Colorectal Cancer Screening: Encouraging Compliance Today and Looking to the Future

by Sunni Hosemann

What if there were a way to cut in half the number of deaths due to colorectal cancer each year, but patients were unlikely to ask for it, insurance companies were reluctant to pay for it, and physicians sometimes failed to recommend it?

According to Bernard Levin, M.D., a professor of medicine and vice president of the Division of Cancer Prevention at The University of Texas M.D. Anderson Cancer Center, if the screening methods we have in hand today were fully deployed—if all of the people in recommended populations were screened—the death rate from colorectal cancer would drop by 50%. Of course, the compliance rate for any screening measure will never reach 100%, but prevention researchers at M. D. Anderson are working to make colorectal screening more accurate, more convenient, and more common, even as they study ways to prevent colorectal cancer altogether.

The importance of screening

Colorectal cancers begin as adenomatous polyps. For now, the goal of screening is to detect and remove these precursor lesions, as well as early-stage (Continued on next page)
cancers, when they are curable. “If we can find it early, we can cure it,” said Stanley Hamilton, M.D., a professor and head of M. D. Anderson’s Division of Pathology and Laboratory Medicine.

The biology of colorectal cancer makes it particularly amenable to screening: colorectal cancers are associated with a low probability of metastasis in early-stage disease, and a variety of effective screening tools can be employed to detect polyps and early-stage cancer. “It is therefore frustrating to see patients present with metastatic colorectal cancer who have never been screened,” Dr. Hamilton said.

The screening tools of today

Current recommendations call for colorectal cancer screening in the general population after age 50 using flexible sigmoidoscopy and a fecal occult blood test (FOBT), double-contrast barium enema, or colonoscopy. Medically, all of these tools are very effective, but they are not ideal, and compliance is difficult to achieve.

Colonoscopy has some advantages over other methods because it provides direct visualization of the entire colon, along with the opportunity to sample or remove significant lesions. However, colonoscopy is more expensive and more invasive than many other screening methods, and it carries a higher risk of complications. Moreover, it is not covered by many health insurance plans as a primary screening device. “So, should we be doing it? Yes,” said Dr. Hamilton, “because this is one of the cancers where screening will make a difference in the number of deaths today.”

But the fact is that most people are not eager to undergo any of the colorectal cancer screening procedures currently available. Therefore, in addition to efforts to encourage screening by raising awareness of its benefits, research is under way to find screening tools that will be better accepted and more readily used.

A better FOBT

FOBT is the least invasive of the screening methods, but it must be used in combination with other screening tests. A new type of FOBT—an immunochemical method—employs antibodies to detect hemoglobin in stool and has significant advantages over the traditional guaiac-based method. One advantage is that it does not react with ingested food, vitamins, or drugs to cause false-positive test results. Another is that the specimen is collected from the surface of the stool with a brush and transferred to a card, a much easier collection method than that required for guaiac-based testing. Data from trials in large screening populations are not yet available, but based on the known enhanced sensitivity and specificity and other advantages of this method, the “American Cancer Society Guidelines for the Early Detection of Cancer, 2004” now recommends its use over guaiac-based testing.

New visualization tools

Two new visualization techniques have attracted the attention of the public and the medical community, but neither is ready for use as a large-scale screening test. Computed tomographic (CT) colonography, popularly known as “virtual colonoscopy,” is an imaging procedure in which a series of helical CT scans of the patient’s colon are rendered by computer into slices that can be visualized as still, rotatable images or serially combined to provide a three-dimensional tour of the colon. So far, this technique has been evaluated only in small trials, mostly conducted in diagnostic (rather than screening) settings in higher-risk patients. The results of those studies indicate that CT colonography is comparable to conventional colonoscopy for the detection of neoplasms and polyps larger than 10 mm but may be less effective at detecting smaller polyps.

