National Institutes of Health

Fact Sheet *Colorectal Cancer*

In the mid-1970s, approximately 60 cases of colorectal cancer were diagnosed per 100,000 people in the United States, and approximately 51% of those diagnosed survived their disease at least five years. Over the last two decades, incidence rates have fallen by nearly 26% between 1984 and 2004. This decline is likely due to increased colorectal cancer screening, which allows physicians to detect and remove colorectal polyps before they progress to cancer. Yet, incidence is still high: colorectal cancer is the third most commonly diagnosed cancer for both men and women. As of 2004, approximately 48 cases of colorectal cancer were diagnosed per 100,000 people in the United States. About 65% of men and women diagnosed with colorectal cancer now survive their disease at least five years.

Yesterday

- Surgery was a long-established treatment for colorectal cancer and could be curative for patients whose cancer had not spread. The "no touch isolation" surgical technique was developed as a way to limit the possible spread of cancer through the bloodstream during colorectal cancer surgery.
- Fluorouracil (5-FU) – an inhibitor of DNA synthesis – was first synthesized in 1957 and became the drug of choice for colorectal cancer treatment. There was little evidence that 5-FU – given alone as a single, large dose — prolonged survival; however, studies suggested that its use improved the quality of life for patients with advanced disease.
- Radiation therapy was used to manage the pain associated with rectal tumors. A variety of clinical trials conducted throughout the 1970s also explored whether various types of radiation therapy – preoperative, adjuvant (following surgery), and "endocavity" (direct contact) – might prevent local cancer recurrence or improve survival in patients with rectal cancer.

Today

- Surgical techniques and survival after surgery have improved over the past 15 years. Surgery can cure about 90 % of colorectal cancers when the disease is found early.
- An NIH-funded study confirmed that less invasive laparoscopic surgery is a safe alternative to conventional surgery for patients with operable colon cancer. This technique is currently being investigated in patients with rectal cancer.
- Advances in chemotherapy led to changes in treatment practice standards and improved survival for colorectal cancer patients. 5-FU remains the cornerstone chemotherapy drug for colorectal cancer; but, today it is administered as part of multidrug regimens.
- Researchers began testing drug combinations with 5-FU as early as the 1980s, and, in the mid-1990s, studies testing the combination of 5-FU and leucovorin as an adjuvant treatment found that this regimen improved the 5-year disease-free survival rate for patients with stage III colon cancer.
- Other agents combined with 5-FU/leucovorin are proving to be even more beneficial. For example, the addition of oxaliplatin to 5-FU/leucovorin – a treatment regimen known as FOLFOX 4 – considerably prolongs disease-free survival when given as an adjuvant treatment to patients with stage III colon cancer. For patients with stage II or stage III rectal cancer, preoperative chemoradiation is usually administered, followed by surgery and postoperative chemotherapy.
- New, targeted therapies offer great promise in the fight against colorectal cancer. These therapies, including drugs and monoclonal antibodies, target specific biological processes used by cancers to grow and spread. Bevacizumab (Avastin), which is a monoclonal antibody that interferes with the development of new blood vessels to tumors, was recently approved as a targeted treatment for advanced colorectal cancer. When given with combination chemotherapy to patients with advanced disease, bevacizumab helped increase median overall survival and reduced the risk of death from colorectal cancer.

- Colorectal cancer prevention is a clinical imperative, and a key part of prevention involves the search for drugs that block or reverse colorectal cancer development. One drug, celecoxib (Celebrex), has been the focus of several NIH co-sponsored clinical trials. Celecoxib blocks the actions of the enzyme cyclooxygenase-2 (COX-2), which is produced in response to inflammation and also by precancerous and cancerous tissues.
- The trials found that regular use of celecoxib significantly reduced the risk of developing precancerous polyps in the colon or rectum. Unfortunately, one NIH co-sponsored study also found that celecoxib was associated with an increased risk of cardiovascular events.
- Researchers are now working to understand how celecoxib might increase the risk of such events. In addition, laboratory studies are moving us toward "molecular prevention" by enabling us to identify biological markers that indicate which people are more likely to benefit from COX-2 inhibition and other "chemoprevention" approaches.
- Colorectal cancer screening has clear clinical benefits, since colorectal cancer can take many years to develop and early detection of the disease greatly improves the chances of a cure.
- Screening also enables physicians to detect and remove colorectal polyps before they progress to cancer. According to current guidelines, people at average risk for this disease should be screened starting at age 50. Unfortunately, only 30 to 40% of people in this age group actually get screened, suggesting that we need to do a better job of educating and encouraging people to take advantage of available screening approaches.
- A number of screening methods are now in use and/or under clinical evaluation. The fecal occult blood test (FOBT) is a relatively inexpensive and noninvasive test that detects hidden blood in stool. FOBT, recommended as an annual screening test, can reduce colorectal cancer deaths by up to 33%, according to study findings.
- Two other methods, flexible sigmoidoscopy and colonoscopy, are invasive procedures that allow a physician to visualize the inside of the lower part of the colon or the entire colon, respectively. Although these methods are more expensive, they allow doctors to see inflamed tissue, abnormal growths, and ulcers. They also are more effective than FOBT in detecting precancerous and cancerous growths; however, their invasiveness poses some risks to patients.
- Researchers are currently evaluating another screening method known as computed tomographic colonography or virtual colonoscopy. Virtual colonoscopy allows the physician to see the same images of the colon as with colonoscopy—without having to probe inside the body.
- Through an ongoing NIH-funded trial, researchers are trying to determine whether virtual colonoscopy is as effective as colonoscopy in detecting polyps and cancer. NIH is also supporting a large-scale clinical trial to determine whether screening with flexible sigmoidoscopy can reduce colorectal cancer deaths. Finally, scientists are testing a new, noninvasive method that looks specifically for mutations in DNA in stool samples that are indicative of colorectal cancer.
- Although certain inherited genetic mutations can increase a person's risk for colorectal cancer, about 75% of colorectal tumors are sporadic and not known to have developed because of inherited genetic mutations.
- Scientists have been working to identify the genetic alterations that underlie these sporadic tumors. Over the last 15 years, studies have shown that mutations in key genes that control cell survival and death occur very early in the development of colorectal cancer.

Tomorrow

- A major challenge in colorectal cancer research is to characterize all of the key genetic changes associated with tumor initiation and progression. The Human Genome Project has established a firm foundation for this effort, and new projects focused on systematically exploring the entire spectrum of genomic changes involved in human cancer promise to bring us closer to meeting this challenge.
- Characterizing the molecular changes associated with colorectal cancer development and progression will allow us to identify both biological markers for this disease and relevant molecular targets for prevention and treatment.
- Developing new cell culture and animal model systems that reflect the full spectrum of this disease will improve our ability to understand the biology of precancerous and cancerous colorectal lesions, learn about the interplay between environmental and genetic risk factors, and develop and test new targeted therapies to prevent and treat this disease.

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