Preventing Colorectal Cancer: A Clinician's Guide

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death in the United States. In 2004, an estimated 146,940 new cases of CRC will be diagnosed and 56,730 people will die of the disease. Risk factors for CRC include older age, family history of CRC, certain hereditary conditions, a diet high in red meat and low in vegetables, excessive alcohol, tobacco use, obesity and sedentary life style.

The cumulative lifetime risk approaches 6% (5.88% for men, 5.49% for women). The incidence of CRC increases with age and occurs with about equal frequency in women and men. However, racial differences in CRC survival have been observed. African-American men and women with CRC have a near 50% greater probability of dying of colon cancer than white men and women. African-Americans may have a more proximal distribution of adenomas and carcinomas than the general population; if this is true, full colonic examination would be more important in screening for CRC in this population. In recent years, the incidence and mortality rates of CRC have decreased, after having consistently increased over the past few decades. These trends could be explained by removal of premalignant polyps, early detection, more accurate diagnosis, lower incidence, or more effective treatment; it is uncertain in what proportions each of these contribute. It is generally accepted that most cancers of the colon and rectum develop from adenomatous polyps. Few adenomatous polyps progress to cancer; the rate is estimated at about 2.5 polyps per 1000 per year. In those that do, the transformation from small adenomas to cancer seems to occur slowly over many years. It has been estimated that it takes an average of about 10 years for an adenomatous polyp, particularly one <1 cm in diameter, to transform into invasive cancer.

The progression from normal mucosa to adenomatous polyp to cancer is associated at the genetic level with an accumulation of somatic or acquired DNA mutations in colonic epithelial cells. These genetic alterations are most often ones that inappropriately activate gene function (oncogenes), inactivate normal suppressive gene function (tumor suppressor genes) or damage normal DNA repair functions (DNA repair genes). The genetic events in turn result in increased cell proliferation, decreased apoptosis and decreased DNA repair. A clone of such rapidly growing cells eventually forms a visible adenomatous polyp. As mutations continue to accumulate in the adenoma, the cells may acquire the ability to invade, circulate and attach to other tissues. By this process the adenoma becomes a malignancy. Several specific genetic abnormalities and specific genes involved in this process have been identified and it is likely that more will be found.

Some relevant mutations are inherited, thereby greatly accelerating the accumulation of genetic events and thus also the progression of normal to adenoma and finally to colon cancer. Environmental and lifestyle factors also play a role in CRC pathogenesis. The cumulative affects of environmental factors alone may, over time, give rise to colonic neoplasms, called sporadic polyps and cancers. Alternatively, environmental factors may interact with mildly to moderately penetrant inherited predisposing factors. This mechanism gives rise to many of the commonly observed cases of familial colon cancer. Finally, some inherited genetic mutations give rise to highly penetrant syndromes with extreme colon cancer risk.

The evolving knowledge of colon cancer epidemiology and genetics has provided great insight into the etiology and pathogenesis of this malignancy. This knowledge, in turn, is translating into improved prevention, screening and genetic diagnostic approaches. This monograph addresses the prevention strategies for colorectal cancer, both screening and primary prevention. The knowledge of genetic and environmental risk factors as well as molecular mechanisms will be reviewed as they are relevant to present prevention approaches.

COLON CANCER SCREENING

KEY POINTS & RECOMMENDATIONS

- Screen all men and women over the age of 50-or younger in the presence of risk factors-for CRC and adenomatous polyps.
- Offer screening options to patients, with information about the advantages and disadvantages of each approach, so that they can make an informed decision.
- The relative virtues of screening methods can be debated but the best test is the one that gets done.
- Combine screening with lifestyle modification, assessment of risk factors, and chemoprevention where appropriate.
- Emphasize to patients that the benefits of screening greatly overshadow those of primary prevention.

The recognized long natural history of colorectal cancer as it evolves from a normal mucosa through the adenoma stage provides a window of opportunity for the early detection of a high proportion of curable cancers. This window also allows for near complete prevention of cancers by identification of adenomatous polyps and polypectomy. Additionally, primary prevention approaches that have been developed from the knowledge of associated environmental and lifestyle factors and chemopreventive agents are being examined and even incorporated in some settings.