Although CT colonography may eventually become an important and widely used screening tool, a few obstacles must be overcome first. The amount of irradiation required for CT colonography is a concern, and the technique requires bowel preparation and insufflation (the two factors that account for most of the objections to colonoscopy) but does not allow for removal of polyps during the procedure, as does colonoscopy. In addition, CT colonography requires a radiologist experienced with the technique (and the learning curve is somewhat high), and no standards exist for performing or interpreting the scans. CT colonography is performed at M. D. Anderson as part of research studies, but according to Dr. Levin, it is not ready to be used as standard care. “It is not specific enough in differentiating between significant and nonsignificant lesions inside and outside of the colon and therefore may prompt additional, unnecessary testing,” he said. “Nevertheless, the technique is evolving rapidly and may become much easier to perform and thus more acceptable to the public.”

Capsule video endoscopy—the “camera-in-a-capsule” technique—has also attracted a good deal of attention. When swallowed, the capsule provides approximately eight hours of videography of the digestive tract. To date, the battery life of the device is one of its limiting factors: it usually runs out before the capsule reaches the lower intestinal tract. Nevertheless, it has been shown to be safe and effective in animal and clinical studies. The wider lumen of the colon poses additional challenges in visualization, so major refinements in equipment and technique will be needed before capsule video endoscopy can be considered for the screening or diagnosis of colorectal cancer.

Genetic and proteomic tumor markers

In the near future, testing stool for tumor DNA may prove more effective than testing for occult blood. Tumors bleed intermittently, but they shed DNA constantly, so markers would be present in any stool sample. Researchers are still determining the best set of markers to include in a test to screen the general population. For more than a decade, Dr. Levin has been collaborating with scientists at The Johns Hopkins University to develop a method for molecular testing.

Yet another area of promise and intense research is serum proteomics—the study of protein patterns circulating in the blood. Such patterns can have a high predictive value, and researchers are working to identify these patterns.
and develop tests that will recognize them as markers of colorectal cancer. These methods promise to have a dramatic impact on colorectal cancer screening. Identifying genetic and proteomic tumor markers has the potential to yield highly sensitive and specific tests that are also less invasive (with fewer associated risks), more convenient, and less expensive than current screening tools. “This would result in a tremendous improvement in compliance and effective screening,” said Dr. Hamilton, “and would move the more invasive procedures such as colonoscopy to a diagnostic, rather than screening, role.”

**Chemoprevention**

“One of the challenges in studying any intervention,” said Patrick Lynch, M.D., an associate professor in the Department of Gastrointestinal Medicine and Nutrition, “is to agree upon what it is important to prevent: an endpoint.” In the interest of time and feasibility, most colorectal cancer prevention trials today do not focus on cancer occurrence but rather on the incidence of polyps.

Calcium and aspirin are the most recent significant findings in the search for colorectal cancer chemopreventive agents. Laboratory, clinical, and epidemiological evidence has long suggested that calcium may help prevent colorectal adenomas, and clinical trials showed a moderate—but significant—reduction in the risk of recurrent colorectal adenomas. In recent landmark studies, a multi-institutional group of researchers that included Robert Bresalier, M.D., professor and chair of the Department of Gastrointestinal Medicine and Nutrition at M. D. Anderson, showed that aspirin reduced the incidence of adenomas. Interestingly, in these and subsequent studies, low-dose baby aspirin (81 mg) worked better than adult aspirin (325 mg).

Current chemoprevention trials are studying cyclooxygenase 2 (COX2) inhibitor agents rather than aspirin. Both are nonsteroidal anti-inflammatory drugs (NSAIDs) and have similar attributes; however, COX2 inhibitors have fewer side effects than does aspirin, a nonspecific NSAID that affects both COX1 and COX2 receptors.

Researchers at M. D. Anderson, in collaboration with those at St. Mark’s Hospital and Academic Institute, London, England; the National Cancer Institute; and Pfizer, Inc., conducted a study of patients with familial adenomatous polyposis (FAP) who had dozens to hundreds of polyps. In the study, COX2 inhibitors reduced the number of polyps by 30%. “This didn’t necessarily prevent cancer or obviate the need for surgery, but it served as proof of the principle that this drug can reduce polyps,” said Dr. Lynch. COX2 inhibitors also are being studied in a pediatric trial of carriers of FAP susceptibility genes to determine whether they can delay onset. “This will not be a cure, and it does not change the need for endoscopic surveillance and frequent screening in these patients,” said Dr. Lynch, “but it may delay surgery for youngsters in whom colectomy is often necessary at a young age.”

