an average of 41 attendees.

In addition to GI, site-specific conferences are held for bone and soft tissue, breast, chest, endocrine, gynecology, head and neck, liver, hematopoietic diseases, neuro-oncology, skin, skull base, stem cell transplant, and urology. Overall, 238 conferences were held in 2009, with a total attendance of 6,760.

Genetically driven changes, the incidence rates shift over time and when the population moves; they don’t appear to be tied to smoking or to alcohol consumption, but may be related to meat and fat consumption.

A working model for the genetic basis of CRC tumorigenesis was first proposed nearly 25 years ago by Vogelstein and colleagues in a landmark paper published in the New England Journal of Medicine. They visualized CRC as stemming from the sequential activation of four or five genes, including APC, ras, and p53. While subsequent research over the years has supported the involvement of these genes, it has turned out that few CRCs actually evolve along the precise pathway envisioned by Vogelstein. As we are learning, the genetic mechanisms involved in colon cancer (and, indeed, in most cancers) are not straightforward. “Probably there are no two colon cancers that are just alike,” said Dr. Boland. “Most are enormously different from one another.” Drs. Boland, Goel, and Koi continue to piece together a better understanding of this enormously complex field, gathering the data that will lead to the improved personalized care of tomorrow.
The Hereditary Cancer Risk Program at Baylor Dallas: Breast and Ovarian Cancer

Genetic Predisposition to Breast and Ovarian Cancer

A case of familial breast cancer was first described in Paris in 1886, the same year that Grover Cleveland dedicated the Statue of Liberty. This year, of the estimated 207,090 women who will be diagnosed with breast cancer, approximately 20% will have a positive family history of the disease. We now know that the degree of risk in a family is a function of the type of relative affected (first or second degree), how many relatives are affected, and the age at which they were affected. For example, the relative risk of developing breast cancer for a woman with a first-degree relation who was diagnosed with breast cancer at an age less than 50 years is nearly twofold higher than if her relation had developed breast cancer at 50 years of age or older. The chance of developing breast cancer if the woman has a second-degree relation with breast cancer is about 1.5 times higher than if she had no family history of breast cancer.

<table>
<thead>
<tr>
<th>Family History of Breast Cancer</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No family history</td>
<td>1.0</td>
</tr>
<tr>
<td>First-degree relation diagnosed at age &lt;50</td>
<td>3.3</td>
</tr>
<tr>
<td>First-degree relation diagnosed at age ≥50</td>
<td>1.8</td>
</tr>
<tr>
<td>2 first-degree relations</td>
<td>3.6</td>
</tr>
<tr>
<td>Second-degree relation</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Although ovarian cancer also tends to run in families, risk analysis in this population has not been as extensive, in part because it is a relatively rare disease; an estimated 22,000 new cases will be diagnosed in 2010, about 10% of the new cases expected for breast cancer. If a woman has a first-degree relative with ovarian cancer, her risk is estimated to be 3 to 4 times higher than that of a woman in the general population. The risk increases if additional first- or second-degree relatives have had ovarian cancer.

In at least some families with a high risk for breast or ovarian cancer, the increased risk is due to the presence of a harmful mutation in BRCA1 or BRCA2, tumor suppressor genes that normally serve to prevent uncontrolled cell growth. Mutations in these genes, which have an autosomal dominant mode of inheritance, are associated with a greatly increased risk of developing breast or ovarian cancer. While women in the general population have a lifetime risk of about 12% of developing breast cancer, that risk jumps to 56% to 87% in women who carry the mutation. For ovarian cancer, the lifetime risk estimate for women in the general population is 1.4% compared with 15% to 40% in women with a harmful BRCA1/2 mutation. Overall, approximately 5% to 10% of all breast cancers and 10% to 15% of all ovarian cancers are associated with inherited BRCA1/2 mutations.

The frequency of BRCA1/2 mutations varies with ethnicity. It is unusually high in the Ashkenazi Jewish population from Eastern Europe and also tends to be high in Norwegian, Dutch, and Icelandic populations. Frequencies of specific mutations may also vary among different racial and ethnic groups in the United States.