Primary prevention is defined as the modification of environment and lifestyle factors, while secondary prevention is screening. Chemoprevention is the use of agents (eg. aspirin and other NSAIDs) to prevent cancer. At present, screening is the most powerful prevention strategy. There is now considerable evidence that colorectal cancer screening is both effective and cost effective in reducing the incidence and mortality of this disease. Since 1996 many international groups and policy making organizations have evaluated the evidence on screening, and recommended that all men and women age 50 and over should be screened for colorectal cancer and adenomatous polyps, and younger in the presence of factors that increase their risk. Screening is applied to people who have or are likely to have an adenomatous polyp or colorectal cancer. Surveillance is defined as the monitoring of people who have already been identified as having a premalignant condition such as adenomatous polyps, inflammatory bowel disease or previously treated cancer of the colon. People with symptoms or signs that suggest the presence

of colorectal cancer or polyps fall outside the domain of screening and should be offered an appropriate diagnostic evaluation.

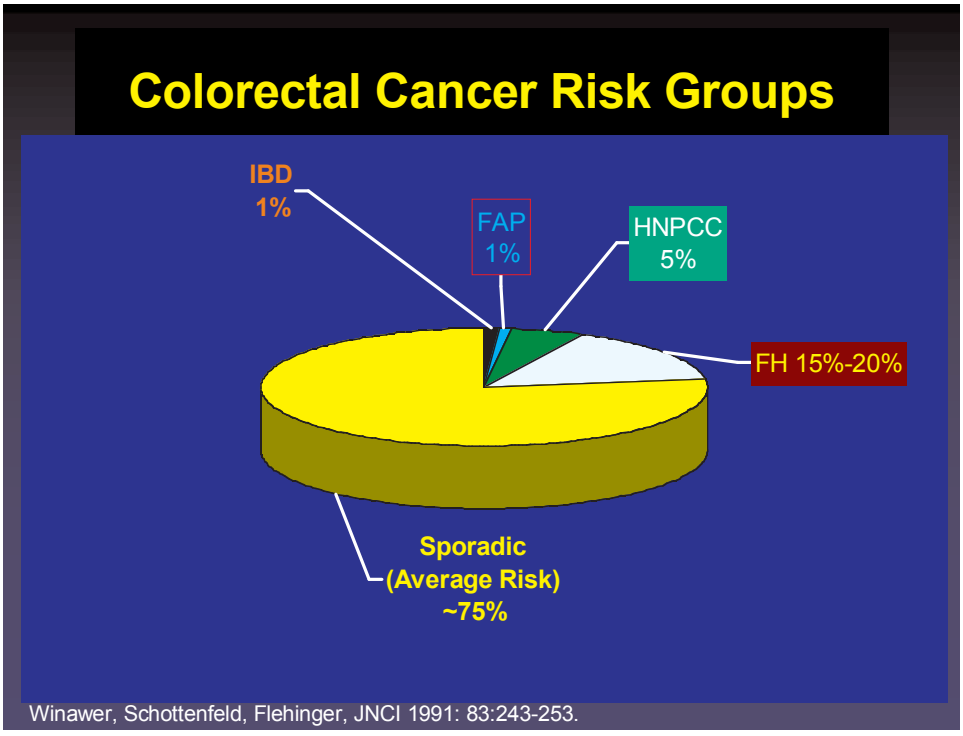
Screening programs should begin by classifying the individual patient's level of risk based on personal, family and medical history, which together determine the appropriate approach to screening in that person. Men and women are considered to be at average risk if they are age 50 years of age or older and have no factors that increase their risk such as a family history of either colorectal cancer or adenomatous polyps below age 60, or a personal history of adenomatous polyps, colorectal cancer or inflammatory bowel disease. (Table 1 and Fig. 1)

Table 1. Factors associated with increased risk for colorectal cancer (CRC)

Increased risk
- Age 50 years or older.
- Prior CRC or adenomatous polyp
- Family history of CRC or adenomatous polyp
- Long-standing inflammatory bowel disease (ulcerative or Crohn's colitis)

High risk
- Hereditary nonpolyposis colorectal cancer syndrome (HNPCC)
- Familial adenomatous polyposis syndrome (FAP)

Figure 1



Several options for screening are now available including fecal occult blood testing (FOBT) by guaiac or immunochemical methods, flexible sigmoidoscopy, barium enema, and colonoscopy. The strength of evidence varies considerably among the options. Screening colonoscopy is the most sensitive and specific but requires the most resources and may not be feasible in most countries. A two-stage screening with either FOBT or flexible sigmoidoscopy or both as a first step could be used to identify a smaller subset of the population requiring colonoscopy. Emerging technology has also been introduced recently including stool DNA mutation testing and virtual colonoscopy. If the result of a screening test is abnormal, physicians should recommend a complete structural examination of the colon and rectum by colonoscopy. Surveillance with colonoscopy should be considered for patients who are at increased risk because they have been treated for colorectal cancer, had a previous adenomatous polyp diagnosed, or have a disease that predisposes to colorectal cancer such as inflammatory bowel disease.