**Polyp precursors**

A new M. D. Anderson prevention trial led by Dr. Bresalier is enrolling patients who are at increased risk for colon or rectal cancer. In the study, aspirin, sulindac, and ursofolic will be evaluated as potential chemopreventive agents. Rather than using cancer or polyps as endpoints, however, this study will look at aberrant crypt foci (ACF), micropolyps that develop before (macro)polyps. Investigators use a special spray dye with illumination that makes these dysplastic spots visible during colonoscopy. The effect is dramatic: in a patient with FAP, for example, there are perhaps five to 15 visible polyps but literally hundreds of precursor spots.

This method takes investigators one step back in the chain of screening markers, from studying polyps as cancer precursors to studying ACF as polyp precursors. “The advantage is that we gain useful information with smaller samples in a shorter period of time,” said Dr. Lynch.

**Diet and vitamins**

Although there seems to be a relationship between diet and the development of colorectal cancer, such a link has not been proved. “There was disappointing news from clinical trials in the past couple of years that ran contrary to epidemiologic data that suggested that fiber in the diet was associated with low risk,” said Dr. Lynch. And despite the interest in the role of vitamins and other dietary supplements in the prevention of colorectal cancer, only calcium has been proved effective. Some epidemiologic data suggest that antioxidants found in fruits and vegetables may confer some protection, but thus far, no convincing evidence has been found to support vitamin supplementation for colorectal cancer prevention.

Tomorrow, research may lead to better recommendations about diet, discover more chemopreventive agents, and deliver screening tools that patients and doctors are more willing and able to use. Meanwhile, most experts recommend colorectal cancer prevention strategies that include periodic screening, regular exercise, a diet high in vegetables and fruits, and in individuals at high risk, chemoprevention using agents such as calcium.

**For more information, contact**
Dr. Levin at (713) 792-3900,
Dr. Hamilton at (713) 792-2040,
Dr. Lynch at (713) 794-5073, or
Dr. Bresalier at (713) 745-4340.
Despite Its Drawbacks, Mammography Is Still Recommended
Researchers Look for Biomarkers That Would Improve Patient Compliance and Screening Accuracy

by Katie Prout Matias

Cancer screening, admittedly, is often inconvenient and uncomfortable, but for years experts have argued that the trade-off is a lower risk of death. Indeed, the mortality rates for common cancers, such as breast and colon cancer, have declined since screening for these became more routine. However, even one of the “gold standards” of screening tests—mammography—has been caught up in a recent swirl of controversy as experts debate its true ability to prevent cancer deaths.

Mammography sits at the forefront of debates over cancer screening. Numerous studies have shown that cancer-related survival is better among screened women than among unscreened women, and experts have agreed for many years that mammography saves lives. The controversy began in 2000 when a Danish study questioned the validity of five of eight randomized trials supporting mammography’s benefit. Even though subsequent reviews have found that four of the five studies were not flawed, the debate still lingers in one form or another. Because the “quality of evidence” in many studies of mammography varies and their results are inconsistent, even the National Cancer Institute has stated that “the existence of [mammography’s]l benefit is uncertain.”

In addition to overall efficacy, some of the issues raised involve false-positive rates and unnecessary interventions, false-negative rates, the use of mammography in younger women, overtreatment of ductal carcinoma in situ (DCIS), and radiation exposure.

Every time a woman undergoes mammography, there is an 11% chance that the result will be a false positive, which not only causes the woman to experience unnecessary anxiety but also can lead to additional, and costly, imaging studies and biopsies. After 10 screenings, this risk increases to 50%. The good news is that studies have shown that women who have had a false-positive screening result are much more likely to adhere to a screening regimen. Alternatively, 10% to 30% of breast cancers present at the time of screening are missed by mammography. If a breast symptom develops after a false-negative mammogram result, both the woman and her physician may be less likely to evaluate it properly.

The wisdom of screening women in their 40s, in particular, has been called into question. Breast cancer tends to grow more rapidly in younger women, but because their breasts are more radiographically dense, mammography is more likely to miss cancer. Still, many believe there are benefits to screening this population. “Even the most conservative estimate is that you can cut down the risk of death by 20%,” said Aman U. Buzdar, M.D., a professor in the Department of Breast Medical Oncology at The University of Texas M. D. Anderson Cancer Center.