BRCA1/2 mutations account for the majority of hereditary breast or ovarian tumors, but mutations in other genes (e.g., TP53, PTEN, MLH1, MSH2) may be involved in some cases. Some of these mutations are associated with other genetic syndromes that carry an increased risk for breast or ovarian tumors. For example, women with Lynch syndrome (associated with mutations in MLH1, MSH2) have a 9% to 12% chance of developing ovarian cancer. It is likely that additional genes will continue to be identified that contribute to the genetic susceptibility for breast or ovarian cancer.

The Hereditary Cancer Risk Program

The Hereditary Cancer Risk Program at Baylor Dallas began in July of 1998; since then, it has seen 2,319 patients for genetic testing and counseling about their risks for breast and ovarian cancer. Over 80% of patients who come to the program are referred by physicians. The remaining 20% self-refer after hearing about the program from a participant, a health fair, or another source. The program
Patients might benefit from genetic testing if they or a family member were diagnosed with breast cancer before the age of 50, ovarian cancer at any age, bilateral breast cancer, or male breast cancer or if they have an Ashkenazi Jewish background with a personal or family history of breast or ovarian cancer. The standard of care is to test for BRCA1 and BRCA2 mutations. Additional testing may be ordered if family history is suggestive, for example, of Lynch syndrome or of a rare genetic syndrome that increases the risk of breast or ovarian cancer, such as Li Fraumeni syndrome or Cowden syndrome.

A new patient meets first with the genetics nurse to learn about genes, mutations, and genetic testing and to review her own medical and family history for risk factors. The nurse makes sure the patient understands that, if she has a BRCA mutation, her risk of developing a breast or ovarian cancer over the course of her lifetime is very high (56% to 87%), but also that some people with mutations never develop cancer. The nurse also discusses what the patient's options are if...
“With the Hereditary Cancer Risk Program, we perform a valuable clinical service that is a fundamentally important tool for the patient and her physician. And because of the power of numbers, we can participate in research trials that will help women in the future.”

Joanne L. Blum, MD, PhD

she tests positive for a mutation. Options can range from increased surveillance all the way to definitive surgery consisting of a double mastectomy and oopherectomy. If the patient decides to undergo genetic testing, her blood is drawn and sent to an outside laboratory. When results are available, she is provided with a summary of risk, a plan of careful monitoring tailored to her level of risk, and a three-generation family tree. The genetics nurse is available for extensive counseling, if necessary. “We don’t charge for the counseling,” says Estelle Brothers. “A positive result can be a relief to some patients, but some are upset. They can become very negative and start questioning everything they have done in their lives. I make sure there is ample time to discuss the results.”

Research Emanating from the Hereditary Cancer Research Program

All patients who participate in the Hereditary Cancer Research Program are invited to enroll in the patient registry. If they agree, they sign a consent form that allows the program to maintain information about them and their genetic status. They can be updated as new information about their condition becomes available and can also be contacted about participation in new clinical studies.

Most patients opt to enroll in the registry. Of the 2,329 patients who have participated in the program since 1998, 2,157 are in the registry. Most are willing to participate in research studies, especially questionnaire studies.

Dr. Blum spoke enthusiastically about what she called “the power of numbers” to get enough information to answer some of the complex questions about breast and ovarian cancer heritability. With the large number of patients available through the cancer registry, she has had the opportunity to collaborate with colleagues throughout North America in major studies that are now reaching maturity. Just this year, a study in collaboration with the University of Pennsylvania looking at the effect of risk-reducing surgery on cancer risk and mortality in BRCA1 or BRCA2 mutation carriers was published in JAMA. A second study in collaboration with investigators at the Mayo Clinic, recently published in Nature Genetics, identifies a locus on chromosome 19 that modifies the risk of breast cancer in BRCA1 mutation carriers. Ongoing studies with investigators from the University of Toronto and Harvard University will provide additional insights about the interplay between genetic mutation and cancer suscceptibility.

Dr. Blum says: “With the Hereditary Cancer Risk Program, we perform a valuable clinical service that is a fundamentally important tool for the patient and her physician. And because of the power of numbers, we can participate in research trials that will help women in the future.”

Did You Know?