A major issue is that population screening rates are low and most people do not take advantage of the benefits of screening. In one study less than 40% of at risk people had a screening test in the past 5 years. An international survey demonstrated that there are multiple system and patient barriers to screening, the most important being patient awareness and financial obstacles. **The relative virtues of each screening test can be debated but the best test is the one that gets done.** Screening needs also to be incorporated into a program of prevention that includes dietary and lifestyle modification, assessment of familial risk factors, and chemoprevention where appropriate.

SCREENING OPTIONS FOR PEOPLE AT AVERAGE RISK

About 75% of all new cases of CRC occur in people with no known predisposing factors for the disease. Incidence increases with age, beginning around age 40 years. Men and women at average risk should be offered screening with one of the following options beginning at age 50 years. The rationale for presenting multiple options is that no single test is of unequivocal superiority and that giving patients a choice allows them to apply personal preferences and may increase the likelihood that screening will occur. The strategies are not equal with regard to evidence of effectiveness, magnitude of effectiveness, risk, or upfront costs.

Fecal Occult Blood Testing (FOBT)

Recommendation: Offer yearly screening with fecal occult blood test (FOBT) using a sensitive guaiac based test with dietary restriction or an immunochemical test without dietary restriction. Two samples from each of two (immunochemical) or three (guaiac) consecutive stools should be examined without re-hydration of guaiac based test. Patients with a positive test on any specimen should be followed up with colonoscopy.

Testing of two samples from each of three consecutive stools for the presence of occult blood using a guaiac-impregnated slide test has been shown in three randomized controlled trials to reduce the risk of death from colorectal cancer. Although the sensitivity of a single guaiac

FOBT is low, in the 30-50% range, a program of repeated annual testing can detect as many as 92% of cancers. Results from three studies indicated that offering yearly FOBT with re-hydration reduced colorectal cancer deaths by 33% after 13 years; biennial testing reduced colorectal cancer deaths by 15 and 18 % after 7.8 and 10 years, respectively, without re-hydration and 21% at 18 years with re-hydration. The incidence of colorectal cancer was also reduced in the screened group. A systematic review of three clinical trials has shown that a restricted diet does not reduce the positivity rate for the older, less sensitive guaiac based tests and that very restricted diets may reduce compliance rates. However, dietary restriction does affect the performance of the more sensitive guaiac based tests more recently introduced into clinical practice. People should be encouraged not to eat red meat three days before developing the test. Dietary restriction can be confined to red meat alone by waiting three days before developing the test. People who actually follow through with screening have a greater benefit.

Yearly testing is recommended because it is more effective than screening every two years. Rehydration is not recommended: although rehydration of the guaiac-based slides increases sensitivity, the readability of the test is unpredictable and rehydration substantially increases the false positive rate. Newer guaiac-based tests are available that have improved sensitivity. Dietary restrictions during testing are recommended to reduce the false positive rate for the more sensitive guaiac based tests.

Disadvantages of FOBT are that currently available tests for fecal occult blood fail to detect many polyps and some cancers. Also, most people who test positive will not have colorectal neoplasia (have a false positive test result) and thus will undergo the discomfort, cost, and risk of colonoscopy without benefit. Colonoscopy is recommended for all those with a positive FOBT because it was the diagnostic procedure used throughout most of the trials, and because it is substantially more accurate than double contrast barium enemas for the detection of both small cancers and adenomas.

One study showed that testing for FOBT at the time of digital rectal examination (office FOBT) has a high positive predictive value for neoplasia but its sensitivity and specificity are not known. A study of screening colonoscopy in people age 40-49 confirmed that colorectal cancers are uncommon in this age group, supporting the recommendation that screening in average risk people begin at age 50 years. One national study showed that only one in three people with a positive FOBT currently undergoes colonoscopy and therefore is in a position to benefit fully from screening. Recent studies have shown that immunochemical tests have the same high sensitivity of guaiac tests but a higher specificity and do not require dietary restriction.

Sigmoidoscopy

Recommendation: Offer flexible sigmoidoscopy every 5 years.

Four case-control studies have reported that sigmoidoscopy was associated with reduced mortality for colorectal cancer. The strongest of these reported that screening sigmoidoscopy reduced colorectal cancer mortality by two thirds for lesions within reach of the sigmoidoscope. Colon cancer risk in the area beyond the reach of the sigmoidoscope was not reduced, affirming the validity of this study. A five-year interval between screening examinations is a conservative choice. It is sup-

ported by the observation that reduction in colorectal cancer deaths related to screening sigmoidoscopy was present up to 10 years from the last screening examination; that repeat colonoscopy five years after a negative colonoscopy found few instances of advanced neoplasia; and that follow-up of a cohort of patients after polyp excision showing that development of advanced neoplasia was rare up to five years after a negative colonoscopy. The interval is shorter than for colonoscopy because flexible sigmoidoscopy is less sensitive than colonoscopy even in the area examined because of the technique and quality of bowel preparation, the varied experience of the examiners performing the procedure, and the effect patient discomfort and spasm may have on depth of sigmoidoscope insertion and adequacy of mucosal inspection.