Another concern with mammography is the overtreatment of DCIS, which accounts for 18% of all breast cancers and 30% of all mammographically detected breast cancers. Countless women receive aggressive treatment for DCIS, including mastectomy and further therapy with tamoxifen, even though many cases of DCIS may never progress. “The question comes up, a lot of these women might die of other causes, and this cancer might not become invasive,” said Dr. Buzdar. “However, data from

Cristi Baker, a mammography technician in Breast Imaging at the Nellie B. Connally Breast Center, assists a patient undergoing a diagnostic mammogram.
some studies illustrate that if you excise it and don’t adequately treat it, a number of times the cancer will come back. The recurrence rates are as high as 27%. Out of those patients, over half the time that the cancer comes back, it is actually invasive cancer. Unfortunately, we don’t have any tests that we can run today and tell a woman, ‘You have a DCIS; if you do nothing, you are going to live a normal life.’ So we offer therapy to all these patients.”

A final issue is that mammography exposes sensitive tissue to radiation. Radiation exposure is a known risk factor for breast cancer; however, for women over age 40, the benefits of annual mammography appear to outweigh any risk from ionizing radiation.

Despite these concerns, there is no denying that mammography is beneficial for older women; it reduces the breast cancer–related mortality rate by 20% to 30%. “There is quite strong evidence to suggest that if mammography is applied adequately and across the board, you can substantially cut the risk of death,” said Dr. Buzdar.

Therese Bevers, M.D., an associate professor in the Department of Clinical Cancer Prevention and director of the Cancer Prevention Center, whose area of expertise is breast cancer prevention, agrees: “I think that overall there is evidence of benefit for mammographic screening,” she said.

Another common breast cancer screening technique that has come under fire is breast self-examination (BSE). A Chinese study of 266,064 women found that women who were taught how to perform BSE had the same breast cancer mortality rates as other women. Several smaller studies have also shown that BSE does not lower the risk of advanced-stage cancer or death.

“For BSE, I think the problem there has been a lack of understanding of what the studies have shown,” said Dr. Bevers. “The study did not show that BSE was not beneficial. The study showed that teaching women a technique with which to do BSE was not beneficial. We don’t need to spend money on shower cards because [women] don’t need the reminder; they don’t need to have a special visual on how to do it. They will find [a breast lump] without that visual or reminder. But I personally think, and I think most experts agree, that women should be involved in their health. They should know what their breasts feel like and should report any problems.”

To encourage women to overcome their apprehension and doubts about breast cancer screening, Dr. Bevers suggests that physicians let their patients know that there are treatment options, including breast conservation therapy. She also suggests that physicians take the initiative to schedule patients for screening. “A lot of times, the patient will not say no if they are already scheduled for it,” said Dr. Bevers.

Dr. Bevers and other researchers at M. D. Anderson are investigating new, less-invasive techniques for breast cancer screening that could one day improve patient compliance and screening accuracy. Dr. Bevers imagines that in the future, using molecular epidemiology, researchers could identify women who have certain markers for breast cancer through blood tests, thus sparing those who do not from mammography. “We have the PSA [prostate-specific antigen] test for prostate cancer screening. It would be nice to have a similar type of blood test for women that would tell us who would need a mammogram,” said Dr. Bevers.

In these studies, researchers are testing several biomarkers, including lysophosphatidylcholine, which is similar to a biomarker being tested for the early detection of ovarian cancer. Elevated levels in the blood could show that a patient is at increased risk for breast cancer. Still, the studies are very preliminary. “We would not ever be able to implement something as a counterpart to or as a replacement for mammography until we had done a large-scale clinical trial that followed women over an extended period of time. We are still trying to get enough preliminary data to say it is worthwhile to do in a larger population with specific risks,” said Dr. Bevers.

FOR MORE INFORMATION, contact
Dr. Buzdar at (713) 792-2817 or
Dr. Bevers at (713) 745-8048.

See page 6 for related story.