Baylor Charles A. Sammons Cancer Center at Dallas’ W.H. and Peggy Smith Breast Center is one of six centers in Texas and 200 in the entire US that is accredited by the National Accreditation Program for Breast Centers (NAPBC). The NAPBC is a consortium of national professional organizations dedicated to improving quality of care and monitoring outcomes of patients with diseases of the breast. Accreditation by the NAPBC is given only to those centers that have committed to providing the highest quality of breast cancer care and that undergo a rigorous evaluation and review of their performance.
Breast Tomosynthesis Mammography: Three-Dimensional Mammography for the 21st Century

For the woman who finds out that she is at high risk of developing breast or ovarian cancer over the course of her lifetime, several options are available, including increased surveillance. For breast cancer, this surveillance has typically been carried out with standard mammography, augmented when necessary with ultrasonography or magnetic resonance imaging. Now, a new adaptation of mammography is being tested at Baylor Dallas as part of a multinational study.

Although standard two-dimensional (2D) mammography has been a powerful tool in reducing breast cancer mortality over the last 35 years, nearly one out of five women diagnosed with breast cancer will have had a negative mammogram within the preceding year. Why is the false-negative rate for 2D mammography so high?

By compressing the breast and collecting images of the breast from two views, standard mammography attempts to visualize a three-dimensional object in two dimensions. Structures within the breast overlap each other, sometimes obscuring lesions. Conversely, these areas of overlap can also mimic the appearance of lesions, resulting in call-backs that are stressful for the patient.

Breast tomosynthesis mammography is a form of three-dimensional (3D) mammography. Like standard mammography, it uses x-ray to form the image, but the x-ray tube moves in an arc above the breast, allowing multiple images to be taken. These images are pieced together using a computer, and the radiologist is then able to “slice” down through the breast. Early studies with this new technology indicated that the use of breast tomosynthesis mammography could show increased sensitivity and specificity compared with 2D mammography, resulting in a lower call-back rate.

Joseph Spigel, MD, a diagnostic radiologist on the medical staff at Baylor Dallas, is concerned about the problem of call-backs. “Patient recalls are problematic at multiple levels,” he said. “Patients pay an emotional price, and it is a sheer inconvenience having to go back for a second appointment.”

Baylor Dallas is participating in a multinational study examining the efficacy of tomosynthesis. The major cause of call-backs is the finding of an asymmetric density on a screening mammogram. For Baylor’s portion of the study, 150 women aged 40 to 85 are being recruited who had a finding of an asymmetric density on a single-view conventional 2D screening mammogram within the previous 3 months. The device used for this research is an investigational tomosynthesis machine that can take both 2D and 3D mammograms while the breast remains in a single compression. (This device has not been approved by the FDA at this time.) The radiologists will be looking to see what percentage of time the diagnosis would change when using 3D tomosynthesis images compared with standard 2D images. If additional areas of interest are discovered on the 3D images, Baylor will pay for the studies needed to investigate them.

Although the tomography images are similar to standard mammographic images, radiologists must learn how to manipulate and view them. “We are seeing breast tissue differently than we have before,” said Dr. Spigel. “There will be a new ‘normal’ with tomosynthesis. We see so many more benign things like cysts that we don’t see in 2D. We need to learn how to filter them down so that we can more accurately determine which patients to send for a sonogram.”

The breast tomosynthesis mammography trial is proving to be very popular, and Baylor Dallas is well on the way to recruiting the required 150 patients. “Here in Dallas we have very educated patients,” said Dr. Spigel, “and with the current state of medicine, the best patient is an educated patient.”
The following key clinical trials are currently open and recruiting patients.

**Colon Cancer**

**Study title:** Phase III study of the effects of selenium on adenomatous polyp recurrence  
**Study ID number:** BRI IRB# 003-120  
**Principal investigator:** C. Richard Boland, MD  
**Sponsor:** University of Arizona, National Cancer Institute  
**Participating site:** Baylor Charles A. Sammons Cancer Center  
**Brief description of study:** This study will measure the effects of treatment with a nutritional supplement, selenium, for 3 to 5 years on the recurrence of colorectal adenomatous polyps, with additional analyses of number, location, size, histologic type, and degree of dysplasia.  
**Volunteers needed:** Men or women aged 40 to 80 years with no previous history of colon cancer, familial adenomatous polyposis, or hereditary nonpolyposis colon cancer who have had one or more adenomatous polyps removed during colonoscopy (3 mm or larger for main study, 10 mm or larger for substudy).