Factors associated with an increased risk of advanced proximal neoplasia include age >65 years, villous histology in distal adenomas and adenomas > 1cm, multiple distal adenomas, and a positive family history of colorectal cancer. Whether persons with only a single distal tubular adenoma <1 cm in size are at increased risk for advanced proximal neoplasia remains uncertain. Polyps > 1 cm in size detected at flexible sigmoidoscopy should generally be assumed to be adenomas, since a very large proportion of these polyps are adenomatous. For polyps <1cm in size, biopsy will distinguish hyperplastic from adenomatous polyps. Identification of villous elements or high grade dysplasia, information that may be useful in deciding whether to proceed with colonoscopy, may not be obtainable when the polyp is adenomatous and approaches 1 cm in size. For these patients, whether to proceed with colonoscopy is an individual clinical decision. Current evidence suggests that the risk of advanced proximal neoplasia in persons with only hyperplastic polyps in the distal colon is comparable to the risk in persons with no distal polyps.

Combined Fecal Occult Blood Testing (FOBT) and Flexible Sigmoidoscopy
Recommendation: Offer screening with FOBT every year combined with flexible sigmoidoscopy every five years. When both tests are performed, the FOBT should be done first.

The effectiveness of this combined screening strategy in reducing mortality has never been studied directly in a randomized trial. It is likely that the combination of both screening methods is more effective than either method of screening alone. FOBT may be less sensitive for distal colon lesions; case-control studies report screening FOBT and sigmoidoscopy each are associated with reduced colorectal cancer mortality after controlling for the other; and a non-randomized controlled trial reported a 43% reduction (which was not statistically significant) in colorectal cancer deaths in people screened with FOBT and sigmoidoscopy relative to sigmoidoscopy alone. When both tests are to be done at any given time, the FOBT should be performed first because a positive result is an indication for colonoscopy, obviating the need for the sigmoidoscopy examination. The disadvantage of the FOBT/sigmoidoscopy strategy is that people incur the inconvenience, cost, and complications of both tests with an uncertain gain in effectiveness.

Colonoscopy
Recommendation: Offer colonoscopy every 10 years.There are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from colorectal cancer in peo-

ple at average risk. However, several lines of evidence support the effectiveness of screening colonoscopy. Colonoscopy was an integral part of the clinical trials of FOBT screening that showed that screening reduced colorectal cancer mortality. Visualization of neoplasms by colonoscopy is at least as good as by sigmoidoscopy. There is direct evidence that screening sigmoidoscopy reduces colorectal cancer mortality and colonoscopy allows more of the large bowel to be examined. Colonoscopy has been shown to reduce the incidence of colorectal cancer in 2 cohort studies of people with adenomatous polyps. Colonoscopy permits detection and removal of polyps and biopsy of cancer throughout the colon. However, colonoscopy involves greater cost, risk and inconvenience to the patient than other screening tests, and not all examinations visualize the entire colon. The added value of colonoscopy over sigmoidoscopy screening therefore involves a tradeoff of incremental benefits and harms.

Choice of a ten-year interval between screening examinations for average-risk people (if the preceding examination is negative) is based on estimates of the sensitivity of colonoscopy and the rate at which advanced adenomas develop. The dwell time from the development of adenomatous polyps to transformation to cancer is estimated to be at least 10 years on average. Few clinically important adenomas are missed by colonoscopy. (6% or less of advanced adenomas). A case-control study of screening rigid sigmoidoscopy found a protective effect from death due to distal cancer lasting up to 10 years from the last screening examination.

In two large prospective studies of screening colonoscopy, about half of patients with advanced proximal neoplasms had no distal colonic neoplasms. Similarly, a prospective study of distal colon findings in a cohort of average-risk persons with cancer proximal to the splenic flexure found that 65% had no neoplasm distal to the splenic flexure, even though 70% of lesions overall were in the area examined by flexible sigmoidoscopy. A randomized controlled trial of sigmoidoscopy with follow-up colonoscopy for all patients with polyps compared to no screening demonstrated a significant reduction in colorectal cancer incidence in the screened patients. A cohort of 154 asymptomatic average-risk persons with negative screening colonoscopies had a < 1% incidence of advanced neoplasms at a second colonoscopy 5 years later, lending support to the recommended interval of 10 years. Two colonoscopy studies suggested that flat and depressed adenomas account for 22 and 30 % of adenomas; and one report suggests that dye spraying is necessary in order not to miss these lesions. However, the precise prevalence and clinical significance of flat adenomas is uncertain.