M. D. Anderson Cancer Center
Breast Screening Guidelines*

- Monthly breast self-examinations from age 20 (optional)
- Clinical breast examination every one to three years from age 20 to 39
- Annual mammogram and clinical breast exam beginning at age 40
  (Try to schedule clinical breast exam at the time of regularly scheduled
  mammogram.)
- For women at increased risk of breast cancer, screening may begin
  earlier and/or may be required more frequently.

* Updated September 2003
Communication Is Essential When Guiding Patients through the Maze of Genetic Breast Cancer Screening

by Katie Prout Matias

Screening patients who may have an inherited predisposition for breast cancer carries a different set of risks and considerations than does screening for the general population. While the actual tests are much less invasive, the psychological burden of a positive result means that physicians must be able to communicate with their patients and their patients' families and help them make tough decisions.

Only 0.1% to 0.2% of the population carries the BRCA1 or BRCA2 mutation, but for those who have inherited this breast cancer gene, the lifetime risk of breast cancer is very high: 55% to 85%. They also have a significantly increased risk of ovarian cancer.

After a patient with breast cancer has been tested for an inherited genetic mutation, it is up to her to decide whether to share the results with the rest of her family, including her daughters or sisters, who have a 50-50 chance of carrying the gene if she does. “We encourage the patient to share, but there are patients who don’t want to share that information, and we have to respect their wishes. We cannot divulge this kind of information,” said Aman U. Buzdar, M.D., a professor in the Department of Breast Medical Oncology at The University of Texas M. D. Anderson Cancer Center.

Laws in 40 states are designed to protect patients with genetic conditions from discrimination by employers and insurance providers, while the federal Health Insurance Portability and Accountability Act (HIPAA) protects patient confidentiality. According to Dr. Buzdar, who chairs one of M. D. Anderson’s institutional review boards, any patient, including those who choose to participate in a clinical trial, can be assured that her information will not be given to anyone who does not need to know it. “Our responsibility is to the patient,” said Dr. Buzdar.

If a patient tests positive for a genetic mutation and decides to share that information with her family members, the family members must then make the daunting decision of whether to get tested. “It is scary to be told you have a one-in-two chance of getting breast cancer in your life,” said Therese Bevers, M.D., an associate professor in the Department of Clinical Cancer Prevention. “But I try to stress to them that it is going to help me to make recommendations that are appropriately targeted to their level of breast cancer risk.”

Women who find that they have an inherited BRCA1 or BRCA2 mutation may choose a wait-and-see approach, often combined with increased cancer screening and chemoprevention, or they may undergo a prophylactic bilateral mastectomy and possibly an oophorectomy as well. “[Prophylactic surgery] cuts down the risk by 90%. Unfortunately, we cannot say 100% because even a small amount of breast tissue could be left,” said Dr. Buzdar.

Many factors must be weighed when making a decision based on the results of genetic testing. In addition to the physical consequences, women often wrestle with emotional, philosophical, moral, and religious considerations. These issues should be carefully discussed with the woman.

Even negative results of genetic tests require discussion, Dr. Buzdar said. “You have to explain to the person what a negative test means,” he said. “A lot of times, the patient thinks, ‘Oh my test is negative; I am free.’ If the test is negative, it means you are at the same risk as the general population of women in the United States.”

Patients with negative results should also be made aware that not all cancer-causing genes have been identified. “There are limitations to testing. Obviously, we have not identified all the genes involved. So it is possible to have a very strong family history where we are just sure something is going on in the family, but we can’t identify it. We really try to make it clear in our counseling sessions with people that we can only test for—and rule out—the genes that we know about,” said Dr. Bevers.

Despite the unknowns of the genome and the difficult decisions that patients and their families must make, most experts agree that genetic screening is beneficial. “I personally see more benefits [than drawbacks] to genetic testing. I think it empowers people to make informed decisions,” said Dr. Bevers.

The Clinical Cancer Genetics Program at M. D. Anderson provides genetic counseling and genetic evaluation services. Call (713) 745-7391 for more information.

Facing Our Risk of Cancer Empowered (FORCE), a national nonprofit organization, recently launched a toll-free hotline at (866) 824-RISK (7475) to provide information and support to individuals concerned about hereditary breast cancer risk.

