Colorectal Cancer

Prevention and Early Detection in Persons at Average, Moderate or Increased Risk

Medical Grand Rounds

January 14, 1999

David K. Spady, M.D.

This is to acknowledge that David K. Spady has no financial interests or other relationships with commercial concerns related directly or indirectly to this presentation.

David K. Spady, M.D.
Professor of Internal Medicine
Division of Digestive and Liver Diseases

Interests: General gastroenterology and Lipid Metabolism

Introduction

The United States is a high-risk country for colorectal cancer (CRC). Americans have an average lifetime risk for developing this cancer of ~6% (1). CRC is second only to lung cancer as a cause of death from cancer in the United States. In 1997, ~131,000 Americans were diagnosed with CRC and ~55,000 died from this disease. It is the only major cancer that affects both men and women almost equally. In 1997, survival from CRC was ~55%. Life expectancy for those with CRC is strongly related to disease stage at diagnosis (Fig. 1). Most CRCs arise in adenomatous polyps that can be detected and removed endoscopically. It seems likely, therefore, that detecting adenomas and early-stage cancers and removing them will improve overall survival from CRC.

Recent research has contributed to a growing consensus that early detection methods can prevent a substantial proportion of morbidity and mortality from CRC. Evidence-based guidelines separately developed or revised by the U.S. Preventive Services Task Force (2), a task force comprised of the Agency for Health Care Policy Research (AHCPR) and five medical and surgical GI professional societies (3), and the American Cancer Society (4) now recommend that all asymptomatic, average-risk Americans over the age of 50 be encouraged to undergo screening for CRC. Selected individuals who are at higher risk because of a personal or family history of CRC or polyps, or longstanding chronic ulcerative colitis, should be offered more intensive surveillance tailored to an estimate of their level of risk. CRC screening is now reimbursed under new Medicare legislation that began in 1997 with expanded coverage as of January 1998. It is estimated that widespread adoption of these recommendations could reduce mortality from CRC by 50% or more.

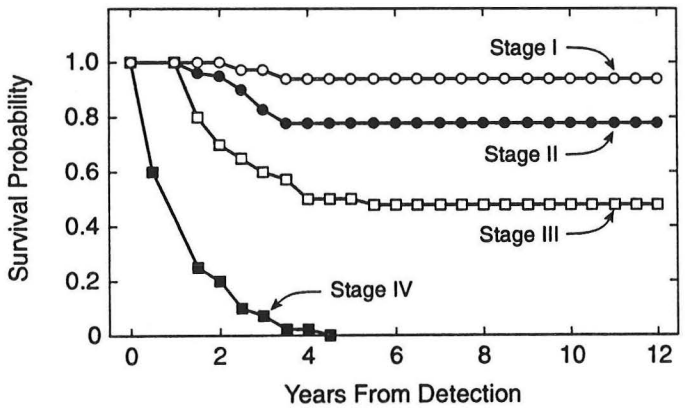


Fig. 1. Survival from colorectal cancer (CRC) as a function of stage of disease at the time of diagnosis (1).

Screening refers to tests that identify persons at risk for a particular disease, but without symptoms, signs, or easily identifiable risk factors. Screening tests for cancer are usually not diagnostic procedures and a certain number of false positive and false negative tests will occur. A positive screening test needs to be followed up by further tests which have a high degree of diagnostic accuracy in order to confirm or deny the presence of the suspected cancer or its precursor lesion. Surveillance is a follow-up at regular intervals, of those with a known risk for colorectal cancer (ie., patients who have a personal or family history of CRC, a genetic polyposis syndrome or inflammatory bowel disease), by using further tests to detect at an early stage the development of new tumors or a recurrence of the cancer. Surveillance for cancer is restricted to smaller high-risk groups. The tests performed for surveillance usually have a high level of diagnostic accuracy.

Biological basis for colorectal cancer prevention

Current data suggest that most CRC arises from adenomatous polyps. Polyps are mucosal masses that can be divided into two major groups: neoplastic (adenomatous polyps and carcinomas) and non-neoplastic (5). About half to two-thirds of colorectal polyps are adenomatous (premalignant) polyps. The remainder are non-neoplastic polyps including hyperplastic polyps, which represent about a quarter of all polyps and have no clinical importance, juvenile polyps, Peutz-Jeghers polyps, and inflammatory polyps.

Adenomatous polyps are subdivided by histology into tubular, villous and tubulovillous adenomas. About 80% of adenomatous polyps are tubular, 5-10% villous, and 10-15% tubulovillous (5). Tubular adenomas are usually small and exhibit mild dysplasia. Villous architecture tends to be found in large adenomas and with more severe forms of dysplasia.

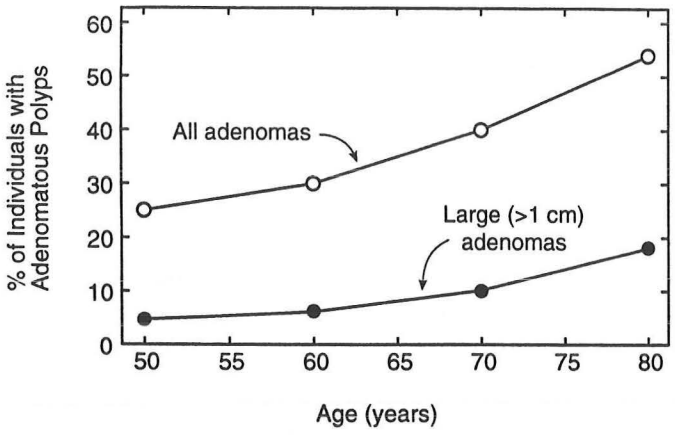
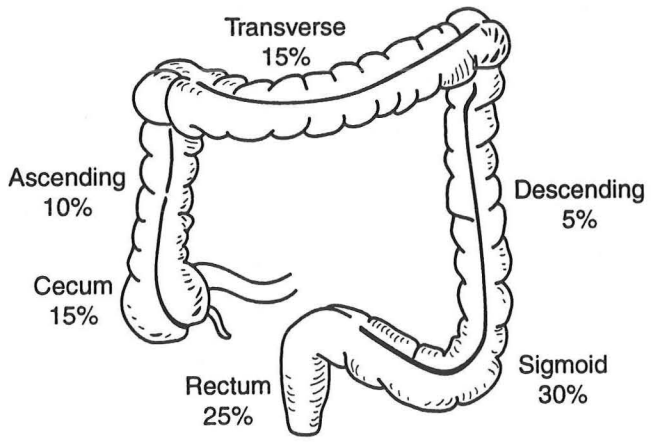


Fig. 2. Prevalence of adenomatous polyps in the general population as a function of age (5).

Adenomatous polyps are found in about a quarter of people by age 50 and the prevalence increases with age to about 50% by age 75 (Fig. 2). The prevalence of polyps >1 cm is much lower: ~5% at age 50 increasing to ~15% at age 75. As with cancers (Fig. 3), polyps are found throughout the colon with about one-third occurring proximal to the splenic flexure. The probability that an adenomatous polyp will progress to cancer, and the probability that the patient will develop other adenomatous polyps or cancer elsewhere in the colon and rectum, can be estimated from the characteristics of the polyp at the time it is first examined. Size >1 cm, tubulovillous or villous histology, severe dysplasia, and multiple polyps predict increased risk of developing further adenomatous polyps as well as cancers (6, 7).

Fig. 3. Anatomic distribution of CRC (1).



Polyp size is determined at the time of colonoscopy. Polyps are generally described as diminutive (<5 mm), small (5-10 mm) or large (>1 cm). Diminutive polyps, even when they prove to be adenomas, are very unlikely to harbor severe dysplasia or carcinoma and have a low risk of progression to cancer. Adenomas are also frequently described according to their risk of containing or developing into a cancer. Adenomas that are >1 cm in diameter, have villous architecture, or are severely dysplastic are generally defined as high-risk (or advanced) adenomas. Tubular adenomas that are <1 cm in diameter and without severe dysplasia have a low risk of containing or progressing to cancer.

Epidemiological evidence suggests that there is a 7- to 12-year progression from normal mucosa to adenoma to cancer (Fig. 4). Adenomatous polyps are thought to arise from a breakdown in the regulation of the normal processes of cell proliferation and cell death. The initial lesion appears to arise in a single colonic crypt in which the proliferative compartment, normally confined to the base of the crypt, is expanded throughout the entire crypt. These "unicryptal" adenomas (or "aberrant crypt foci") are thought to progress to microadenomas, larger polyps and eventually cancer although for a given stage, the fraction of lesions that progress to the next stage is small (Fig. 5). A cascade of genetic changes is associated with these morphologic changes, lending support to the adenoma-cancer hy-

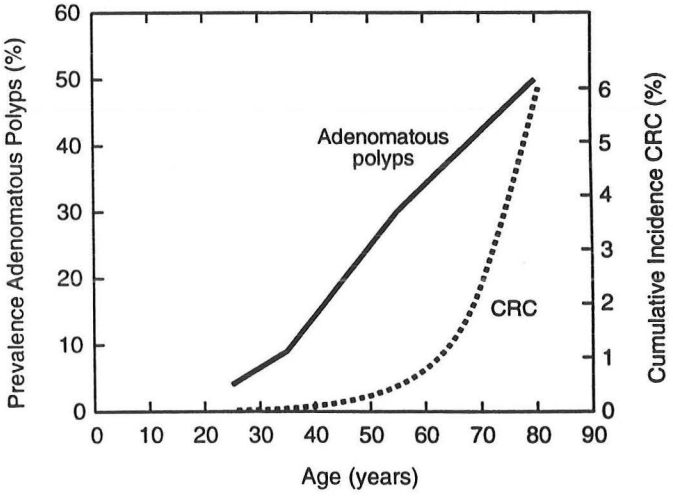


Fig. 4. Prevalence of adenomatous polyps and cumulative incidence of CRC in the general population as a function of age.

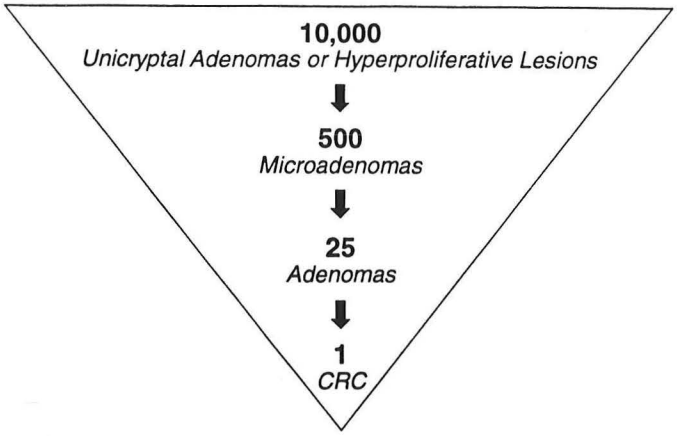


Fig. 5. Frequency of precursor lesions that give rise to one adenocarcinoma.

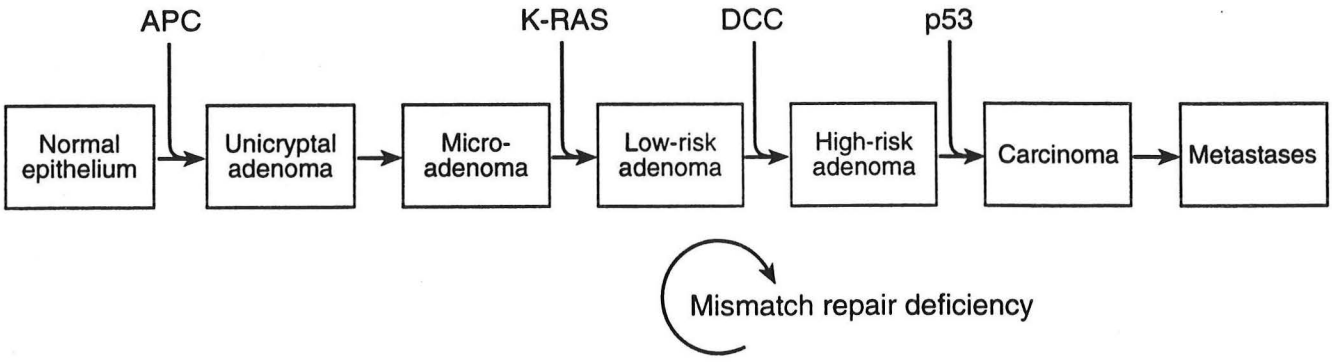
pothesis (Fig. 6)(8-11). Each successive mutation or chromosomal loss results in a clone of cells that divides and grows faster than surrounding epithelial cells until cancer cells capable of invasion and metastases are produced. In most CRC, acquired mutations occur in individual epithelial cells in response to environmental factors or events that somehow alter DNA in the cell's chromosomes. In cases of familial cancer, an inherited, germ-line mutation affecting every cell in the body serves as the first genetic event. In both sporadic and familial colorectal cancer the progressive accumulation of at least 6-8 discrete genetic injury events are required over time to ultimately produce cancer (9).

While it is generally accepted that most cancers of the colon and rectum develop from adenomatous polyps, direct evidence of this is sparse. There are no studies reporting the progression of small adenomas to large adenomas to local cancer to invasive cancer. However, at the population level, the prevalence of adenomatous polyps and colon cancer increases with age with the development of adenomas preceding that of carcinoma by ~10 years (Fig. 4)(3, 12). Around the world, the prevalence of adenomatous polyps parallels that of colon cancer and the prevalence of both adenomas and cancer increases in migrants from low- to high-risk cancer regions. At the histological level, colorectal cancer frequently contains remnant adenoma tissue; conversely, small foci of carcinoma are commonly found in large adenomatous polyps. The strongest evidence in support of the hypothesis that most cancers arise from adenomas comes from the National Polyp Study, where it was demonstrated that colonoscopic removal of adenomas results in a lower incidence of subsequent CRC (13).