Double-Contrast Barium Enema

Recommendation: Offer double-contrast barium enema (DCBE) every 5 years.There are no randomized trials evaluating whether screening DCBE reduces the incidence or mortality from colorectal cancer in people at average risk of the disease. The sensitivity of DCBE for large polyps and cancers is substantially less than with colonoscopy, the procedure does not permit removal of polyps or biopsy of cancers, and it is more likely than colonoscopy to identify artifacts and other findings (such as stool) as polyps. Patients with an abnormal barium enema need a subsequent colonoscopy.

DCBE is included as an option because it offers an alternative (albeit less sensitive) means to examine the entire colon, is widely available and because it detects about half of large polyps, which are most likely to be clinically important. Adding flexible sigmoidoscopy to DCBE is not recommended in the screening setting. The incremental detection rate achieved by adding flexible sigmoidoscopy is uncertain and probably small, and there is increased cost and patient inconvenience associated with the combination. A five-year interval between DCBE examinations is recommended because DCBE is less sensitive than colonoscopy in detecting colonic neoplasms.

In a prospective study of DCBE in a surveillance population with a spectrum and prevalence of disease similar to a screened population, DCBE detected 53% of adenomatous polyps 6-10 mm in size and 48% of those > 1 cm in size compared to colonoscopy. In a non-randomized study of 2,193 consecutive colorectal cancer cases in community practice the sensitivity for cancer was 85% with DCBE and 95% with colonoscopy.

FAMILIAL RISK, INHERITED SYNDROMES AND GENETIC TESTING

Colon cancer is perhaps the most familial of all common malignancies and inheritance plays a role in the pathogenesis of up to a third of colon cancer cases. Genetic-environmental interactions are also important in many cases with inherited predisposition. A small fraction of colon cancer cases arise in the setting of highly penetrant autosomal dominantly inherited colon cancer syndromes.

In view of both the common familial risk among colon cancer cases and the inherited colon cancer syndromes, most health policy organizations now include familial risk as a consideration in determining the most appropriate colon cancer screening for individuals and families. This section will review common familial colon cancer risk and screening guidelines relevant to this risk together with an approach to identifying the inherited syndromes of colon cancer.

Screening Persons with a Family History of Colon Cancer

Up to 10% of adults have an immediate relative (first-degree relative) with colon cancer. Additionally, having a family history of colon cancer increases one's risk of developing this malignancy two- to three-fold over the general population risk. Risk is increased further in families with multiple relatives or younger relatives with a colon cancer diagnosis. (Table 2).

Most familial clustering of colon cancer cases is believed to arise from inherited predisposition. The causative genes are known for the rare syndromes but not yet for the more common but less severe types of familial colon cancer.

Screening strategies have been developed to address the familial risk of commonly observed colon cancer. Screening recommendations are empiric and combine the known effectiveness of available screening tools with the observed risks associated with family history. If a person has a first-degree relative with colon cancer, average risk colon cancer screening is recommended, but starting at age 40 years. The decreased age is given because the risk at age 40 years for those with an affected first-degree relative is similar to the risk at age 50 years for the general population. An individual with