**Breast and Ovarian Cancers**

**Study title:** Prospective cohort study of BRCA1 and BRCA2 mutation carriers and noncarriers with compelling family history (UPENN PROSE study)  
**Study ID number:** BRI IRB# 006-037  
**Principal investigator:** Joanne L. Blum, MD, PhD  
**Sponsor:** Baylor Charles A. Sammons Cancer Center, in collaboration with the University of Pennsylvania  
**Participating site:** Baylor Charles A. Sammons Cancer Center  
**Brief description of study:** The goal of PROSE (Prevention and Observation of Surgical Endpoints) is to evaluate breast and ovarian cancer risk reduction after the use of risk-reduction surgery in women who carry BRCA1 and BRCA2 mutations.  
**Volunteers needed:** Women who are over the age of 20 who have undergone genetic testing and have been found to be carriers of deleterious mutations in the BRCA1 or BRCA2 gene.

**Study title:** Risk factor analysis of hereditary breast and ovarian cancer  
**Study ID number:** BRI IRB# 010-116  
**Principal investigator:** Joanne L. Blum, MD, PhD  
**Sponsor:** Baylor Charles A. Sammons Cancer Center  
**Participating site:** Baylor Charles A. Sammons Cancer Center, in collaboration with the University of Toronto  
**Brief description of study:** The primary objectives of this study are to estimate the incidence of cancers of all types in a prospective cohort of BRCA1 and BRCA2 carriers and to evaluate whether or not oral contraceptive use reduces the risk of peritoneal cancer following oophorectomy in these patients.

---

Patients and their physicians can now access information about open clinical trials in oncology at Baylor Sammons Cancer Center by following these steps:

- Go to BaylorHealth.com/CancerResearch.  
- Click on “Search for Cancer Clinical Trials.”  
- From the drop-down box under Step 2, click on a diagnosis.  
- A list of studies will appear under Step 2. Click on the study that is of interest to you to view details such as the inclusion/exclusion criteria.

For additional details or questions about the studies, please contact the Office of Clinical Oncology Research Coordination at 214.818.8472 or via e-mail at cancer.trials@baylorhealth.edu.
Volunteers needed: Women 25 years of age or older with a mutation in the BRCA1 or BRCA2 gene.

**Study title:** Lesions and/or asymmetric densities identified on a single-view mammograph compared to 3D tomosynthesis.

**Study ID number:** BRI IRB #009-182

**Principal investigator:** Joseph Spigel, MD

**Sponsor:** Hologic Inc., Bedford, MA

**Participating site:** Baylor University Medical Center at Dallas

**Brief description of study:** This study will compare tomosynthesis 3D mammography to conventional 2D mammography during a diagnostic workup, following screening mammography showing a potential lesion or asymmetric density on a single view.

**Volunteers needed:** Women aged 40 to 85 years with a finding of an asymmetric density on a single-view conventional 2D screening mammogram within the last 3 months.

---

**Upcoming Meetings of Interest to Oncologists**

**ASTRO 52nd Annual Meeting**
(American Society for Therapeutic Radiation and Oncology)
October 31–November 4, 2010
San Diego Convention Center
San Diego, CA
www.astro.org/Meetings/AnnualMeetings/index.aspx

**Innovations in Cancer Prevention and Research Conference**
(Hosted by the Cancer Prevention and Research Institute of Texas with support from the CPRIT Foundation)
November 17–19, 2010
Austin Convention Center
Austin, TX
www.cprit.state.tx.us/cprit_conference_2010.html

**52nd Annual Meeting of the American Society of Hematology**
December 4–7, 2010
Orange County Convention Center
Orlando, FL
www.hematology.org/Meetings/Annual-Meeting/

**33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium**
December 8–12, 2010
Henry B. Gonzalez Convention Center
San Antonio, TX
www.sabcs.org

**2011 Gastrointestinal Cancers Symposium**
January 20–22, 2011
The Moscone West Building
San Francisco, CA
www.gicasymposium.org/

**BMT Tandem Meetings**
(Combined annual meetings of the Center for International Blood and Marrow Transplant Research and the American Society of Blood and Marrow Transplantation)
February 17–21, 2011
Hawaii Convention Center
Honolulu, HI
www.cibmtr.org/Meetings/Tandem/index.html#2011BMTTandemMeetings
Cancer Screening Programs

The following cancer screening programs are offered at Baylor Charles A. Sammons Cancer Center at Dallas each year:

• **Prostate cancer:** This annual event occurs in September. All men 50 years of age or older (40 years for men at high risk) are eligible, but are seen by appointment only. The screening takes 10 to 20 minutes and includes a digital rectal exam and a blood test to measure prostate-specific antigen levels. Participants are given an information packet about prostate cancer. This program screens up to 320 men per year.