Risk assessment

For the purposes of screening, individuals are usually described as being at average risk, moderate (or intermediate) risk, or high risk for developing CRC (3, 4). Average risk is defined by exclusion as anyone who is not otherwise defined as being at increased risk. For the vast majority of patients with "sporadic" CRC, few if any risk factors have been identified. Age is a major risk factor with 90% of CRC diagnosed after age 60. About 65 million Americans are at average risk for CRC simply because they are over the age of 50. 75-80% of all CRC occurs among people at "average" risk (Fig. 7). There are no factors yet identified that would place a

Fig. 6. Genetic changes associated with colorectal carcinogenesis. Mutations in genes involved in mismatch repair accelerate the progression from adenoma to carcinoma. APC, adenomatous polyposis coli gene; DCC, deleted in colorectal cancer gene. From Kinzler and Vogelstein (9).



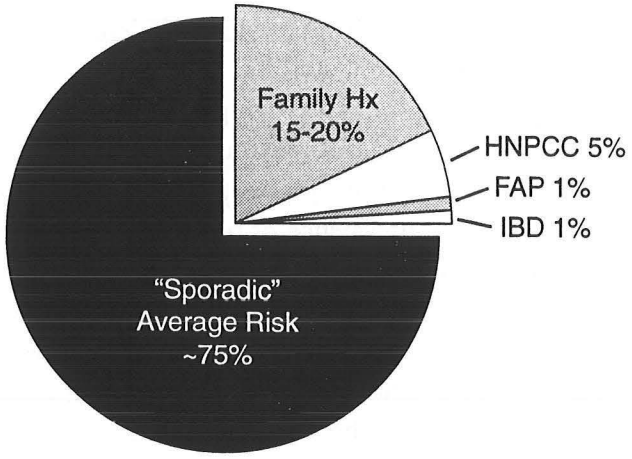


Fig. 7. Main factors associated with annual new cases of CRC. HNPCC, hereditary nonpolyposis colorectal cancer; FAP, familial adenomatous polyposis; IBD, inflammatory bowel disease.

person at lower than "average" risk for an initial approach to screening.

About 15-20% of CRCs occur among people at moderate risk because of a personal or family history of CRC or adenomas. In general, the closer the familial relationship, the younger the age of onset, and the larger the number of affected family members, the greater the risk (14-16). There is also an increased risk for CRC in persons who have a first-degree relative with adenomatous polyps, especially if they were diagnosed before the age of 60 (17, 18).

Approximately 5% of all CRCs occur among people at high risk. Most of these have one of two genetic syndromes or inflammatory bowel disease.

Screening tests and results of screening studies

Fecal occult blood test (FOBT)

Most colorectal cancers and some polyps bleed; however, bleeding is intermittent, not evenly distributed throughout the stool and often not noticed by the patient. The amount of bleeding increases with the size of the polyp and the stage of the cancer. FOBT detects ~10-15% of polyps >1cm and 25-50% of CRCs (19); improved detection rates can be expected with repeated testing over several years (20).

Guaiac-based cards for FOBT have been most widely used and studied and are currently recommended (21, 22). Stool Guaiac cards test for peroxidase activity using a colorless indicator, guaiac gum, that is oxidized to pigmented quinone in the presence of peroxidase and hydrogen peroxide. Hemoglobin has pseudoperoxidase activity, therefore bleeding from the GI tract will give a positive reaction. Sensitivity of guaiac-based tests are closely related to the amount of blood in the stool. Stool hemoglobin concentrations less than 2 mg/g of stool usually result in a negative test. Blood loss from the *colon* must exceed 1-2 mL per day to produce a consistently positive result on FOBT (Table II). Additional factors may influence the sensitivity and specificity of the test, including rare red meats, turnips, horseradish (false positive), vitamin C (false negative), and salicylates (false positive). There has been considerable debate as to the effect of oral iron on stool guaiac tests. Although oral iron probably does not cause false positive reactions or induce GI bleeding, the black pigment in stools of patients on iron supplements could be misinterpreted as positive. The length of storage may affect test sensitivity with false negatives after ~7 days. Rehydration improves sensitivity at the cost of increased false positives and is not recommended (3, 4, 21).

Immunochemical methods have a number of advantages over guaiac-based tests for CRC screening as shown in Table I and II. Immunochemical methods recognize antigenic sites on the globin portion and are least affected by diet or proximal gut bleeding (21). However, the antigen may be destroyed

Table I. Characteristics of guaiac and immunochemical tests for fecal occult blood.

	Guaiac test	Immunochemical test
Currently available	Hemoccult II HemoccultSENSA	HemeSelect HemoQuant
Biochemical basis	Peroxidase activity	Immunoreactive
Compounds detected	Hemoglobin (all) Myoglobin (all) All hemes Nonheme peroxidases	Hemoglobin (human) Globin (human)
Test affected by meds	Yes	No
Test affected by diet	Yes	No

Table II. Sensitivities of guaiac and immunochemical fecal occult blood tests according to site and amount of blood lost.

	Blood loss (mL per day)	
	Colonic	Gastric
Guaiac (hemoglobin, heme)	>1	10-20
Immunochemical (hemoglobin)	>0.25	>100

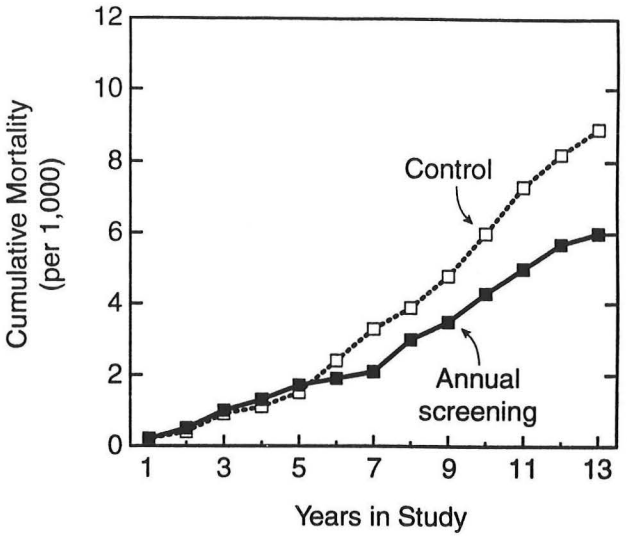


Fig. 8. Effect of annual FOBT screening on CRC mortality (23).

by fecal flora during colorectal transit or fecal storage. Immunochemical tests are not widely used at the present time because of higher cost and the need to process samples in a laboratory. Office-based immunochemical tests have been developed and may replace guaiac-based cards in the future.

Three randomized controlled trials of FOBT have been completed (23-25), all of which showed a significant reduction in death from CRC in patients screened with FOBT, followed by colonoscopy in the guaiac positive individuals. The results of these 3 trials (one American and two European) are summarized in Table III. The Minnesota trial included two screening regimens—annual and biennial—whereas the European trials evaluated only biennial screening. In the Minnesota trial through 13 years of follow-up there was a 33% reduction in CRC mortality in the annual screening group (Fig. 8) and a nonsignificant 6% decrease in CRC mortality in the biennial group (23). After 18 years of follow-up, CRC mortality was reduced by 36% and 21% in the annual and biennial groups, respectively (20, 26). These data are consistent with the European studies, which also showed significant reductions (15% and 21%) in CRC mortality with biennial screening. Reductions in CRC mortality were the result of a shift toward earlier stage cancers in the screened groups. For

Table III. Summary of the three major randomized controlled trials of fecal occult blood testing (23-25).

	Minnesota USA	Nottingham England	Funen Denmark
Number of study participants	46,551	150,850	61,933
Age group	50-80	50-74	45-75
Screening test	Hemoccult	Hemoccult	Hemoccult II
Diagnostic test	Colonoscopy	Colonoscopy	Colonoscopy
Slides rehydrated	Yes	No	No
Diet restrictions	Yes	Yes	Yes
Frequency of screening	Annual, biennial	Biennial	Biennial
Number of screens	Annual (11) Biennial (6)	3-6	5
Median years of follow-up	13	8	10
Compliance with first screen	85%	53%	67%
Rescreening compliance	75%	60%	54%
Slides positive	9.8%	1.7%	1.2%
Positive predictive value for CRC	2.2%	12%	12%
Positive predictive value for adenomas	29%	35%	27%
Percent of screen group colonoscoped	31%	4%	4%
Shift toward earlier stage cancers in screened	Yes	Yes	Yes
Decrease in CRC mortality	33% (annual)	15%	21%

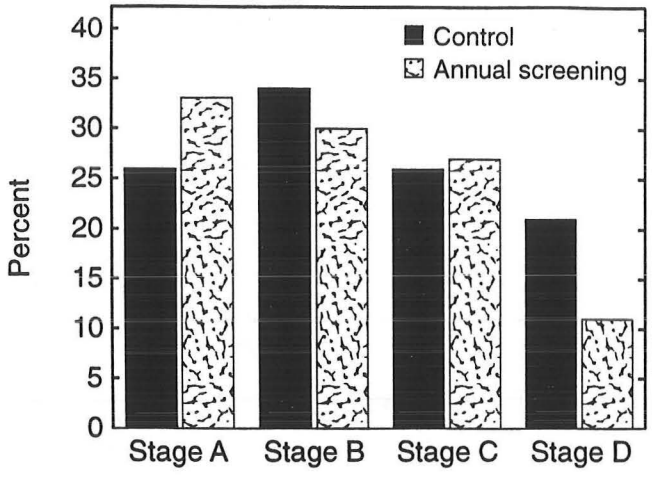


Fig. 9. Effect of annual FOBT on cumulative 13-year incidence of CRC according to Duke's stage (23).

example, in the Minnesota trial, annual screening increased the incidence of Stage A and decreased the incidence of incurable Stage D CRCs by ~50% (Fig. 9). In contrast, the overall incidence of CRC was not affected by screening reflecting the long lead time from polyp to cancer and the fact that FOBT is very insensitive to precursor adenomas (Fig. 10). CRC accounted for a relatively small proportion of total mortality during the 13 year Minnesota trial and as a consequence, total mortality was not altered by CRC screening (Fig. 11).

The Minnesota trial used rehydrated slides resulting in a positivity rate of 10% (23). Thus, 10% of screenees underwent colonoscopy with each round of FOBT testing such that during the 13-year study period about a third of the screened group was colonoscoped. The positive predictive value of a positive test was only ~2% for CRC, ie., ~50 colonoscopies needed to be performed for each CRC that was identified and 339 colonoscopies were required to prevent one death from CRC. The large number of colonoscopies performed in the Minnesota trial would be expected to decrease the incidence of CRC (ie., prevent CRC) due to the removal of precursor adenomas. While the incidence of CRC was not significantly reduced by screening at the end of the 13-year study period (Fig. 10), further follow-up to 18 years shows a 20% reduction in CRC incidence with FOBT (26). In contrast to the Minnesota trial, the European trials used nonrehydrated slides resulting in positivity rates of ~1.5% with only ~4% of the screened groups undergoing colonoscopy during the study period. The positive predictive value of a positive test for CRC in the European trials was ~12%, ie., ~8 colonoscopies needed to detect one cancer.

Of the potential screening tests available, direct evidence (from randomized controlled trials) that screening (with appropriate follow-up and treatment of positives) reduces CRC mortality exists only for FOBT. However, it is also clear that FOBT has major limitations. First, since few polyps bleed, the effect of FOBT on CRC mortality is the result of early detection of cancer after it develops—and not prevention—of CRC. Second, since cancers bleed intermittently,

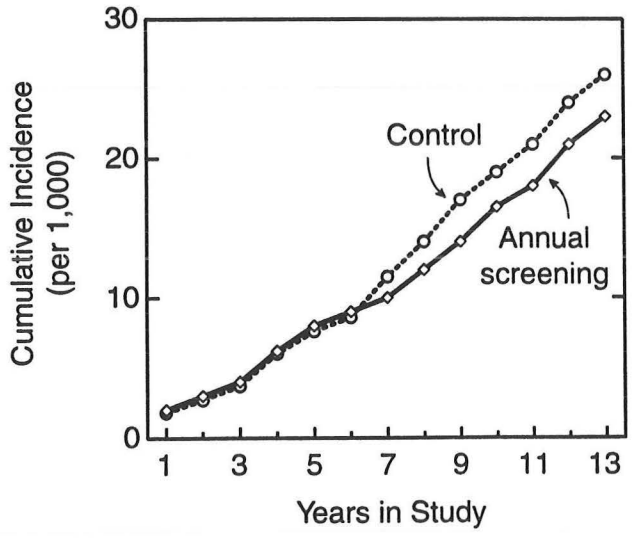


Fig. 10. Effect of annual FOBT screening on CRC incidence (23).

