U.S. practices for colon cancer screening

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Abstract. As the prevalence of gastric cancer decreases in Japan, the prevalence of colon cancer has been increasing. Examination of the screening practices for colon cancer in the United States can offer insight into practices that may be useful in Japan. This paper will review the epidemiology and risk factors for colon cancer, the genetics of colon cancer, prevention issues, screening modalities, and current recommendations in U.S. practice. (Keio J Med 54 (4): 179–183, December 2005)

Key words: colon cancer, screening, genetics

Colon Cancer Epidemiology

In 2002, there were approximately one million new cases of colon cancer worldwide with a male to female ratio of 1.2:1.¹ There were approximately 529,000 deaths attributed to colon cancer in that same year.¹ The five year survival rate of individuals diagnosed with colorectal cancer is directly proportional to the stage of the cancer when it is identified. Dukes’ stage A is confined to the mucosa and submucosa. In Dukes’ stage B, there is progression through the muscularis propria and serosa. For Dukes’ stage C, there is involvement of lymph nodes while in Dukes’ stage D, distant metastases are present. Dukes’ stage A, B, C and D carry a five year survival rate of >80%, 60–80%, 30–40%, and 5% respectively. Colorectal cancer progresses in sequence from normal mucosa to adenoma, then to severe dysplasia before making the final transition into cancer. These characteristics of colon cancer raise the issue of screening.

Screening for colorectal cancer is aimed to detect a curable and prevalent disease. Screening is done on patients to search for neoplasia without prior evidence of neoplasia. Patients with positive symptoms or a positive screening test such as fecal occult blood test undergo diagnostic evaluation.

Colorectal cancer is ideal for screening. It is common
and serious. It starts as an identifiable and slow growing precursor lesion. Once developed, colon cancer advances through stages slowly. Early detection can cure.

Who Should Be Screened?

Multiple risk factors have been shown to increase the incidence of colorectal cancer including diet, geography, age, family history, a history of chronic colitis, a history of adenomas, and a previous history of colorectal cancer. The age-adjusted mortality is higher in men than in women. However, the lifetime risk of diagnosis and death from colorectal cancer are similar in both sexes. Women over 60 years of age are as likely to develop colorectal cancer as breast cancer. Relatives of individuals with adenomatous polyps are also at an increased risk for developing colorectal cancer. Patients with newly diagnosed adenomatous polyps were interviewed regarding the history of colorectal cancer in their patients and siblings. In this study, 1199 patients with adenomatous polyps were interviewed. After the exclusion of patients with incomplete information and patients referred secondary to a family history of colorectal cancer, there were 1031 patients with 4246 first-degree relatives (1865 parents and 2381 siblings) included. The study used 1411 spouse controls. The relative risk of developing cancer for first-degree relatives of patients with adenomatous polyps was 1.78 compared with spouse controls.

Genetics of Colon Cancer

Colon cancer can be classified as sporadic (75%), familial (20%), and genetic syndromes such as Hereditary Nonpolyposis Colorectal Cancer (HNPCC) and Familial Adenomatous Polyposis (FAP) (5%).

HNPCC is an autosomal dominant condition in which there is an increased risk of developing colorectal cancer with an earlier age of onset than sporadic colorectal cancer. HNPCC has a right colon predominance and affected individuals are at risk of developing other primary cancers. Females are at an increased risk of developing endometrial and ovarian cancer. All individuals are at increased risk for developing other extracolonic malignancies including keratoacanthomas and sebaceous gland neoplasia, hepatobiliary, stomach, small bowel, and uroepithelial cancers. A thorough family history is essential to help identify families that may be affected by HNPCC. The Amsterdam Criteria is used to help diagnose patients with HNPCC. To fulfill the Amsterdam Criteria, patients must have 3 or more relatives with colorectal cancer, one of whom is a first-degree relative of the other two, two or more generations affected, and at least one of the relatives diagnosed before the age of 50.