• **Melanoma:** This screening event takes place in May and is held in conjunction with the American Dermatological Society. People are seen on a first-come, first-served basis. The clinician examines their back, face, and arms for unusual moles, skin irregularities, or anything else that the individual wants them to look at. Last year, 222 people were screened in this program. Participants are given an information bag containing sunscreen and an information sheet about how to recognize suspicious moles.

• **Head and neck:** The head and neck cancer screening program is held in April during Oral Head and Neck Cancer Awareness Week. It is conducted in collaboration with the Baylor College of Dentistry. People are examined for any suspicious lesions in the mouth or any lumps in the neck or shoulder area. Each participant receives an information bag that includes information about smoking, smoking cessation materials, and dental supplies.

These screening programs are held on the Baylor Dallas campus and are free of charge to the participants. If something suspicious is found during a screening, the individual is given a physician referral sheet or, if appropriate, is connected with a patient navigator to assist with referrals and follow-up.

For more information about cancer screening programs at Baylor Sammons Cancer Center, call 1.800.4BAYLOR.

Navigating the Cancer Journey

Modern cancer care can be complex and multidisciplinary. To obtain a timely diagnosis and treatment, the patient with a suspected cancer needs to understand and access this care efficiently. Baylor Charles A. Sammons Cancer Center’s Patient Navigation Program offers assistance in navigating this cancer journey. The patient navigator, a specially trained nurse, helps patients by

• Simplifying access to services such as education, support, and identification of needed resources
• Facilitating contact with the specialists and support teams that will be needed in the management of the cancer
• Helping to schedule appointments
• Providing information so that patients and their caregivers understand their disease and their personalized plan of care

For more information, call the cancer center patient navigation program at 214.820.3535.
Cancer Center Construction Update

We eagerly anticipate the spring 2011 opening of the outpatient cancer center and the 2013 completion of the dedicated cancer hospital. Construction continues on schedule, and work on the outpatient center’s top floor and concrete and glass exterior has now begun. We anticipate the building will earn LEED certification from the U.S. Green Building Council as an environmentally friendly structure.

The new, 467,000-square-foot outpatient cancer center will provide the capacity to offer care to a growing number of cancer patients and survivors. Cancer research will expand with additional space for clinical trials and research laboratories to offer more advanced and innovative treatments.

This growth includes new and broadened programs for patients and families. Exercise and rehabilitation programs will be conveniently located in the cancer center. The center will also house a new integrative medicine program, and expanded pain management, and lymphedema programs. The specialized cancer and gift boutique, education, and support resource center will have more space to augment programs.

The dedicated cancer hospital will open in three short years with construction in progress on the sky bridge that will link the cancer center to the dedicated cancer hospital and parking garage. Work also has begun on a new power plant that will support the cancer hospital, as well as the south side of the Baylor campus.

Coming in 2011: Marvin J. Stone Lectureship

Baylor Sammons Cancer Center and the department of internal medicine at Baylor University Medical Center at Dallas will present the 3rd annual Marvin J. Stone Lectureship on March 29, 2011. This lectureship was instituted in 2009 in honor of Marvin J. Stone, MD, MACP. Dr. Stone served as chief of oncology at Baylor Dallas and medical director of Baylor Sammons Cancer Center from 1976 to 2008. He currently heads the internal medicine clerkship for third-year medical students and the medical oncology fellowship program at Baylor Dallas.

This year’s recipient of the Marvin J. Stone Lectureship is James Armitage, MD, professor of internal medicine in the division of hematology and oncology at the University of Nebraska Medical Center in Omaha. Dr. Armitage developed and was the director of the bone marrow transplantation program at the University of Iowa. At Nebraska, he has served as chief of the division of oncology/hematology, chairman of the department of internal medicine, and dean of the College of Medicine. He has authored or co-authored 440 articles, 95 book chapters, and more than 450 abstracts and is the editor or co-editor of 24 books.

The lectureship will be presented at 8:00 a.m. at internal medicine grand rounds in the Beasley Auditorium on Baylor Dallas campus.

For more information about this lectureship, please call 214.820.3535.
Cancer. We’ve got its number.

OPENING 3/26/2011