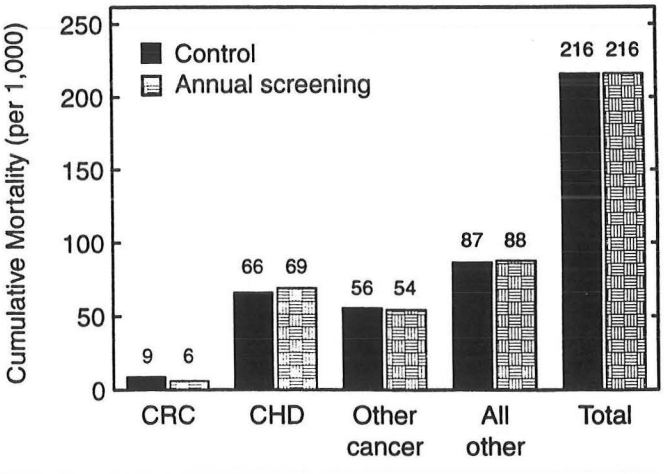


Fig. 11. 13-year cumulative mortality by cause in Minnesota FOBT trial (23). CHD, coronary heart disease.

the majority of CRC will still be missed. In the trials discussed above, only 25-50% of CRCs were detected by screening; the remainder were "interval" cancers that were diagnosed during the evaluation of symptoms between screens. The use of immunochemical tests may improve the sensitivity and specificity of FOBT for early cancer detection but it is unlikely to result in the prevention of cancer due to inability to distinguish individuals with and without high-risk adenomas.

Flexible sigmoidoscopy

The major advantages of flexible sigmoidoscopy as a screening tool are that (1) the bowel is visualized directly, and (2) lesions can be biopsied resulting in high sensitivity and specificity for polyps in the part of the bowel that is examined. Thus, in addition to detecting early cancers, sigmoidoscopy offers the potential for prevention of CRC through the detection and subsequent removal of premalignant adenomas.

The major limitation of flexible sigmoidoscopy is that only about half of adenomas are within reach of the 60 cm flexible sigmoidoscope. Another limitation is that it does require some expertise: 25-30 exams under instruction is usually adequate but even then skill varies widely among individual practitioners. The risk from the procedure is minimal. Perforation is the major complication and occurs ~1-2 per 10,000 exams (3). Antibiotics to prevent endocarditis should be considered in high risk individuals including those with prosthetic valves, previous endocarditis or surgically constructed systemic-pulmonary shunts (3).

The evidence for screening flexible sigmoidoscopy comes from 3 case-controlled studies (27-29). The strongest is a retrospective case-controlled study that compared the use of screening rigid sigmoidoscopy during the 10-year period prior to diagnosis in 261 patients who died of rectosigmoid cancer with 868 matched controls (Fig. 12). The results demonstrated a 60% reduction in cancer within reach of the sigmoidoscope (27). The protective effect lasted for at least 10 years following sigmoidoscopy (27). The other two case-controlled studies showed similar results with CRC patients less likely to have had a screening sigmoidoscopy than controls (28, 29). No randomized controlled trials evaluating the efficacy of flexible sigmoidoscopy for CRC screening have been published. American and

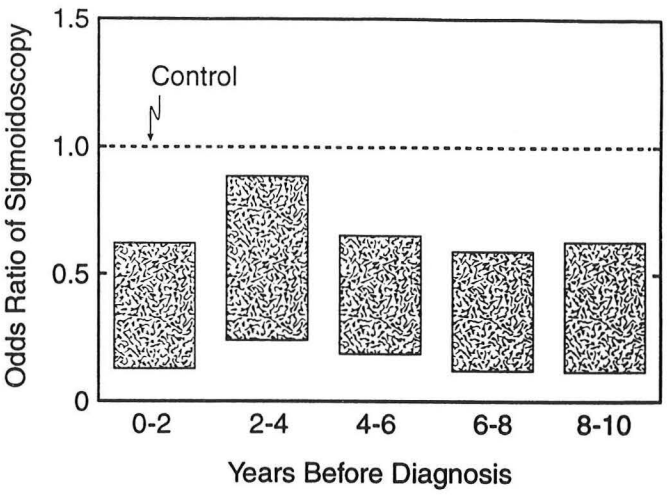


Fig. 12. Odds ratios (95% confidence intervals) of having a screening sigmoidoscopy during the 10 years prior to diagnosis of fatal cancer within reach of the sigmoidoscope (27).

English trials are underway but the results will not be available for several years.

Colonoscopy

Colonoscopy is the most sensitive and specific test available for examination of the colon and is already recommended for patients known to be at high risk for CRC, including those with hereditary adenomatous polyposis syndromes or long-standing colitis (3, 4). Colonoscopy is also recommended and paid for by Medicare for patients who have one or more first degree relatives with CRC. Although no studies in average-risk individuals have evaluated whether screening colonoscopy alone can reduce colorectal cancer incidence or mortality, the high sensitivity and specificity of colonoscopy should make it extremely effective in this setting. Several clinical studies looking at the yield of colonoscopy in average-risk individuals have been performed (30-32). Of those screened, 25-40% had adenomatous polyps that could be removed at the time of colonoscopy. The National Polyp Study showed that if patients with adenomatous polyps had removal of all visible polyps, their subsequent risk of CRC was reduced by 76-90% when compared with expected rates from three different reference populations (Fig. 13) and CRC mortality was reduced to zero (13). The reference groups in this study were not true "controls"; nevertheless, the data strongly suggest that colonoscopy

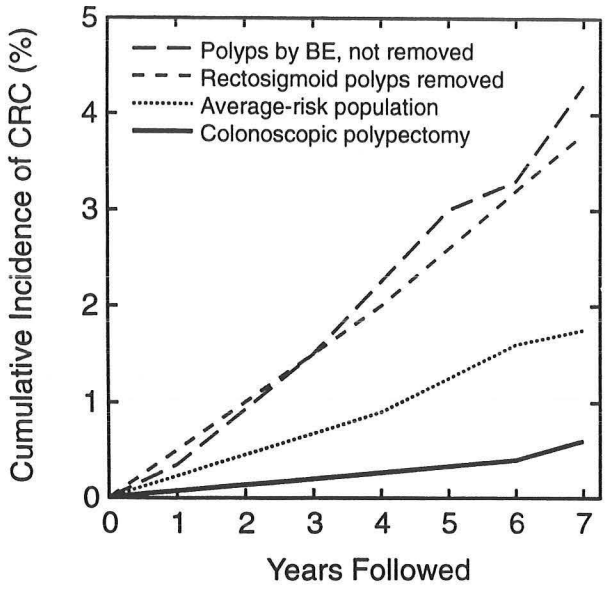


Fig. 13. Cumulative incidence of CRC in a cohort of patients with adenomas following polypectomy compared to three reference groups: (1) polyps by BE but not removed, (2) polyps found at sigmoidoscopy and removed but colon not examined, and (3) the general population (13).

would be effective as a primary screening tool. Potential complications of colonoscopy are generally quoted as perforation (~1/1,000 exams), hemorrhage (~3/1,000 exams), and death (~1/10,000 exams).

Air contrast barium enema

Barium enema has never been evaluated in a clinical screening trial. The sensitivity of ACBE for polyps was evaluated as part of the National Polyp Study. The trial was unique in that it used expert GI radiologists and both radiologists and colonoscopists were kept fully blinded. The study showed that ACBE detected only 44 % of polyps >1 cm (33), clearly a group that has a high risk of developing CRC (7). In addition, barium studies may have a high rate of equivocal or falsely positive results, which will require full colonoscopy for evaluation. Current data do not support the use of barium studies for screening although the clinical guidelines put forth by both the Agency for Health Policy Research (3) and the American Cancer Society (4) list ACBE, presumably in combination with sigmoidoscopy, as a screening option for average-risk individuals and as an option for the work-up of a positive FOBT.

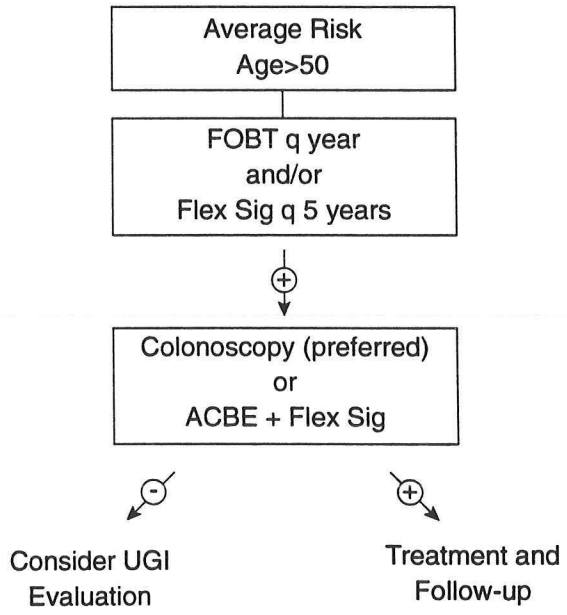
Genetic testing

At the present time, genetic testing is primarily used in the management of families with Familial Adenomatous Polyposis or Hereditary Nonpolyposis Colorectal Cancer (see below).

Screening for CRC in persons at average risk

Average risk is defined as all men and women over the age of 50 without a history of inflammatory bowel disease, a genetic syndrome associated with CRC, or a personal or family history of CRC or adenomatous polyps. Individuals with symptoms suggestive of colorectal neoplasia are not candidates for screening but should undergo diagnostic tests to evaluate these symptoms. Recommendations for screening of average-risk individuals include annual FOBT testing **and/or** flexible sigmoidoscopy every 5 years beginning at age 50 (Fig. 14) (3, 4).

Fig. 14. Algorithm for CRC screening in average-risk individuals.



Fecal occult blood testing (FOBT)

Testing of two samples from each of three consecutive stools should be carried out as described in Table IV. The recommendation for yearly testing is based

Table IV. Performance of fecal occult blood test.

- Avoid the following for 3 days before and during test:
  - Red meat
  - Peroxidase-containing foods (broccoli, cauliflower, cantaloupe, horseradish)
  - Iron supplements, vitamin C, aspirin, NSAIDs
- 2 samples of 3 consecutive stools should be tested
- Slides should be developed within 1 week

largely on the Minnesota trial that showed an effect of annual, but not biennial, FOBT on CRC mortality (23). If a FOBT is positive, the patient should undergo full colonoscopy. Double contrast BE in combination with flexible sigmoidoscopy is an alternative approach (3, 4).

Flexible sigmoidoscopy

The 5-year interval for screening flexible sigmoidoscopy is based on case-control evidence that sigmoidoscopy is protective for up to 10 years (Fig. 12)(27) and the observation that few polyps arise and progress to cancer in a 5-year period in average risk individuals. A positive screening flexible sigmoidoscopy should be followed by colonoscopy although what constitutes a positive flexible sigmoidoscopy is controversial. Certainly anyone with cancer, a polyp >1 cm or multiple polyps should be referred for full colonoscopy. What to do with adenomas <1 cm in diameter is less certain and current guidelines do not make specific recommendations on this point. If there are one or two polyps <1 cm, they should be biopsied. Hyperplastic polyps are not premalignant and require no follow-up (34). On the other hand, if histology reveals a villous or severely dysplastic tubular adenoma, the patient should be referred for colonoscopy and polypectomy. The need for colonoscopy in patients with one or two tubular adenomas <1 cm in diameter is debated. Patients with small tubular adenomas within reach of the flexible sigmoidoscope have a 25-30% chance of having more proximal adenomas, although most will not be high-risk (>1 cm, villous or severely dysplastic). One study found that patients with only a single small tubular adenoma on sigmoidoscopy had <1% occurrence of a proximal high-risk adenoma (35). Two studies suggest that the risk of subsequent colon cancer in patients with

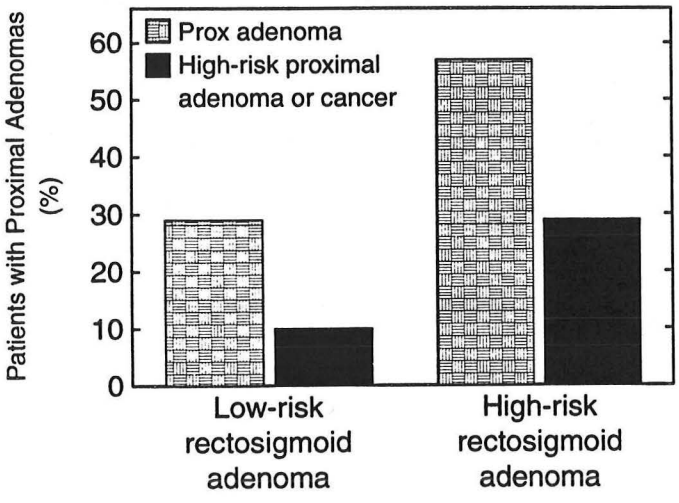


Fig. 16. Prevalence of proximal adenomas in patients with high- and low-risk adenomas at flexible sigmoidoscopy (38).