FAP is also an autosomal dominant syndrome characterized by multiple adenomatous polyps. Affected individuals may develop adenomatous polyps in the gastric, duodenal, jejunoileal, and colorectal areas. Individuals may also develop extra-intestinal features including congenital hypertrophy of retinal pigment epithelium (CHRPE), brain tumors, epidermal cysts, osteomas, and desmoid tumors. Patients with FAP have an inevitable progression for colon cancer, usually within 8–10 years.

Genetic mutations involved in the pathogenesis of colorectal cancer may be either inherited or acquired. Inherited mutations are also called germline mutations, indicating that they are present in the initial embryonic germ cell. A germline mutation will thus also be found in all daughter cells, and therefore in every cell of the body. Acquired mutations are also called somatic mutations and often occur later in life. They are only present in the cell in which they occur, although if not repaired, the mutation may be replicated during cell division and thereby be present in daughter cells. The mutations that occur as part of colon cancer pathogenesis can be divided into three categories: mutations of tumor suppressor genes, oncogenes, or DNA repair genes.

Tumor suppressor genes normally suppress or control cell growth. When this function is lost through mutation, cell growth becomes uncontrolled, constant, or constitutive. Both alleles of a tumor suppressor gene needed to be damaged or lost for the gene to be completely lost. Damage or loss occurs in several ways. The first allele can be inherited in a mutated form, as it is in FAP, or may be somatically mutated, as it is in the setting of sporadic colon cancer. If the second allele acquires a somatic mutation, gene function is lost. Another common mechanism for loss of the second allele is called “loss of heterozygosity” (LOH). This is an important mechanism of tumor genesis, although how it occurs is not completely understood. With LOH, there appears to be an asymmetric distribution of chromosomal materials during a flawed mitosis. This may result in loss of the entire normal allele, thereby unmasking the mutated tumor suppressor genes of that gene’s normal function. Tumor suppressor genes involved in the pathogenesis of colorectal cancer include APC, p53, and a yet to be identified gene on chromosome 18.

The normal function on an oncogene, called a proto-oncogene before it is mutated, is to stimulate cell growth as part of an intracellular growth-signaling pathway. Such pathways respond to external growth signals and transfer the signal to the nucleus through multiple steps. Only one allele of an oncogene needs to be mutated to cause dysfunction. When this occurs, the growth signal becomes constant or constitutive, rather than regulated.
and responsive to external stimuli. K-ras is the primary oncogene involved in the pathogenesis of colon cancer.\(^6\)

The function of DNA repair genes is to correct DNA errors that occur either during DNA replication or from mutational damage. These genes either repair DNA error or induce apoptosis if the error cannot be repaired. Dysfunction of repair genes leads to the accumulation of mutations in daughter cells. Eventually genes are affected that are important to colon cancer tumorigenesis.\(^7\)

The adenomatous polyposis coli (APC) gene is a tumor suppressor gene located on the long arm of chromosome 5. It was first identified as the gene mutated in FAP. It was later determined that this gene plays a critical role in the pathogenesis of colon cancer and is the first gene inactivated in over 80% of colon malignancies.\(^8\) This mutation is present even in the smallest of adenomas, with a similar frequency to that seen in larger adenomas and cancer. This suggest that APC inactivation is an early event. It is now known that the most common order of genetic events is APC gene inactivation, followed by K-ras mutation, chromosome 18 gene inactivation, and finally p53 inactivation. The benign to malignant change is approximately concurrent with p53 inactivation.\(^9\)

The change from normal mucosa to adenoma involves mucosal hyperproliferation and DNA hypomethylation. Oncogene mutations are involved in an adenoma changing to severe dysplasia. From this stage, allelic deletions help progress the dysplasia to cancer.

In the general population, people over the age of 50 are at average risk of developing colorectal cancer. Individuals with a personal or family history of colorectal cancer or polyps are at moderate risk. Those at high risk include individuals with a history of Inflammatory Bowel Disease (IBD), HNPCC, or FAP.