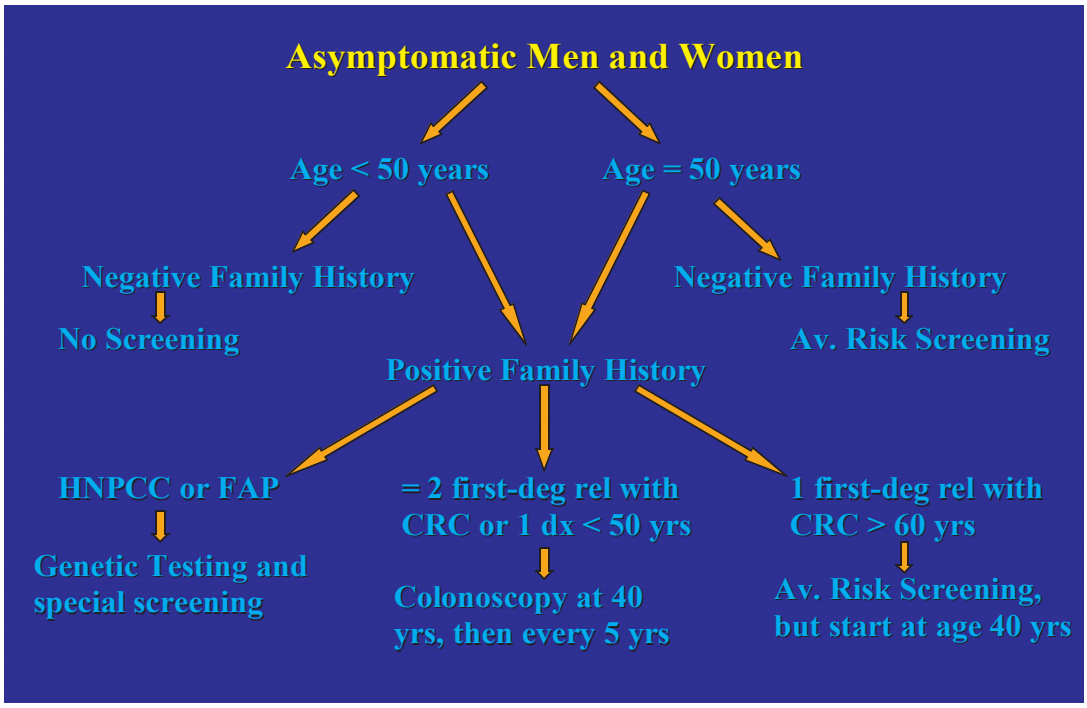
two first-degree relatives affected with colon cancer or one first-degree relative diagnosed under the age of 50 years should have colonoscopy beginning at age 40 years, or 10 years younger than the earliest case in the family. Colonoscopy should be repeated every five years if negative. An even stronger family history of colon cancer should suggest the consideration of one of the inherited syndromes of colon cancer. Figure 2 illustrates an overall approach for utilizing family history to determine the most appropriate screening for colon cancer.

Table 2. Familial Risk for Colon Cancer

Familial Setting	Approximate Lifetime Risk of Colon Cancer
General population risk in the U.S.	6%
One first-degree relative with colon cancer[1]	2- to 3-fold increased
Two first-degree relatives with colon cancer[1]	3- to 4-fold increased
First-degree relative with colon cancer diagnosed at 50 years	3- to 4-fold increased
One second- or third-degree relative with colon cancer[2,3]	About 1.5-fold increased
Two second-degree relatives with colon cancer[2]	About 2- to 3-fold increased
One first-degree relative with an adenomatous polyp[1]	About 2-fold increased

[1]First-degree relatives include parents, siblings, and children
[2]Second-degree relatives include grandparents, aunts, and uncles
[3]Third-degree relatives include great-grandparents and cousins
Modified from Burt RW. Colon cancer screening. Gastroenterology 2000. 119:837-53. With permission

Figure 2



Inherited Syndromes of Colon Cancer and Genetic Testing

A small fraction of persons and families with colon cancer will have an inherited syndrome, where the risk of colon cancer is extreme. A most important development in medicine in the last decade is genetic testing for the precise diagnosis of the rare inherited colon cancer syndromes. Strategies have now also been established to assist the clinician in determining when genetic testing should be applied to diagnose these syndromes. The relevant inherited syndromes will be briefly described, followed by the recommended approaches used to identify those who should have genetic testing for these syndromes.

The inherited syndromes of colon cancer are divided into those in which colonic adenomatous polyps occur and those in which hamartomatous polyps are found. The adenomatous polyp syndromes include familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). The hamartomatous polyp syndromes include Petuz-Jeghers syndrome, Juvenile polyposis and Cowden syndrome. Genes associated with each of these syndromes have now been identified and are given in Table 3.

FAP occurs in about 1 in 10,000 persons and accounts for less than 0.5% of colon cancer cases. It is characterized by the presence of hundreds to thousands of colonic adenomatous polyps, and a near 100% risk of colon cancer if the colon is not removed. There is a mild or attenuated form of FAP in which the number of colonic polyps is extremely variable, but averages about 30, and the emergence of polyps and cancer is delayed by about 10 years. HNPCC does not have a distinctive clinical phenotype but is defined by family history as outlined in Table 4.

Individuals with HNPCC have an 80% risk of colon cancer, average age 44 years, as well as some risk for cancers of the endometrium, ovary, stomach, urinary tract, kidney, bile ducts, CNS and small bowel also occur. Three to 5% of all colon cancers arise from HNPCC. Peutz-Jehgers syndrome, juvenile polyposis and Cowden syndrome are all extremely rare conditions

characterized by histologically specific types of hamartomatous polyps and an increased risk of colon and other cancers. Colon cancer risks and screening guidelines for each of the inherited syndromes are given in Table 3.