For more information, contact Dr. Buzdar at (713) 792-2817 or Dr. Bevers at (713) 745-8048.
Cancer Epidemiology, Step-by-Step

**Cancer epidemiology:** the science concerned with the study of the factors determining and influencing the frequency and distribution of cancer and its causes in a defined human population for the purpose of establishing programs to prevent and control cancer development and spread.

Epidemiology is a very important science in cancer research and prevention because it helps identify people at risk for certain kinds of cancer. But how do epidemiologists find out which people are at risk, and what is then done with that information? Below are the steps that epidemiologists follow to identify these special groups of people and the ways in which their work benefits everyone.

1. **Epidemiologists start with questions such as the following:**
   - Are certain cancers more common?
   - Are certain cancers more common in certain groups of people?
   - Are certain cancers becoming more common?

2. To start to answer these questions, epidemiologists first look for possible characteristics that people with certain cancers have in common—characteristics such as:
   - Diet
   - Lifestyle
   - Age
   - Ethnic group
   - Gender
   - Occupation
   - Environmental exposures
   - Medical history
   - Familial history of cancer
   - Health-care access and usage
   - Genetic factors
   - Educational level
   - Biological factors
   - Geographic factors.

3. Next, epidemiologists test for the actual presence of the suspected factors in a large group of people with and without the certain cancer. They do this by:
   - Doing surveys
   - Having people fill out questionnaires
   - Looking at people’s medical histories
   - Doing laboratory tests
   - Getting family histories.

4. After this, epidemiologists look closely at their findings to see if there are any patterns. They look for characteristics that many of the patients with certain kinds of cancer do or do not have in common.

5. Once they have this information, epidemiologists can help:
   - Develop screening tests
   - Develop information campaigns targeted to certain groups of people
   - Raise public awareness about certain kinds of high-risk behavior
   - Encourage certain groups of people to get screened regularly for the cancer.

6. The result?
   - Cancers can be diagnosed at earlier, more treatable, stages.
   - Certain cancers can be prevented.
   - People live longer and better lives!

Epidemiologic research has benefited us by:

- Helping to identify smoking as a risk factor for lung cancer
- Discovering that exposure to asbestos is a risk factor for mesothelioma
- Discovering that people who eat high-fat diets are at risk for uterine cancers
- Finding that a certain kind of virus infection is associated with a high risk of cervical cancer
- Finding that the prostate-specific antigen level could be used to identify men with prostate cancer
- Finding that women with certain mutated genes were at very high risk for breast cancer
- Finding that cancers are found at later stages in people who have poor access to health care.

For more information, contact your physician or contact the M. D. Anderson Information Line:

- **Telephone:** (800) 392-1611, Option 3, within the United States, or
- **Telephone:** (713) 792-3245 in Houston and outside the United States.

February 2004

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On Being a Volunteer

Anderson Network volunteer

I was diagnosed with adenocarcinoma of the duodenum in the summer of 1999 and underwent a Whipple procedure at M. D. Anderson Cancer Center. As I was recovering from that unnamed volunteer and from the Anderson Network volunteers who coached me in person.

In a world in which many of us feel that we can be easily replaced in our day jobs, this position of survivor/volunteer is one that I am uniquely qualified to fill. When people ask me why I volunteer, I am likely to tell them that I am “turning lemons into lemonade.” I am hoping to make a difference as so many have done for me these past few years. As an added benefit, I also am reminded weekly of how blessed I am to continue to experience a full and healthy life.

“We make a living by what we get, but we make a life by what we give.”
— Winston Churchill

I have been delighted by the professionalism of the Anderson Volunteer Services organization: they are dedicated to making sure that every patient has the experience of being in a caring place each and every day and night. The doctors and nurses at M. D. Anderson also volunteer their care and concern every day. There was my surgeon, who returned my call to his pager while taking his daughters to a record store on a Saturday; my radiation oncology nurse, who offered me her home phone number to call if I needed her after hours (and I really did); and many others who took just a moment to give a smile or an understanding response to a question. They all made a big difference during this ordeal of mine.

My efforts as a volunteer are dedicated to all of you who have made such a difference in my life!