**Prevention of Colon Cancer**

Colon cancer is preventable. Primary prevention involves teaching individuals behavior modification and elimination of risk factors. To decrease the risk of colorectal cancer, individuals should increase physical activity, eat more vegetables, and consume a diet high in fiber and low in fat. Aspirin, NSAID’s and calcium may also decrease the risk of developing colorectal cancer.\(^10\) Obesity, increased consumption of alcohol, and increased red meat\(^5,10\) may lead to an increase in the risk of developing colorectal cancer. A diet high in fat and low in fiber may also increase the risk of developing colorectal cancer.\(^10\)

The secondary prevention involves early tumor detection with proper use of screening, surveillance, and diagnostic evaluations. Tertiary prevention involves decreasing mortality with established tumors by proper medical management.

**Screening Modalities**

There are multiple screening options available including fecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), barium enema x-ray, and colonoscopy.\(^11–13\)

*Fecal occult blood testing*

In a study to test the effectiveness of using FOBT as a screening tool, 46,551 participants age 50 to 80 years of age were randomly assigned to be tested annually, biennial, or to a control group.\(^12\) The 13 year cumulative mortality from colon cancer per 1000 was 5.88 in the annually screened group, 8.33 in the biennially screened group, and 8.83 in the control group. Thus, the mortality from colon cancer was decreased by 33% in the annually screened group compared to the control group. FOBT offers several advantages as a screening tool in that it has been proven effective in randomized trials, it is non-invasive, and cost effective. However, the mortality reduction is low (15–33%) and the proper evaluation of a positive test is often inadequate.\(^14\)

*Flexible sigmoidoscopy*

Flexible sigmoidoscopy (FS) can also be used as a screening tool. The procedure can be done in the office without sedation, it is inexpensive and cost-effective, it has been shown to reduce rectal cancer mortality by 60–70%, and the preparation is much easier on the patients compared to colonoscopy. However, FS detects only half of adenomas and 40% of cancers are proximal to the splenic flexure. Up to 75% of proximal lesion have no distal lesions that would be identifiable by FS. The test itself is often limited by patient discomfort and poor preparation.

There is rationale to recommend combining FOBT and FS by offering FOBT annually and a FS every five years.\(^11\) This method allows for visualization of the left colon and provides good sensitivity with FOBT for proximal cancers that are beyond the reach of FS. Although the combination has never been directly studied in a randomized trial, a recent study did show that the addition of a one time FOBT with FS increased the detection rate of advanced neoplasia from 70% with FS alone to 76%.\(^15\)

*Barium enema X-ray*

Barium enema x-ray examinations (BE) has the benefit of being cost effective and examining the entire
undergone sigmoidoscopy or colonoscopy within the previous 5 years.

Colonic symptoms. Proper patient education is needed to help overcome these perceptions.

They also feel that screening is not needed without a history of colorectal cancer, compliance was greater at 62.9% versus 39.7%.

The most common reason given by patients for not undergoing screening is "the test was never recommended." Of those offered testing, only 4% declined.

The American College of Gastroenterology recommends for patients at average risk, to begin screening at age 50 with FOBT annually and a FS every five years or preferably, a colonoscopy every 10 years. For patients with a positive family history of colorectal cancer, a colonoscopy should be done at age 40 or 10 years younger than the age at which the youngest affected relative was diagnosed. For those with a single first-degree relative that was affected at age >60 years, a colonoscopy every 10 years should be done. For patients with 2 or more first-degree affected or one first-degree relative affected before the age of 60, a colonoscopy should be done every 3–5 years.

Patients with a genetic diagnosis or a clinical diagnosis of HNPCC via Amsterdam Criteria should have a colonoscopy done beginning at age 20–25 or 10 years prior to the youngest age of colon cancer diagnosis in the family. Colonoscopy should be done every two years until the age of 40, then annually. Screening for endometrial, ovarian, pancreatic, gastric, small bowel, and urinary tract cancers should also be done.

Recommendations differ for special situations include FAP, ulcerative colitis, Crohn’s disease, and pelvic irradiation.