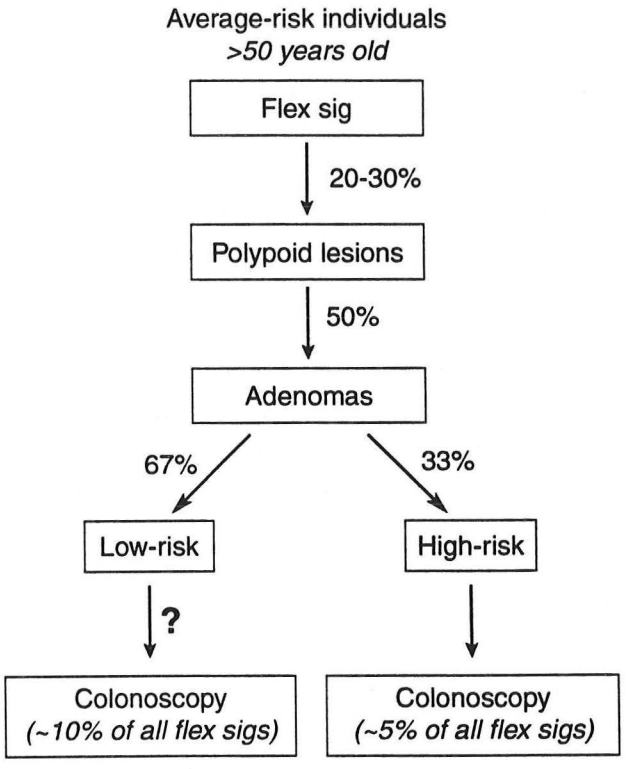


Fig. 17. Typical yield from screening flexible sigmoidoscopy program. The necessity of performing colonoscopy in patients with low-risk rectosigmoid adenomas is debated but results in a tripling of the number of colonoscopies (from ~5% to 15% of all flex sigs) and increases the number of proximal high-risk adenomas detected and removed by ~2-fold.

rectosigmoid polyps who do not undergo follow-up colonoscopy is low (6, 36); however, both studies have methodological problems. More recent studies show a 3-10% prevalence of high-risk adenomas or carcinoma in patients with rectosigmoid tubular adenomas <1 cm (37-39) and stress the importance of colonoscopic evaluation in these patients. Data from a recent paper published in the N. Engl. J. Med. are shown in Fig. 16. The overall effect of referring patients with low-risk rectosigmoid adenomas for full colonoscopy is to double the number of high-risk proximal adenomas detected at the expense of tripling the number of colonoscopies performed as illustrated in Fig. 17.

Combination FOBT and flexible sigmoidoscopy

The American Cancer Society has long recommended the combination of FOBT and sigmoidoscopy for average risk individuals. Other U.S. agencies and 5 surgical and GI Societies now recommend FOBT, flexible sigmoidoscopy or a combination of the two for this population (3). Only one controlled trial addresses the additional benefit of adding FOBT to screening sigmoidoscopy (40). After 5-11 years of follow-up, CRC mortality was lower in patients receiving FOBT plus sigmoidoscopy than in those receiving sigmoidoscopy alone. However, the study was nonrandomized and compliance with FOBT was only 20% after the first year. There are theoretical reasons for recommending the combination of FOBT and flexible sigmoidoscopy. For example, in one of the FOBT trials discussed above, two-thirds of the interval cancers that were missed by FOBT were within reach of the flexible sigmoidoscope (24).

Alternative strategies

The American Cancer Society (4) and the Agency for Health Policy Research task force (3) both list air contrast BE (presumably in combination with flexible sigmoidoscopy) at 5-10 year intervals or colonoscopy at 10 year intervals as alternative screening modalities.

One time colonoscopy in the sixth decade has considerable appeal as a CRC screening modality. As shown in Fig. 4, a minority of CRCs (<10%) occur before age 60, whereas the majority of persons who will develop adenomas will have done so by this time. The risk of CRC is probably very low in the subsequent 10-15 years after a normal colonoscopy. Patients with significant polyps could have them removed and could be entered into surveillance programs. The National Polyp Study showed that removing polyps detected at colonoscopy decreased the incidence of CRC by 76-90% relative to various historical control groups and eliminated CRC mortality (13). If colonoscopy screening is infrequent, cost-effectiveness compares favorably with other methods of screening (41). Obstacles to using colonoscopy as a screening test include concerns about risk, cost, and availability of resources to perform population screening as well as the fact that no randomized clinical trial has been performed in average-risk individuals to document that screening colonoscopy alone can reduce colorectal cancer incidence or mortality. Most payers including Medicare do not reimburse for screening colonoscopy in average-risk individuals.

Screening for CRC in persons at increased risk

Specific genetic syndromes

Familial adenomatous polyposis (FAP) – Familial adenomatous polyposis (FAP) is an inherited, autosomal dominant syndrome caused by germ-line mutations of the adenomatous polyposis coli (APC) gene (42, 43). FAP typically presents with CRC in early adult life (Fig. 18) secondary to extensive adenomatous polyps of the colon. Polyps also develop in the upper gastrointestinal tract and malignancies may occur in

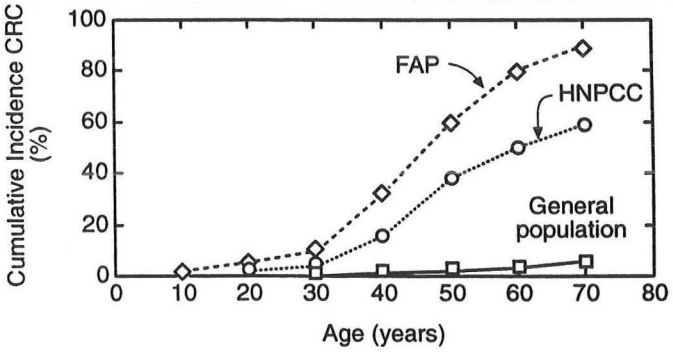


Fig. 18. Cumulative incidence of CRC in patients with familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer compared to that in the general population.

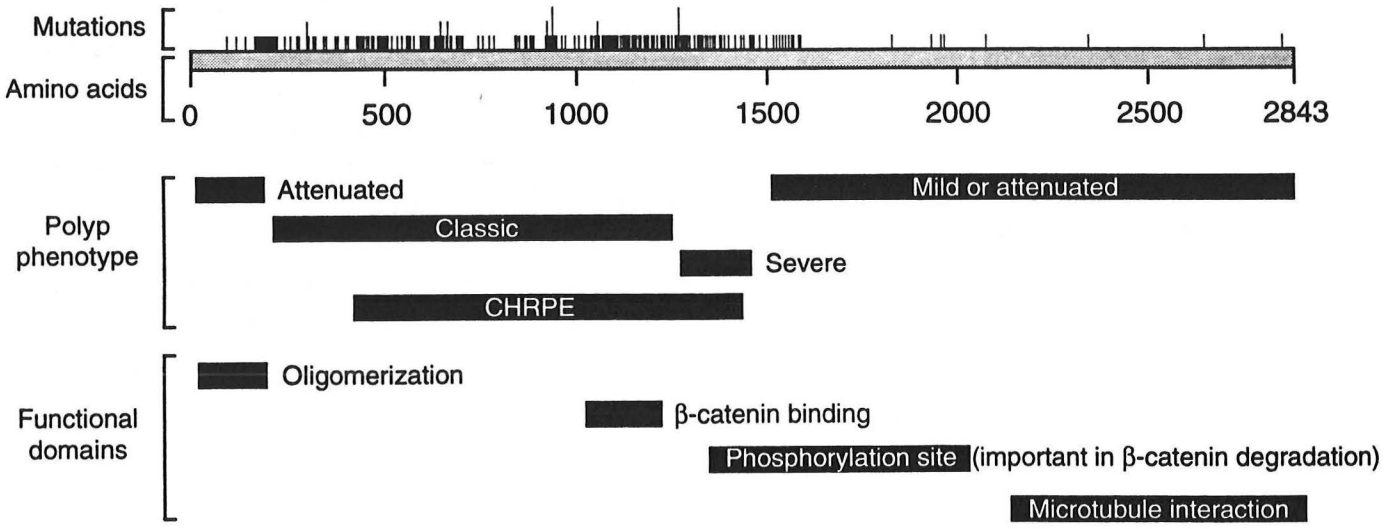
other sites including brain, hepatobiliary tract, adrenal glands and bladder. Other extracolonic manifestations in FAP include desmoid tumors (44, 45) and congenital hypertrophic retinal pigment-epithelial lesions (CHRPE) (46, 47). In the past, patients with extracolonic features were treated as a distinct phenotype labeled Gardner syndrome. However, detailed evaluation has shown that most patients with FAP have one or more extracolonic manifestations and Gardner syndrome is now known to be a phenotypic variant of FAP, caused by mutations of the APC gene (43, 48). Gardner syndrome and FAP may occur in sibships and may be associated with identical pathological mutations in the APC gene (49). Clinical diagnosis of FAP is usually based on the presence of >100 colonic adenomas. Onset of polyps usually occurs between 10-40 years of age and, if not treated, CRC develops at a mean age of ~39 years (5). Thus, a firm diagnosis of FAP can usually be made on clinical grounds even in the index case.

In 1991, the groups of Bert Vogelstein (50, 51) and Ray White (49, 52) simultaneously and independently announced the identification and characterization of the APC gene together with identification of mutations in the gene. APC is a large (>300 kD) multifunctional protein with distinct sequence motifs that specify interactions with diverse protein partners (Fig. 19)(9). The central third of APC harbors a series of β-catenin-binding sites. Using these sites, APC regulates the intracellular turnover of β-catenin, a protein involved in cellular adhesion, communication, and cell signaling pathways linked to apoptosis and cell growth. In addition, the expression of c-MYC oncogene is repressed by wildtype APC and activated by β-catenin (53). Thus APC mutations lead to overexpression of c-MYC—an oncogene long associated with various sorts of cancers—which results in neoplastic growth. This is the first example of the loss of a tumor-suppressor gene leading to activation of a cancer-promoting oncogene, a scenario thought to be prevalent in the initiation of many cancers but never previously documented.

The majority of germ-line APC mutations cause truncated products and predominantly occur in the first half of the gene (54). Some phenotypic variants of FAP have been specifically associated with distinct mutation patterns in the APC gene (9, 43). The occurrence of CHRPE is correlated with mutations in the region spanning exons 9-15 (55), and desmoid tumors are associated with mutations in the region spanning codons 1444-1578 (45).

A less severe form of FAP, attenuated FAP, has been recognized in which patients have fewer polyps (usually <100) and a somewhat older age of CRC (55 vs 39) in affected family member (56-58). The polyps tend to be proximal to the splenic flexure. These patients also have mutations of APC and they tend to be located at the extreme 5′ and 3′ ends of the transcript. In contrast, a profuse phenotype (>5000 polyps) is as-

Fig. 19. Pathogenic and functional characteristics of APC gene (9).

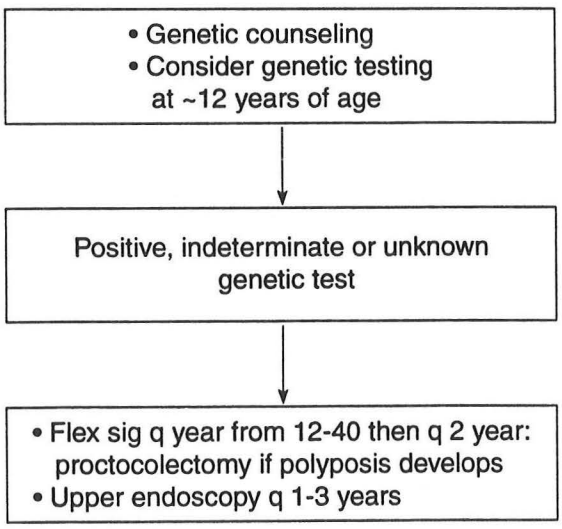


sociated with APC mutations spanning codons 1250-1464 (59, 60). The correlation between genotype and phenotype is not perfect in that identical mutations may produce different physical manifestations in different patients. This is likely the result of environmental modifiers or other genes that interact with the APC gene to affect phenotype.

Turcot's syndrome is characterized by the concurrence of a primary brain tumor and multiple colorectal adenomas. This association can result from at least 2 distinct types of germline defects: mutation in the APC gene, which is responsible for FAP, or mutations in mismatch repair genes (61). APC mutations were associated with meduloblastomas, whereas glioblastoma was the brain tumor in most cases with mismatch repair gene mutations.

Recommendations for CRC surveillance in persons with a family history of FAP are outlined in Fig. 20. All at-risk individuals should undergo genetic counseling and consider genetic testing. Commercially available genotyping for FAP became available in 1994 with the development of the in vitro-synthesized protein assay or protein truncation assay (62). This test takes advantage of the finding that most APC gene mutations result in stop codons leading to truncation of the APC gene product (Fig. 21). In the protein truncation assay, DNA from the tested person's blood is amplified

Fig. 20. Recommendations for CRC screening in persons with a family history of familial adenomatous polyposis.



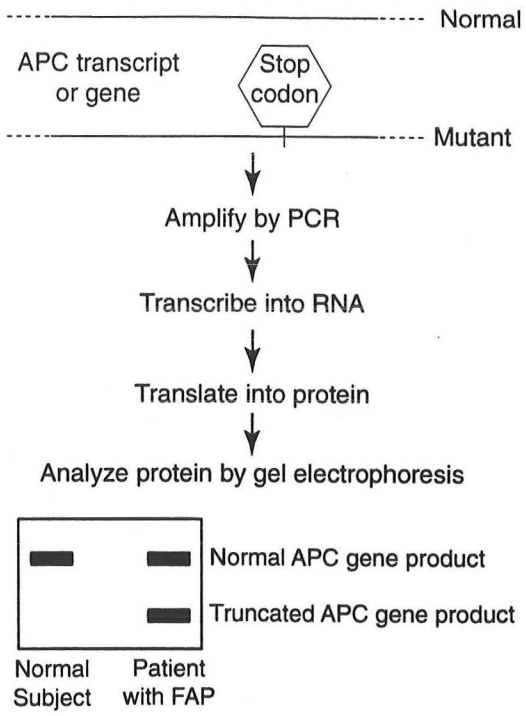


Fig. 21. The in vitro-synthesized protein or protein truncation assay for detecting mutations in the APC gene.

and transcribed into RNA, the RNA is translated into protein, and then the protein is analyzed by gel electrophoresis. A normal person's 2 normal alleles produce 1 band. Patients with FAP, however, produce 2 bands; a full-length protein from the normal allele and a truncated protein from the mutated allele. The test identifies an APC gene mutation in ~80% of FAP-affected pedigrees (62). Genetic testing should be performed first on the proband or an affected family member. If the in vitro-synthesized protein assay does not reveal a truncated gene product in the proband, the test is not informative and there is no point in testing other family members using this assay. On the other hand, if a germline APC gene mutation is documented in a pedigree, genotyping of at-risk relatives has virtually 100% positive predictive value and 100% negative predictive value. In this setting, half of at-risk family members have a negative test ruling out the diagnosis. These individuals and their children can forego the intensive endoscopic surveillance described below. There is no point in performing genetic testing on at-risk individuals before age 10-12 since cancer (and even polyps) rarely develops before puberty. Genetic testing can also be

used in combination with in vitro fertilization techniques to allow the selection and transfer of only unaffected embryos to the uterus (63). The use and interpretation of APC gene testing has been evaluated in a nationwide survey of 177 patients (64). Impressively, ~80% of patients tested had a valid indication and appropriate testing strategy. However, only 18% had pretest counseling and only 16% gave informed consent. Moreover, if not for intervention, 30% of patients would have received an incorrect test interpretation, ie., that the test was negative rather than noninformative (a negative result without a positive result in an affected family member). Commercially, LabCorp in Research Triangle Park, N.C. offers APC gene testing.