Genetic testing is indicated for each of the inherited syndromes when certain features of the syndrome are present (Table 3). A clear understanding of genetic testing and its implications is necessary and can often be accomplished through the use of genetic counselors.

To perform genetic testing, peripheral blood is drawn and DNA is obtained from the white blood cells. Genetic studies are then done on the relevant genes to detect disease causing mutations. The success of finding a mutation in the first person in a family clinically identified as having one of the syndromes is also given in Table 3. If a mutation cannot be found in that first person, the genetic test is said to be "uninformative." Cancer screening must be then done on all family members. But if a relevant mutation is found in the first person, or index case, then other family members can undergo "mutation specific" genetic testing. Only the exact mutation found in the first family member is tested for in other family members. This testing is much

Table 3. GI colon cancer syndromes: Colon cancer risk and screening; Responsible gene(s) and genetic testing

Syndrome	Colon cancer risk (average age of colon cancer diagnosis)	Colon cancer screening	Gene (frequency mutation can be found in index case)	Indication for genetic testing when mutation not already known	Age to consider genetic testing when the disease causing mutation in the family is known
FAP[1]	100% (39 years) attenuated FAP, 80% (50 years)	Annual sigmoidoscopy beginning at age 10 to 12 years, colonoscopy beginning in late teens if attenuated FAP	APC (80 to 90%)	20 or more adenomatous polyps	10 to 12 years, late teens for attenuated FAP
HNPCC[2]	80% (44 years)	Every two-year colonoscopy starting at age 25 years	Mismatch repair genes (50 to 70%)	Amsterdam II or revised Bethesda criteria (see text and Tables 4 and 5)	25 years, sometimes younger
Peutz-Jeghers syndrome	39% (46 years)	Colonoscopy every 3 years starting with symptoms or late teens if symptoms have not occurred	STK11(LKB1) (50% to 60%)	Any Peutz-Jeghers polyps or typical pigmentation	When symptoms occur or late teens if symptoms have not occurred
Juvenile polyposis	9 to 68% (34 years)	Colonoscopy every 3 years starting with symptoms or early teens if symptoms have not occurred	SMAD4(DPC4), BMPR1A (53%)	5 or more juvenile polyps	When symptoms occur or early teens if symptoms have not occurred
Cowden syndrome	about 9%	None given	PTEN (80% to 90%)	Typical findings or typical colonic polyps	By age 25 years, mostly for breast cancer screening

[1]FAP, Familial Adenomatous Polyposis
[2]HNPCC, Hereditary Nonpolyposis Colorectal Cancer

less expensive and is near 100% accurate, both positive and negative. Special screening can then be directed to those who have the disease causing mutation, while those who don't need only average risk screening.

Choosing which patients need genetic testing is relatively straightforward for FAP and the hamartomatous polyp syndromes, as outlined in Table 3. The biggest challenge for the clinician is selecting those who should be tested for HNPCC because of the lack of a specific phenotype. The initial approach is to obtain a family history on all patients presenting for screening. If the Amsterdam criteria are met (Table 4), genetic testing should be done as described above. The first person to be tested should be the person with the earliest age colon cancer in the family. If a disease causing mutation is found in that person, mutation specific testing can then be undertaken in other family members and screening recommendations can be based on genetic testing results. If a mutation is not found in the index person, all family members must be screened as possibly having the syndrome.

Table 4. Revised or Amsterdam II criteria for HNPCC

Amsterdam II criteria

Three or more relatives with HNPCC-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter or renal pelvis) plus all of the following:

1. one affected patient should be a first-degree relative of the other two;
2. two or more successive generations should be affected;
3. cancer in one or more affected relatives should be diagnosed before the age of 50 years;
4. familial adenmoatous polyposis should be excluded in any cases of colorectal cancer;
5. tumors should be verified by pathological examination.

Applying the Amsterdam criteria, however, probably identifies only about half of those with HNPCC. Thus a more inclusive set of criteria have been established, called the Bethesda criteria (Table 5). If the Amsterdam criteria are not met, the clinician should determine if one of the Bethesda criteria are met. If any of these latter criteria are met, "microsatellite instability" (MSI) testing on colon cancer tissue is indicated. MSI is a genetic feature of tumors in which frequent mutations are found in small stretches of DNA called microsatellites. Almost all colon cancers in HNPCC express MSI.