Third, the payors must be convinced that screening is cost-effective. In the U.S., the cost for colonoscopy varies widely from institution to institution. It has been shown that if colonoscopy costs are less than $750, a one-time colonoscopy is more cost-effective than other programs at every level of compliance. The incremental cost-effectiveness ratio of screening for colorectal cancer is estimated to cost $6,600 per life year gained. This compared favorably with the incremental cost-effectiveness ratios of other common medical practices such as breast cancer screening at $22,000, heart transplantation at $160,000, and cervical cancer at $250,000.

Improving the screening tests may also increase compliance and screening. Colonoscopy compliance may be improved with better preparation choices. Current gut lavage solutions include polyethylene glycol electrolyte solutions (PEG-ELS; GoLytely, CoLyte, Niflce) and sulfate-free electrolyte lavage solutions (SF-ELS; NuLytely; Trilyte). PEG-ELS and SF-ELS are isotonic, poorly absorbed solutions that pass through the GI tract with no net water or electrolyte absorption or secretion. They reach a steady state equilibrium when given on large volumes at high infusion rates (1.5 1/hr). The main complaints with lavage solutions are flavoring and volume. Improving the taste and reducing the volume consumed may help improve compliance. Saline laxatives, such as oral sodium phosphate, phos-

Colonoscopy

Colonoscopy can help prevent colon cancer by detection of adenomatous polyps and polypectomy. Colonoscopy allows for visualization of the entire colon so proximal as well as distal lesions can be identified. It also has the best sensitivity of the current screening methods. The disadvantage of colonoscopy is the cost, increased risks such as perforation and bleeding, difficult preparation for the patients, and the need for sedation.

When compared, colonoscopy has been shown to be a more effective method of surveillance than double contrast barium enema. After colonoscopic examination with polypectomy, 580 patients underwent surveillance with paired colonoscopy and double control barium enema (DCBE). Out of the 392 cases where colonoscopy found polyps, DCBE showed polyps in 139 (35%) of those same cases. DCBE accurately detected 34% of adenomas <0.5 cm, 53% of adenomas 0.6 to 1.0 cm, and 48% of adenomas >1.0 cm. Colonoscopy by retesting was found to have missed 20% of adenomas, of which none were >1.0 cm.

Screening Recommendations

Utilization of colorectal cancer screening methods remains low. In patients without a personal or family history of colorectal cancer or personal history of polyps, 50%, 19.6%, 39.8%, and 17.5% reported ever having had FOBT, FS, barium enema, and colonoscopy, respectively. Among those with positive family history of colorectal cancer, compliance was greater at 62.9% versus 39.7%. In a National Survey of U.S. residents >50 years of age in 1999, only 33.6% had undergone sigmoidoscopy or colonoscopy within the previous 5 years.

How can utilization of screening tests be increased to help make screening more effective? First, the public must be convinced of the importance and benefits of colorectal cancer screening. There seems to be two important barriers to convincing the public. Most are afraid to undergo screening for the fear that it will hurt. They also feel that screening is not needed without symptoms. Proper patient education is needed to help overcome these perceptions.

Second, health care providers must offer colorectal cancer screening to the patients. The most common
phate tablets, magnesium citrate, and magnesium sulfate are also used for colonic preparation. In Japan, some colonoscopers perform colonoscopy without sedation. U.S. colonoscopists typically use a narcotic (meperidine or fentanyl) and a sedative (midazolam). Improving sedation and discomfort with the use of medications such as fentanyl derivatives and propofol may also help improve colonoscopy compliance.

In the future, virtual colography, capsule colonoscopy, stool-based DNA testing, and chromomagnification endoscopy show promise as new methods of colorectal cancer screening. These methods are not yet well enough developed to be offered as routine screening options.

**Summary**

The key message is that colon cancer screening has been proven effective and should be used as standard medical care. Colon cancer is preventable. Using current screening options and recommendations, physicians can greatly reduce the incidence of colorectal cancer and improve quality of life. Health care providers must educate patients on not only screening, but preventative strategies to help reduce the risk of developing colorectal cancer. It is expected that in Japan, colon cancer screening will become as important as currently utilized gastric cancer screening modalities.

**References**