At-risk persons who have a positive or indeterminate genetic test or who do not undergo genetic testing should be offered yearly flexible sigmoidoscopy beginning at about 12 years of age. After age 40 the screening interval can be reduced to every other year. Proctocolectomy should be recommended for patients who develop polyposis (3, 5). In addition, endoscopic evaluation of the upper GI tract should be carried out q 1-3 years. If a diagnosis of attenuated FAP is made (see above) colonoscopy rather than flexible sigmoidoscopy should be advised for surveillance because of the right-sided distribution of polyps in these families (56-58).

Hereditary nonpolyposis colorectal cancer (HNPCC) – HNPCC (previously known as Lynch syndrome or cancer family syndrome) is characterized by early onset of colorectal cancer (average age at diagnosis is 45 years), an increased proportion of proximal (right-sided) colon cancers (~70% proximal to splenic flexure), and an increased risk for other cancers, mainly endometrial but also ovarian, gastric, urinary tract, small bowel and bile duct (65). Variants include Turcot's syndrome (HNPCC or FAP plus brain tumor as discussed above) and Muir-Torre syndrome (HNPCC plus sebaceous adenomas, sebaceous carcinomas and keratoacanthomas). HNPCC is inherited in an autosomal dominant fashion.

Table V. Amsterdam criteria for diagnosing hereditary nonpolyposis colorectal cancer (66).

- 3 or more family members with colorectal cancer, one a first-degree relative of the others
- 2 or more generations affected
- 1 or more patients <50 years of age at time of diagnosis

HNPCC is the most common hereditary colon cancer syndrome and is thought to account for up to 5% of all CRC. Efforts to document the frequency of HNPCC have been handicapped by the fact that until recently the diagnosis rested on descriptive criteria. In an effort to standardize reporting of putative families, an international panel meeting in Amsterdam put forth a list of criteria that must be satisfied for a diagnosis of HNPCC (Table V)(66). The Amsterdam criteria require: (1) at least 3 relatives with histologically verified colorectal cancer with one being a first-degree relative of the others, (2) at least 2 successive generations affected (3) at least one relative with colorectal cancer diagnosed before age 50, and (4) FAP excluded. The Amsterdam criteria are fairly restrictive. Small families are not likely to meet criteria for diagnosis and extracolonic malignancies, which clearly are an important component of the syndrome, are not given any diagnostic weight.

The molecular basis of HNPCC involves genetic instability resulting from defective mismatch repair (MMR). DNA replication fidelity is enhanced by a system that identifies, excises, and corrects mismatched sequences. Mismatches arise during DNA replication either by incorrect base pairings or by slippage of DNA polymerase on the template strand (9, 67). To date, 6 human genes that appear to participate in the MMR process have been identified (MLH1, MSH2, MSH3, MSH6, PMS1 and PMS2). The working hypothesis is that mismatch repair genes function like tumor suppressor genes so that heterozygous cells have normal or nearly normal repair activity but loss or mutation of the wild-type allele in persons who inherit a mutation of the other allele resulting in cells with defective mismatch repair. Germ line mutations in five of these genes (MLH1, MSH2, MSH6, PMS1 and PMS2) have been identified in HNPCC kindreds. To date more than 120 germline mutations have been identified in these genes with the vast majority in MLH1 and MSH2 (68). Although the mutator defect that arises from the MMR deficiency can affect any DNA sequence, microsatellite sequences are particularly sensitive to MMR abnormali-

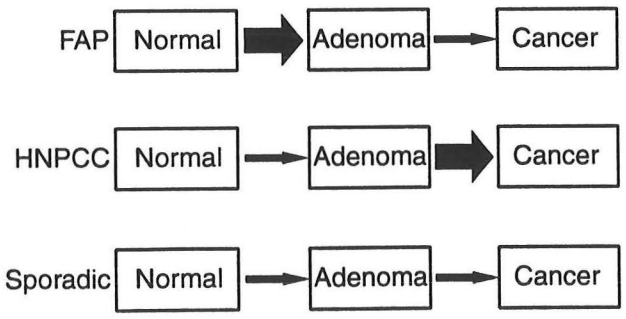
ties. Microsatellites are repeating sequences that are distributed throughout the human genome. Their function is unknown, but they are useful in genetic linkage studies because of their high degree of polymorphism. It was found that virtually all CRCs in HNPCC families had microsatellite instability, ie., the length of the microsatellites varied between tumor DNA and nontumor DNA from the same patient. Microsatellite instability is therefore a useful indicator of defective MMR. In addition to its occurrence in virtually all tumors from HNPCC patients, microsatellite instability occurs in a small fraction (10-15%) of sporadic CRCs (69).

Mismatch repair-deficient cells accumulate mutations at a rapid rate. Although mutations seem to occur in the same oncogenes and tumor suppressor genes (APC, K-ras, p53 etc) as sporadic CRC, certain mutations are characteristic of tumors with microsatellite instability. For example, 90% of CRCs with microsatellite instability have frameshift mutations of the TGF-β type II receptor gene (70). TGF-β inhibits the growth of colon epithelial cells. If the receptor is inactivated, growth inhibition cannot be accomplished. This receptor may be preferentially mutated in patients with defective mismatch repair because the gene contains a stretch of 10 consecutive A bases and such long-repeat sequences are particularly prone to mismatch errors. Similarly, >50% of CRCs with microsatellite instability contain frameshift mutations in the BAX gene as a result of insertion or deletion of a single nucleotide in a poly G tract (71). Inactivation of BAX, which is involved in apoptosis, could provide a growth advantage.

Patients with HNPCC form adenomas at about the same rate as the general population, although adenomas may appear at a younger age. There is also good evidence that adenomas are the precursor lesion for CRC in HNPCC, just as they are in the general population. However, whereas the rate of progression from polyp to carcinoma in the general population is usually slow, with an estimated course of 10-15 years, adenomas in HNPCC progress to carcinoma at a more rapid rate. Loss of DNA mismatch repair in HNPCC has little or no effect on tumor initiation, but progression is accelerated (Fig 22). The dwell time is shorter and the polyp to cancer ratio is decreased. In HNPCC it is estimated that a cancer is prevented for every ~3 polypectomies (72) whereas in the general population ~50-100 polypectomies are necessary to prevent one cancer (13). Importantly, from a clinical standpoint, the presence or absence of colonic adenomas, unless they occur at a very young age (<35 years), does not help identify affected individuals. Even in known HNPCC families, the discovery of an adenoma in a family member whose gene status is unknown does not confirm affectedness.

The finding that HNPCC is the result of germline mutations mismatch repair genes offers the potential to detect asymptomatic carriers with subsequent cancer prevention through surveillance or prophylactic colectomy. The question is: How frequent are germline mutations in mismatch repair genes and who should be tested for them? This question is further complicated by the difficulty and expense of screening for mutations in the mismatch repair genes. As noted above, over 120 mutations have been identified so far. Although most identified mutations are in 2 genes (MLH1 and MSH2), there is little clustering of mutations making it necessary to screen exon by exon (19 in MLH1 and 16 in MSH2) to make an accurate diagnosis (68). In contrast to FAP, where the vast majority of mutations result in a truncated protein, missense substitutions account for a sizable fraction of the identified mu-

Fig. 22. Relative effects of mutations in APC and DNA mismatch repair genes on carcinogenesis (11). In FAP, mutations in APC lead to the development of hundreds of adenomas. Because of their great numbers, some adenomas are virtually guaranteed to progress to cancer. In HNPCC, adenomas develop at about the same rate as in patients with sporadic adenomas, but a higher percentage of these progress to cancer. Thus, APC mutations markedly increase tumor initiation whereas mismatch repair deficiency accelerates tumor progression.



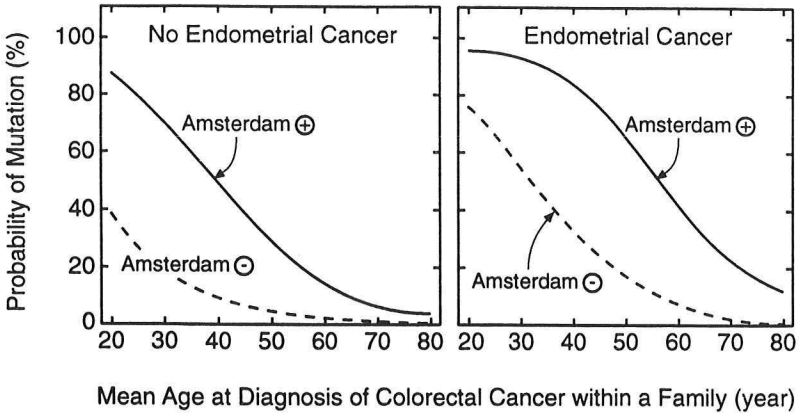


Fig. 23. Probability of mutation in mismatch repair genes as a function of mean age of diagnosis of CRC within families fulfilling Amsterdam criteria for HNPCC and in families having a dominant pattern of CRC transmission but not fulfilling Amsterdam criteria (81).

tations in HNPCC making the protein truncation assay of limited value (73, 74). In HNPCC, the majority of tumors will show microsatellite instability but this is also true of 10-15% of sporadic CRCs (69).

Genetic testing for mutations in mismatch repair genes has been carried out in a variety of groups ranging from sporadic CRC to HNPCC families meeting Amsterdam criteria. The results of these studies are summarized in Table VI (46, 69, 73, 75-82). In this country, germline MMR gene mutations are found in only about 50-70% of families meeting Amsterdam criteria for HNPCC despite the fact that CRC in most of these families show tumor microsatellite instability. This suggests that mutations in other genes involved in MMR, mutations in noncoding sequences or hypermethylation (83) may account for defective MMR in these patients. In small relatively homogeneous countries like Finland, HNPCC is caused by one of only a few MMR gene mutations, most of which have been identified (79). Germline MMR gene mutations are found in only ~2% of patients with sporadic CRC (69). The major factors that predict germline MMR gene mutations are fulfillment of Amsterdam criteria, family history of endometrial cancer and age <35 (81 and Fig. 23). It appears that extracolonic cancers may be more common in families with mutations of MSH2 than in families with mutations in MLH1 (84).

As shown in Table VI, HNPCC families fulfilling Amsterdam criteria are most likely to have an identifiable germline mutation. These patients should be offered genetic counseling and are candidates for genetic testing. The youngest affected individual would be the best candidate for initial testing. The technique that is currently used for gene testing in HNPCC is to amplify and analyze all exons of the MMR genes (starting with MSH2 and MLH1 which account for the majority of known mutations) by direct sequencing. In some strategies, exons are first analyzed by two-dimensional denaturing gradient gel electrophoresis (detects ~90% of point mutations) or in vitro-synthesized protein assay (detects ~65% of known mutations). Such an analysis is time-consuming, costly and not readily available through commercial labs. Of the 50 or so NCI-designated cancer centers, several offer genetic testing for HNPCC as part of ongoing studies or on a commercial basis. Examples include the cancer centers at University of Pennsylvania, Creighton, Memorial Sloan-Kettering, Johns Hopkins and Ohio State.

As also shown in Table VI, patients with a family history suggesting HNPCC (autosomal dominant pattern but not formally meeting Amsterdam criteria), and patients who develop CRC at a very young age may also be candidates for genetic testing based on the frequency of germline mutations in these settings. In patients who lack a family history fulfilling Amsterdam criteria it is probably useful to use tumor microsatellite instability to select out those who are most likely to benefit from genetic testing (69, 77). Maintenance of patient confidential-

Table VI. Results of testing for tumor microsatellite instability and germline mismatch repair gene mutations in patients with colorectal cancer (46, 69, 73, 75-82).

Phenotype	Tumor microsatellite instability	Germline MMR gene mutation identified
	%	
HNPCC (Amsterdam+)	80-95	30-86
Strong Fmly Hx	15-40	7-60
Age <35	~50	~25
All CRC	10-15	2

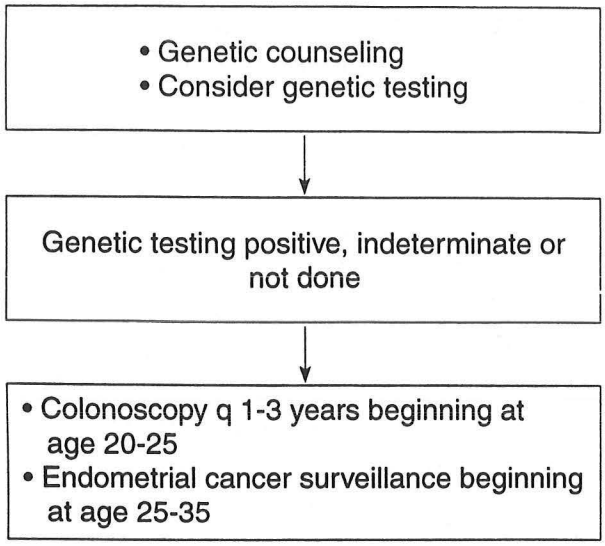


Fig. 24. Recommendations for CRC screening in at-risk members of HNPCC families or patients with an HNPCC-associated mutation (86).

ity is a key issue associated with genetic testing for cancer susceptibility genes that has yet to be fully resolved. Lynch et al have reviewed their experience with genetic testing in HNPCC families (65, 85). Genetic testing is clearly not as straightforward in HNPCC as in FAP. In contrast to FAP, HNPCC cannot be diagnosed in an individual based on colonoscopic findings. Moreover, genetic testing is not perfectly predictive of an individual's risk of developing the disease. Existing tests for HNPCC fail to detect mutations in 20% to 40% of individuals who have HNPCC fulfilling Amsterdam criteria. Being positive for the mutation doesn't absolutely mean that the individual will develop the disease as about 20% of people who carry the mutation never develop the disease or do so late in life.

Current recommendations for surveillance in at-risk members of HNPCC families or patients with HNPCC-associated mutations are summarized in Fig. 24 (86) and includes a colonoscopy every one to three years beginning at age 20-25. The risk of second (metachronous) CRC is high in patients with HNPCC: 30% at 10 years and 50% at 15 years following segmental resection of CRC. Therefore, patients who develop CRC should consider subtotal colectomy (with continued surveillance of rectal segment) or total proctocolectomy. Women from families with endometrial and/or ovarian cancer should consider bilateral oopherectomy and hysterectomy, especially if postmenopausal. Patients with polyps or known gene carriers without polyps may want to consider prophylactic colectomy as well.

While colonoscopy for detection of adenomas and cancer is believed to be beneficial (87, 88), there is no proof yet that endoscopic surveillance can reliably and indefinitely prevent cancer in these high-risk patients. A 10-year prospective study does show a significant reduction in CRC in subjects undergoing surveillance at 3-year intervals compared to those refusing colonoscopy or BE (89). Interestingly, for a given stage of CRC, survival is better in patients with HNPCC than in patients with sporadic CRC (72).

One or two first-degree relatives with CRC

Case-control studies show that people with close relatives with CRC have an increased risk of CRC and tend to develop CRC at a younger age as shown in Fig. 25 (14-16). Risk is increased ~two-fold in patients whose index family member was over the age of 55 at the time of cancer diagnosis and is increased 3- to 4-fold if the index case developed CRC before age 55 (Fig. 26)(14). Risk for CRC is also increased if a first-degree relative has adenomatous polyps, especially if they were diagnosed before age 50-60 (18, 82). Current guidelines are summarized in Fig. 27 and suggest that people who have a single first-degree relative diagnosed with CRC or adenomatous polyps after 55-60 years of age should undergo the same screening as average-risk patients but starting at the age of 40 rather than 50 (3, 4). People who have a first-degree relative

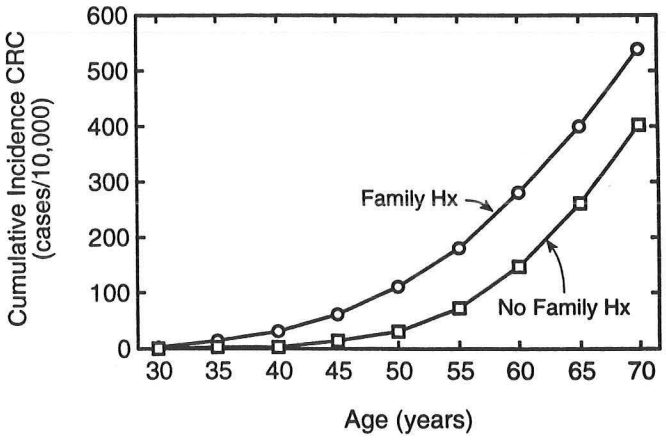


Fig. 25. Cumulative incidence of CRC according to age in the presence of absence of a family history of CRC (16).

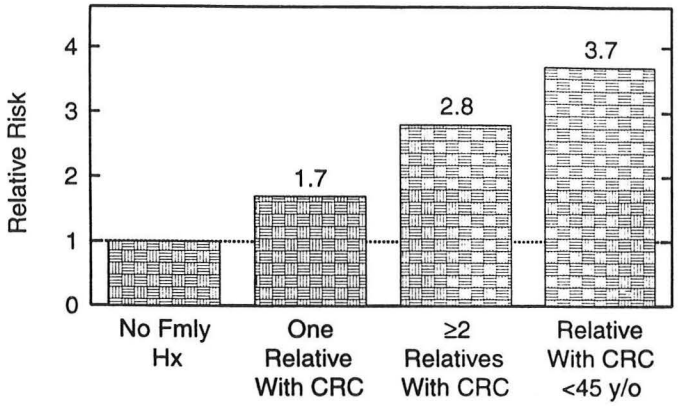


Fig. 26. Risk of CRC in presence of a positive family history of CRC in a first-degree relative (16).

who was diagnosed with CRC or adenomatous polyps before 55-60 years of age or who have 2 or more first-degree relatives with CRC or adenomas should probably undergo colonoscopy (preferred) or ACBE/flexible sigmoidoscopy q5 years beginning at age 40 or 10 years before the youngest case in the family although there are no studies that address the effectiveness of this approach.

Personal history of CRC

Patients who develop CRC are at increased risk for both synchronous and metachronous neoplastic lesions, in addition to recurrent disease. In patients with CRC, the reported rate of synchronous cancers is 2-5% and of adenomas is 25-40%. Similarly, after a curative resection, subsequent development of metachronous colorectal cancer has been reported to occur in 3-8% and adenomas in 25-40% of patients. The primary goal of postsurgical surveillance is to clear the colon of missed synchronous and subsequent metachronous adenomas. There is no evidence that the polyp to cancer progression is more rapid in patients with a history of colon cancer. Current recommendations for surveillance after curative-intent segmental resection of CRC are for a full colonoscopy pre- or post-operatively to clear colon of synchronous lesions followed by colonoscopy in 3 years, and if normal every 5 years thereafter (3, 4).

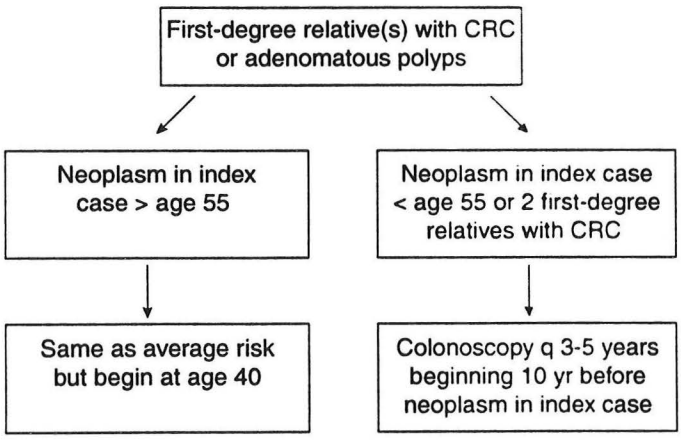


Fig. 27. Recommendations for CRC screening in patients with 1 or 2 first-degree relatives with CRC or adenomatous polyps.

Prior history of adenomatous polyps

Much debate and some controversy exist regarding the follow-up surveillance of patients who have had adenomatous polyps removed. The National Polyp Study showed that colonoscopic polypectomy greatly reduces the expected incidence of CRC (13) and that follow-up colonoscopy can be deferred for at least 3 years (90). Moreover, if the first surveillance colonoscopy was negative, subsequent examinations were highly unlikely to reveal further adenomatous polyps (90). Another more recent study in patients with adenomatous polyps showed that following colonoscopic polypectomy, the yield for clinically important adenomas at a 4-year follow-up colonoscopy was very low (91). It is likely that follow-up colonoscopy could be deferred for 5 to 10 years or even longer with minimal loss of the protective effect but this has not been proved. Obviously, the frequency of colonoscopic follow-up of patients found to have adenomatous polyps will strongly influence the overall cost of the screening program.

Current recommendations suggest that patients in whom high-risk (>1 cm, villous or severely dysplastic) or multiple (usually defined as 3 or more) adenomatous polyps are found and removed at colonoscopy should have follow-up colonoscopy in 3 years and if normal, or only a single small tubular adenoma is found, follow-up colonoscopy in 5 years. In some cases (polyp with invasive cancer, large sessile polyp, many adenomas) a shorter interval may be necessary.

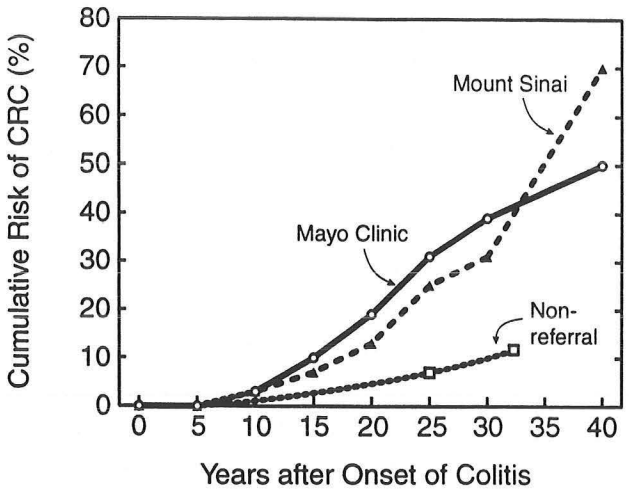


Fig. 28. Cumulative incidence of CRC in patients with ulcerative colitis.

Inflammatory Bowel

Although <1% of all CRC cases occur in patients with idiopathic inflammatory bowel disease (ulcerative colitis, Crohn's disease), the increased relative risk and excess mortality from CRC in this population appears to justify surveillance for CRC. The cumulative incidence of CRC in patients with inflammatory bowel disease is increased in proportion to the duration and anatomic extent of the disease. The risk is low in the first decade; thereafter the cumulative incidence increases at a rate of about 0.05% per year (Fig. 28). Patients with pancolitis or inflammation extending proximal to the splenic flexure are at greatest risk. The risk of CRC is higher in patients seen at tertiary referral centers than in patients seen in the primary care setting (who presumably have less extensive disease). Although the increased risk of CRC in chronic ulcerative colitis has long been recognized, it is now believed that for a similar duration and extent of colonic disease, the increased risk for CRC is similar in Crohn's colitis and ulcerative colitis. CRC associated with inflammatory bowel disease manifests the same spectrum of somatic gene mutations as sporadic cancer and similar genetic factors appear to affect the development of CRC in both settings (92). Thus, a family history of sporadic CRC increases the risk of CRC in patients with inflammatory bowel disease. Similarly, CRC in a patient with inflammatory bowel disease increases the risk of sporadic CRC in noncolitic relatives.

As in precancerous adenomas, dysplasia is a precursor to carcinoma in inflammatory bowel disease (93). Dysplasia is classified by grade as mild (low-grade) or severe (high-grade). Retrospective analyses report that 90% of colons from patients with ulcerative colitis and cancer contain dysplastic mucosa. About 40% of patients with severe rectal or colonic dysplasia have or will shortly develop carcinoma. The aim is to identify patients at high risk by detecting high-grade dysplasia and then to prevent mortality by recommending colectomy. Unfortunately, low-grade dysplasia is also predictive of cancer with 19% of those patients having or developing cancer. Moreover, dysplasia can be patchy and difficult to define and grade, especially in the setting of inflammation.

Although there are no prospective randomized trials to support surveillance for CRC in patients with inflammatory bowel disease, two retrospective studies suggest reduced mortality in patients participating in a routine surveillance program (94, 95). Current guidelines suggest that surveillance colonoscopy begin after ~8 years of pancolitis or 15 years of disease limited to the left colon and that colonoscopy be repeated at 1-2 year intervals (3, 4). Biopsies are typically taken in all 4 quadrants of the colon at 10 cm intervals.

Hamartomatous polyposis syndromes

Peutz-Jeghers syndrome is a dominantly inherited disorder characterized by melanin pigmented macules on the lips and mucous membranes, multiple gastrointestinal polyps and an increased risk of benign and malignant neoplasms of the GI tract and other organs. Patients typically develop symptoms in the second or third decade when the polyps become large enough to bleed or cause intussusception or obstruction. The gene responsible for Peutz-Jeghers syndrome was recently identified and encodes a novel serine threonine kinase (LKB1) that apparently functions as a tumor suppressor gene (96). The relative risk of a Peutz-Jeghers patient developing a malignancy is 18 times greater than expected in the general population (97).

Juvenile polyposis coli is also dominantly inherited and is characterized by the development, throughout the GI tract, of hamartomatous polyps (histologically different from Peutz-Jeghers polyps). Patients usually

present in the first decade of life with bleeding, diarrhea or protein-losing enteropathy. The risk of developing a GI malignancy (especially colon cancer) is increased, ranging from 10-50% depending on the family (98, 99). Juvenile polyposis coli is due to germline mutations in genes encoding SMAD4 (a cytoplasmic signal transduction molecule in the TGF-β pathway that mediates growth inhibitory effects)(99) or PTEN (a dual-specificity phosphatase that likely affects a host of processes)(100). Patients with a diagnosis of Peutz-Jehgers syndrome or juvenile polyposis should undergo upper and lower endoscopy every 3-5 years to remove large, dysplastic or bleeding polyps.

Current Medicare policy

In 1997 Health and Human Services approved CRC screening for Medicare patients and coverage was expanded in 1998. Medicare now covers FOBT q12 months and screening flexible sigmoidoscopy q 48 months for those over 50. Screening colonoscopy is covered at a frequency of q 24 months for those at high risk for CRC. High risk is defined as first-degree relative with CRC, personal history CRC, family history of FAP or HNPCC, or inflammatory bowel disease involving the colon.

Cost effectiveness

Several cost-effectiveness analyses, including one recently prepared by the Office of Technology Assessment of the U.S. Congress, have concluded that any of the screening options for average-risk persons can cost less than $20,000 per year of quality life saved, a figure comparable or better than that for other commonly accepted preventive screening modalities such as breast or cervical cancer screening (41, 101, 102). The cost of not screening for CRC is substantial. In rough figures, the cost of treatment for CRC is ~2.5 billion per year. The cost of screening including surveillance colonoscopy for those found to have adenomas would be about the same if compliance was 100%. Early detection of CRC, as is the goal of FOBT, has relatively little effect on the costs of treating CRC. However, the detection and removal of premalignant adenomas offers the potential to markedly reduce the incidence, and thus the cost, of caring for CRC (23). For this reason, modeling studies show that one time colonoscopy with polypectomy is both the most effective strategy for reducing CRC mortality and comparable in cost to other CRC screening strategies (41).

Primary prevention of CRC

Several lines of evidence suggest that environmental factors are important in the pathogenesis of CRC (12). There is marked geographic variation in CRC rate with >10-fold difference between countries with the highest and those with the lowest rates. All high-risk countries consume a diet high in total fat and in animal fat and protein and low in fruits, vegetables, and fiber. Moreover, numerous migration studies have shown that emigrants from low-risk countries to high-risk countries assume the higher risk of their new country within a generation as they "Westernize" their diets. Other lifestyle factors that are related to a higher risk of CRC are excess caloric intake/inactivity/obesity, excess alcohol and smoking. The National Cancer Institute makes the following recommendations (103). Americans should eat a diet that is low in total fat, and high in fruits, vegetables and fiber. Specifically, fat should not exceed 25-30% of total calories. The diet should contain substantial amounts and varieties of fruits and vegetables—cruciferous vegetables (cabbage, broccoli, cauliflower, and Brussels sprouts) may be especially beneficial. Total fiber intake should equal 20-30 grams a day (104). Total caloric intake should not exceed energy requirements, so that normal body weight consistently is maintained. People should avoid smoking and excessive alcohol ingestion. The effect of this type of diet on a variety of endpoints including colon cancer is being tested in a large NIH-sponsored trial, The Women's Health Initiative.

Cancer chemoprevention is defined as the use of specific compounds to prevent, inhibit or reverse carcinogenesis. A number of compounds have been shown to have chemopreventive activity in animal models of CRC including calcium, aspirin and NSAIDs, and several vitamins (vitamin C, vitamin E, folate and β-carotene). Epidemiological and case-control data suggest

that these may also be protective in humans. Controlled clinical trials are ongoing to test these compounds but the data available to date are either negative or equivocal and do not support the routine use of these compounds for CRC prevention in the general population at this time (105, 106).

To date, the most promising data have come from studies of aspirin and NSAIDs. Waddell and Loughry were the first to make the connection between NSAIDs and colon cancer (107). They observed the disappearance of rectal polyps in a patient with Gardner syndrome and attributed this to treatment with sulindac, an NSAID that was given for unrelated reasons. Sulindac was subsequently shown in controlled trials to reduce the number and size of colorectal adenomas in patients with FAP, although the effect was incomplete (108, 109). Evidence for the role of COX2 in carcinogenesis was obtained when mice carrying an APC gene mutation were bred to mice with a disrupted COX2 (Ptgs2) gene. Animals homozygous for wildtype COX2 developed an average of 652 polyps at 10 weeks while heterozygotes had 224 polyps and homozygously

Table VII. Summary of current recommendations for CRC screening (3-5). See Figs. 14, 20, 24, 27 and text for more details.

Risk category	Age to begin	Screening tests	Frequency	Comment
Average Risk				
Average-risk*	50	FOBT and/or Flex Sig	Yearly q 5 yrs	Medicare pays Medicare pays
Increased Risk§				
CRC or adenomas in 1 first-degree relative >55-60 y/o	40	Same as average-risk	Same as average-risk	
CRC or adenomas in 2 first-degree relatives or 1 <55-60 y/o	40 or 10 yrs before index case	Colonoscopy	q 5 yrs	
Personal hx CRC or adenomas	At initial diagnosis	Colonoscopy	q 3-5 yrs	
IBD-pancolitis IBD-distal colitis	after 8-10 yrs after 12-15 yrs	Colonoscopy/bx Colonoscopy/bx	q 1-2 yrs q 1-2 yrs	
Family hx FAP	~12	Consider genetic test: Flex sig if genetic test pos, indeterm or not done	yearly	Proctocolectomy and endo q 1-3 yrs if polyposis
Family hx HNPCC	20-25	Consider genetic test: Colonoscopy if genetic test pos, indeterm or not done	q 1-3 yrs	Endometrial screening beginning age 25-35

*Colonoscopy q 10 yrs or ACBE/flex sig are alternatives for average-risk persons but no clinical data to support these strategies and Medicare doesn't cover.

§Medicare will cover colonoscopy every 2 years in all situations listed as "increased risk".

FOBT, fecal occult blood test; CRC, colorectal cancer; IBD, inflammatory bowel disease; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer

deficient mice had only 93 polyps, raising hopes that COX2-selective inhibitors may be effective in chemoprevention of colon cancer (110, 111).

Despite the fact that aspirin/NSAIDs are highly active chemopreventive agents in animal models, and appear to be protective against CRC in dozens of cohort and case-control clinical studies, the only published randomized clinical trial showed that aspirin did not reduce the incidence of CRC in male physicians (112). This study can be criticized because of the relatively short treatment period and relatively low dose of aspirin; however, case-controlled studies have suggested that aspirin would be protective under these conditions. At present, it is premature to recommend aspirin/NSAIDs for the primary prevention of CRC, at least in average-risk individuals.

Conclusions

Colon cancer is a prevalent disease with substantial morbidity and mortality. Randomized, controlled trials have shown with certainty that screening reduces mortality from CRC in average-risk populations and is cost-effective relative to other commonly accepted preventive interventions such as screening mammography. It is important to identify high risk families as this will change the approach to more aggressive screening beginning at an earlier age.

Adenomatous polyps are the major neoplastic finding in most screening programs and evidence demonstrates that removal of adenomas reduces the incidence of CRC. Thus, CRC appears to be uniquely suited for screening because, in contrast to most malignancies, it usually exists in an easily detectable, readily curable preclinical stage for many years.

Nevertheless, few Americans participate in routine screening programs. In the past, differences in opinion among professional groups about colorectal cancer screening have been a barrier to colorectal cancer prevention. However, a growing consensus now exists that even though we do not yet have trial data to compare precisely the various methods for screening, there is both a compelling case for screening and a reasonable set of methods that clinicians and patients can consider.

References Cited

1. *Facts and Figures. http://www3.cancer.org/cancerinfo/acs_frame.asp?frame=statmenu.html.* American Cancer Society.

2. US Preventive Task Force. 1996. Guide to Clinical and Preventive Services. Wiliams & Wilkens, Baltimore.

3. Winawer, SJ, RH Fletcher, L Miller, et al. 1997. Colorectal cancer screening:Clinical guidelines and rationale. *Gastroenterology.* **112**:594-642.

4. Byers, T, B Levin, D Rothenberger, et al. 1997. American cancer society guidelines for screening and surveillance for early detection of colorectal polyps and cancer:Update 1997. *CA Cancer J. Clin.* 47:154-160.

5. Itzkowitz, SH, and YS Kim. 1998. Colonic polyps and polyposis syndromes. *In* Gastrointestinal and Liver Disease. M Feldman, BF Scharschmidt, and MH Sleisenger, editors. Saunders. 1865-1905.

6. Atkin, WS, BC Morson, and J Cuzick. 1992. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N. Engl. J. Med.* **326**:658-662.

7. Stryker, SJ, BG Wolff, CE Culp, et al. 1987. Natural history of untreated colonic polyps. *Gastroenterology.* **93**:1009-1013.

8. Jass, JR. 1995. Colorectal adenoma progression and genetic change: Is there a link? *Ann. Med.* 27:301-306.

9. Kinzler, KW, and B Vogelstein. 1996. Lessons from hereditary colorectal cancer. *Cell.* **87**:159-170.

10. Fearon, ER. 1997. Human cancer syndromes: Clues to the origin and nature of cancer. *Science.* 278:1043-1050.

11. Kinzler, KW, and B Vogelstein. 1998. Landscaping the cancer terrain. *Science.* **280**:1036-1037.

12. Bresalier, RS, and YS Kim. 1998. Malignant neoplasms of the large intestine. *In* Gastrointestinal and Liver Disease. M Feldman, BF Scharschmidt, and MH Sleisenger, editors. Saunders. 1906-1942.

13. Winawer, SJ, AG Zauber, MN Ho, et al. 1993. Prevention of colorectal cancer by colonoscopic polypectomy. *N. Engl. J. Med.* **329**:1977-1981.

14. St. John, DJB, FT McDermott, JL Hopper, et al. 1993. Cancer risk in relatives of patients with common colorectal cancer. *Ann. Intern. Med.* **118**:785-790.

15. Kune, GA, S Kune, and LF Watson. 1989. The role of heredity in the etiology of large bowel cancer: Data from the Melbourne colorectal cancer study. *World J. Surg.* **13**:124-131.

16. Fuchs, CS, EL Giovannucci, GA Colditz, et al. 1994. A prospective study of family history and the risk of colorectal cancer. *N. Engl. J. Med.* **331**:1669-1674.

17. Winawer, SJ, AG Zauber, H Gerdes, et al. 1996. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. *N. Engl. J. Med.* **334**:82-87.

18. Ahsan, H, AI Neugut, GC Garbowski, et al. 1998. Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. *Ann. Intern. Med.* **128**:900-905.

19. Ahlquist, DA. 1997. Fecal occult blood testing for colorectal cancer:Can we afford to do this? *Gastroenterol. Clin. N. A.* **26**:41-55.

20. Mandel, JS. 1997. Colorectal cancer screening. *Cancer Metastasis Rev.* **16**:263-279.

21. Ransohoff, DF, and CA Lang. 1997. Suggested technique for fecal occult blood testing and interpretation in colorectal cancer screening. *Ann. Intern. Med.* **126**:808-810.

22. Ransohoff, DF, and CA Lang. 1997. Screening for colorectal cancer with the fecal occult blood test:A background paper. *Ann. Intern. Med.* **126**:811-822.

23. Mandel, JS, JH Bond, TR Church, et al. 1993. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N. Engl. J. Med.* **328**:1365-1371.

24. Hardcastle, JD, JO Chamberlain, MHE Robinson, et al. 1996. Randomised controlled trial of faecal-occult screening for colorectal cancer. *The Lancet.* **348**:1472-1477.

25. Kronberg, O, C Fenger, J Olsen, et al. 1996. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *The Lancet.* **348**:1467-1471.

26. Markowitz, A, and SJ Winawer. 1997. Screening and surveillance for colorectal carcinoma. *Hematol. Oncol. Clin. N. Am.* **11**:579-608.

27. Selby, JV, GD Friedman, CP Quesenberry Jr, et al. 1992. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N. Engl. J. Med.* **326**:653-657.

28. Muller, AD, and A Sonnenberg. 1995. Prevention of colorectal cancer by flexible endoscopy and polypectomy. *Ann. Intern. Med.* **123**:904-910.

29. Newcomb, PA, RG Norfleet, BE Storer, et al. 1992. Screening sigmoidoscopy and colorectal cancer mortality. *J. Natl. Cancer Inst.* **84**:1572-1575.

30. Lieberman, DA, and FW Smith. 1991. Screening for colon malignancy with colonoscopy. *Am. J. Gastroenterol.* **86**:946-951.

31. Rex, DK, GA Lehman, TM Ulbright, et al. 1993. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: Influence of age, gender, and family history. *Am. J. Gastroenterol.* **88**:825-831.

32. Foutch, PG, H Mai, K Pardy, et al. 1991. Flexible sigmoidoscopy may be ineffective for secondary prevention of colorectal cancer in asymptomatic average-risk men. *Digest. Dis. Sci.* **36**:924-928.

33. Zauber, A. Unpublished data from US National Polyp Study.

34. Rex, DK, JJ Smith, TM Ulbright, et al. 1992. Distal colonic hyperplastic polyps do not predict proximal adenomas in asymptomatic average-risk subjects. *Gastroenterology.* **102**:317-319.

35. Zarchy, TM, and D Ershoff. 1994. Do characteristics of adenomas on flexible sigmoidoscopy predict advanced lesions on baseline colonoscopy? *Gastroenterology.* **106**:1501-1504.

36. Spencer, RJ, LJ Melton III, RL Ready, et al. 1984. Treatment of small colorectal polyps: a population-based study of the risk of subsequent carcinoma. *Mayo Clin. Proc.* **59**:305-310.

37. Grossman, S, ML Milos, IS Tekawa, et al. 1989. Colonoscopic screening of persons with suspected risk factors for colon cancer: II. Past history of colorectal neoplasms. *Gastroenterology.* **96**:299-306.

38. Read, TE, JD Read, and LF Butterly. 1997. Importance of adenomas 5 mm or less in diameter that are detected by sigmoidosocopy. *New Eng. J. Med.* **1997**:8-12.

39. Schoen, RE, D Corle, L Cranston, et al. 1998. Is colonoscopy needed for the nonadvanced adenoma found on sigmoidoscopy? *Gastroenterology.* **115**:533-541.

40. Winawer, SJ, BJ Flehinger, D Schottenfeld, et al. 1993. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. *J. Natl. Cancer Inst.* **85**:1311-1318.

41. Lieberman, DA. 1995. Cost-effectiveness model for colon cancer screening. *Gastroenterology.* **109**:1781-1790.

42. O'Sullivan, MJ, T McCarthy, and CT Doyle. 1998. Familial adenomatous polyposis:From bedside to benchside. *Am. J. Clin. Path.* **109**:521-526.

43. Baba, S. 1997. Recent advances in molecular genetics of colorectal cancer. *World J. Surg.* **21**:678-687.

44. Klemmer, S, L Pascoe, and J DeCosse. 1987. Occurrence of desmoids in patients with familial adenomatous polyposis of the colon. *Am. J. Med. Genet.* **28**:385-392.

45. Lynch, HT. 1996. Desmoid tumors: Genotype-phenotype differences in familial adenomatous polyposis-a nosological dilemma. *Am. J. Hum. Genet.* **59**:1184-1185.

46. Beck, NE, IPM Tomlinson, T Homfray, et al. 1997. Genetic testing is important in families with a history suggestive of hereditary non-polyposis colorectal cancer even if the Amsterdam criteria are not fulfilled. *Br. J. Surg.* **84**:233-237.

47. Rushwurm, I, M Zehetmayer, C Dejaco, et al. 1997. Ophthalmic and genetic screening in pedigrees with familial adenomatous polyposis. *Am. J. Ophthal.* **125**:680-685.

48. Giardiello, FM, GM Petersen, S Piantadosi, et al. 1997. APC gene mutations and extraintestinal phenotype of familial adenomatous polyposis. *Gut.* **40**:521-525.

49. Nishisho, I, Y Nakamura, Y Miyoshi, et al. 1991. Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science.* **253**:665-669.

50. Groden, J, A Thliveris, W Samowitz, et al. 1991. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell.* **66**:589-600.

51. Joslyn, G, M Carlson, A Thliveris, et al. 1991. Identification of deletion mutations and three new genes at the familial polyposis locus. *Cell.* **66**:601-613.

52. Kinzler, KW, MC Nilbert, L-K Su, et al. 1991. Identification of FAP locus genes from chromosome 5q21. *Science.* **253**:661-665.

53. He, T-C, AB Sparks, C Rago, et al. 1998. Identification of c-MYC as a target of the APC pathway. *Science.* **281**:1509-1512.

54. APC gene mutation database. http://www.uwcm.ac.uk/uwcm/mg/search/119682.html.

55. Reck, AC, D Bunyan, D Eccles, et al. 1997. The presence of congenital hypertrophy of the retinal pigment epithelium in a subgroup of patients with adenomatous polyposis coli mutations. *Royal College of Ophthalmology.* **11**:298-300.

56. Spirio, L, S Olschwang, J Groden, et al. 1993. Alleles of the APC gene:An attenuated form of familial polyposis. *Cell.* **75**:951-957.

57. Giardiello, FM, JD Brensinger, MC Luce, et al. 1997. Phenotypic expression of disease in families that have mutations in the 5' region of the adenomatous polyposis coli gene. *Ann. Intern. Med.* **126**:514-519.

58. Soravia, C, T Berk, L Madlensky, et al. 1998. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. *Am. J. Hum. Genet.* **62**.

59. Gayther, S, D Wells, S SenGupta, et al. 1994. Regionally clustered APC mutations are associated with a severe phenotype and occur at a high frequency in new mutation cases of adenomatous polyposis coli. *Hum. Mol. Genet.* **3**:53-56.

60. Caspari, R, W Friedl, M Mandl, et al. 1994. Familial adenomatous polyposis: mutations at codon 1309 and early onset of colon cancer. *Lancet.* **343**:629-632.

61. Hamilton, SR, B Liu, RE Parsons, et al. 1995. The molecular basis of Turcot's syndrome. *N. Eng. J. Med.* **332**:839-947.

62. Powell, SM, GM Petersen, AJ Krush, et al. 1993. Molecular diagnosis of familial adenomatous polyposis. *N. Engl. J. Med.* **329**:1982-1987.

63. Ao, A, D Wells, AH Handyside, et al. 1998. Preimplantation genetic diagnosis of inherited cancer:Familial adenomatous polyposis coli. *Genetics.* **15**:140-144.

64. Giardiello, FM, MS Brensinger, GM Petersen, et al. 1997. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *N. Engl. J. Med.* **336**:823-827.

65. Lynch, HT, and T Smyrk. 1996. Hereditary nonpolyposis colorectal cancer (Lynch Syndrome). *Cancer.* **78**:1149-1167.

66. Vassen, HFA, J-P Mecklin, P Meerakhan, et al. 1991. The international collaborative group on hereditary nonpolyposis colorectal cancer. *Dis. Colon Rectum.* 34:424-425.

67. Chung, DC, and AK Rustgi. 1995. DNA mismatch repair and cancer. *Gastroenterology.* **109**:1685-1699.

68. HNPCC mutation database. http://www.nfdht.nl/database/mdbchoice.htm.

69. Aaltonen, LA, R Sankila, R lovaara, et al. 1998. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *New Eng. J. Med.* **338**:1481-1487.

70. Parsons, R, L Nyeroff, B Liu, et al. 1995. Microsatellite instability and mutations of the transforming growth factor β type II receptor gene in colorectal cancer. *Cancer Res.* 55:5548-5550.

71. Rampino, N, H Yamamoto, Y Ionov, et al. 1997. Somatic frameshift mutations in the BAX gene in colon cancers of the microsatellite mutator phenotype. *Science.* 275:967-969.

72. Sankila, R, LA Aaltonen, HJ Jarvinen, et al. 1996. Better survival rates in patients with MLH1-associated hereditary colorectal cancer. *Gastroenterology.* **110**:682-687.

73. Dunlop, MG, SM Farrington, AD Carothers, et al. 1997. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum. Mol. Genet.* 6:105-110.

74. Luce, MC, G Marra, DP Chauhan, et al. 1995. In vitro transcription/translation assay for the screening of hMLH1 and hMSH2 mutations in familial colon cancer. *Gastroenterology.* **109**:1368-1374.

75. Vasen, HFA, JT Wunen, FH Menko, et al. 1996. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology.* **110**:1020-1027.

76. Tomlinson, IPM, NE Beck, T Homfray, et al. 1997. Germline HNPCC gene variants have little influence on the risk for sporadic colorectal cancer. *J. Med. Genet.* 34:39-42.

77. Moslein, G, DJ Tester, NM Lindor, et al. 1996. Microsatellite instability and mutation analysis of hMSH2 and hMLH1 in patients with sporadic, familial and hereditary colorectal cancer. *Hum. Mol. Gen.* 5:1245-1252.

78. Liu, B, R Parsons, N Papadopoulos, et al. 1996. Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. *Nature Med.* 2:169-174.

79. Nystrom-Lahti, M, Y Wu, A-L Moisio, et al. 1996. DNA mismatch repair gene mutations in 55 kindreds with verified or putative hereditary non-polyposis colorectal cancer. *Hum. Mol. Genet.* 5:763-769.

80. Wijnen, J, P Meere Khan, H Vasen, et al. 1997. Hereditary nonpolyposis colorectal cancer families not complying with the Amsterdam criteria show extremely low frequency of mismatch-repair-gene mutations. *Am. J. Hum. Genet.* **61**:329-335.

81. Wijnen, JT, HFA Vasen, PM Khan, et al. 1998. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *N. Engl. J. Med.* 339:511-518.

82. Liu, T, S Wahlberg, C Rubio, et al. 1998. DGGE screening of mutations in mismatch repair genes (hMSH2 and hMLH1) in 34 Swedish families with colorectal cancer. *Clin. Genet.* 53:131-135.

83. Herman, JG, A Umar, K Polyak, et al. 1998. Incidence and functional consequences of *hMLH1* promoter hypermethylation in colorectal carcinoma. *Proc. Natl. Acad. Sci. USA.* 95:6870-6875.

84. Lin, KM, M Shashidharn, CA Ternent, et al. 1998. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. *Dis. Colon Rectum.* 41:428-433.

85. Lynch, HT, S Lemon, T Smyrk, et al. 1996. Genetic counseling in hereditary nonpolyposis colorectal cancer:An extended family with MSH2 mutation. *Am. J. Gastroenterol.* **1996**:2489-2493.

86. Burke, W, G Petersen, P Lynch, et al. 1997. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. *JAMA.* 277:915-919.

87. Syngal, S, J Weeks, D Schrag, et al. 1998. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. *Ann. Intern. Med.* **129**:787-796.

88. Vasen, HFA, M van Ballegooijen, E Buskens, et al. 1998. A cost-effectiveness analysis of colorectal screening of hereditary nonpolyposis colorectal carci-

noma gene carriers. *Cancer.* **82**:1632-1637.

89. Jarvinen, HF, J-P Mecklin, and P Sistonen. 1995. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology.* **108**:1405-1411.

90. Winawer, SJ, AG Zauber, MJ O'Brien, et al. 1993. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. *N. Engl. J. Med.* **328**:901-906.

91. Van Stolk, RU, GJ Beck, JA Baron, et al. 1998. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. *Gastroenterology.* **115**:13-18.

92. Nuako, KW, DA Ahlquist, DW Mahoney, et al. 1998. Familial predisposition for colorectal cancer in chronic ulcerative colitis: A case-control study. *Gastroenterology.* **115**:1079-1083.

93. Lennard-Jones, JE. 1996. Prevention of cancer mortality in inflammatory bowel disease. *In* Prevention and early detection of colorectal cancer. GP Young, P Rozen, and B Levin, editors. Saunders. 217-238.

94. Choi, PM, FW Nugent, DJ Schoetz, et al. 1993. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. *Gastroenterology.* **105**:418-426.

95. Connell, WR, IC Talbot, N Harpaz, et al. 1994. Clinicopathological characteristics of colorectal carcinoma complicating ulcerative colitis. *Gut.* **35**:1419-1425.

96. Jenne, DE, H Reimann, J Nezu, et al. 1998. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nature Genet.* **18**:38-43.

97. Giardiello, FM, SB Welsh, SR Hamilton, et al. 1987. Increased risk of cancer in the Peutz-Jeghers syndrome. *N. Engl. J. Med.* **316**:1511-1514.

98. Jarvinen, H, and KO Franssila. 1984. Familial juvenile polyposis coli: Increased risk of colorectal cancer. *Gut.* **25**:792-800.

99. Howe, JR, S Roth, JC Ringold, et al. 1998. Mutations in the SMAD4/DPC4 gene in juvenile polyposis. *Science.* **280**:1086-1088.

100. Olschwang, S, OM Serova-Sinilnikova, GM Lenoir, et al. 1998. PTEN germ-line mutations in juvenile polyposos coli. *Nature Genet.* **18**:12-14.

101. Eddy, D. 1990. Screening for colorectal cancer. *Ann. Intern. Med.* **113**:373-384.

102. Wagner, JL, S Tunis, M Brown, et al. 1996. Cost-effectiveness of colorectal cancer screening in average-risk adults. *In* Prevention and early detection of colorectal cancer. GP Young, P Rozen, and B Levin, editors. W. B. Saunders, London. 321-356.

103. Butrum, RR, CK Clifford, and E Lanza. 1988. NCI dietary guidelines: Rationale. *Am. J. Clin. Nutr.* **48**:888-895.

104. Howe, GR, E Benito, R Castelleto, et al. 1992. Dietary intake of fiber and decreased risk of cancers of the colon and rectum:Evidence from the combined analysis of 13 case-control studies. *J. Natl. Cancer Inst.* **84**:1887-1896.

105. Lippman, SM, SE Benner, and WK Hong. 1994. Cancer chemoprevention. *J. Clin. Oncol.* **12**:851-858.

106. Greenberg, ER, JA Baron, TD Tosterson, et al. 1994. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N. Engl. J. Med.* **331**:141-146.

107. Waddell, WR, and RW Loughry. 1983. Sulindac for polyposis of the colon. *J. Surg. Oncol.* **24**:83-87.

108. Giardiello, FM, SR Hamilton, AJ Krush, et al. 1993. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N. Engl. J. Med.* **328**:1313-1316.

109. Nugent, KP, KCR Farmer, AD Spigelman, et al. 1993. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br. J. Surg.* **80**:1618-1619.

110. Oshima, M, JE Dinchuk, SL Kargman, et al. 1996. Suppression of intestinal polyposis in *Apc* knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell.* **87**:803-809.

111. Prescott, SM, and RL White. 1996. Self-promotion? Intimate connections between *APC* and prostaglandid H synthase-2. *Cell.* **87**:783-786.

112. Sturmer, T, RJ Glynn, I-M Lee, et al. 1998. Aspirin use and colorectal cancer:Post-trial follow-up data from the physicians' health study. *Ann. Intern. Med.* **128**:713-720.