Table 5. The revised Bethesda guidelines for testing colorectal cancer tumors for microsatellite instability (MSI)

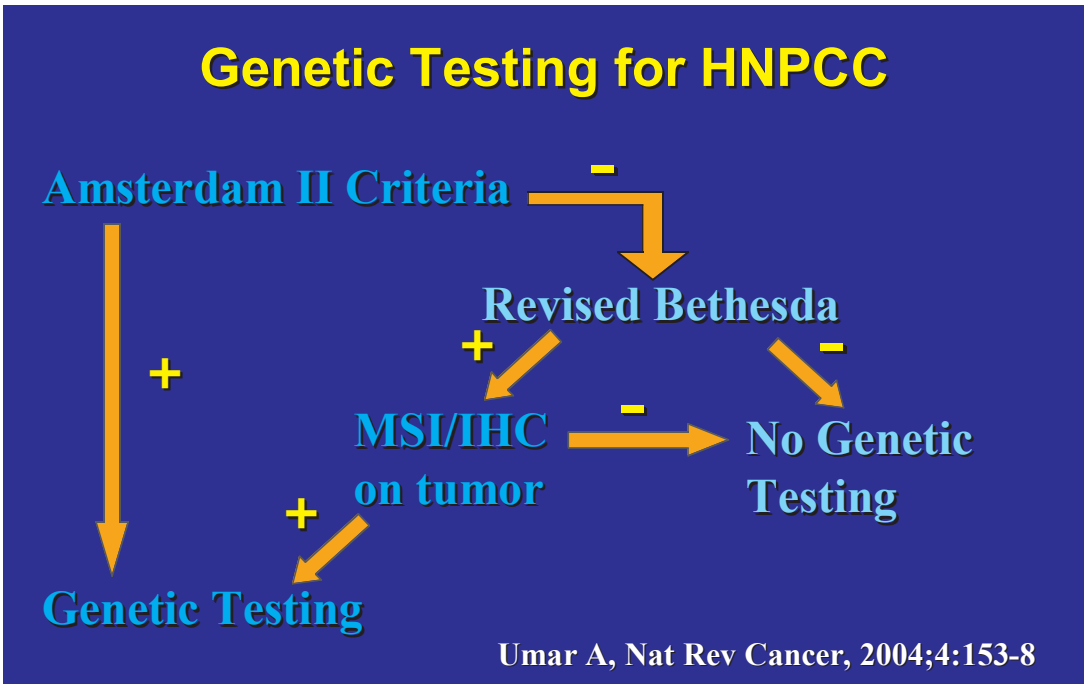
Tumors from individual should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal cancer, or other HNPCC-associated tumors (endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain tumors-usually glioblastoma, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel), regard less of age.
3. Colorectal cancer with MSI-H histology (presence of tumor infiltrating lym phocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient who is less than 60 years of age.
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

Unfortunately MSI is not diagnostic of HNPCC because it is present in about 15% of sporadic colon cancers. Thus, the presence of MSI in a tumor only makes HNPCC more likely. When MSI is present in the tumor tested because of Bethesda criteria, the clinician should then proceed to genetic testing by blood draw to examine DNA for inherited mutations. If MSI is not present in the tumor, HNPCC is very unlikely and genetic testing is usually not indicated. If tumor tissue is not available, a

decision to go directly to genetic testing on the basis of a positive Bethesda criterion should be considered. The entire approach to the genetic diagnosis of HNPCC is summarized in Figure 3. It is estimated that if this approach is utilized, approximately 10% to 15% of persons diagnosed with colon cancer

Figure 3



will undergo genetic testing to find those with HNPCC and about 0.2% to 0.3% of all adults presenting for colon cancer screening will undergo genetic testing to find those with HNPCC.

EMERGING SCREENING TESTS: VIRTUAL COLONOSCOPY AND DNA-BASED STOOL TESTS

Two new methods of screening for colorectal cancer, virtual colonoscopy (CT colonography) and DNA-based stool tests have recently been introduced clinically and may soon be added to the menu of screening options. The current screening guidelines, emphasize however, that before a new test can be recommended for population based screening, it first should be shown to be as safe, available, acceptable, effective, and cost-effective as the methods it might replace. This chapter presents the advantages and limitations of these two new screening tests, discusses how well they currently satisfy these performance criteria, and identifies issues and questions that still need to be addressed.

Virtual Colonoscopy

Virtual colonoscopy or computerized tomographic (CT) colonography is a new imaging technique that combines thin-section rapid helical CT scanning of the abdomen with sophisticated computer software capable of rendering two- and three-dimensional images of the large bowel. Modern CT scanners now are capable of obtaining hundreds of thin section slices in less than a minute during a single breath hold, eliminating motion artifacts that previously prevented high-

KEY POINTS & RECOMMENDATIONS

- Computerized tomographic (CT) colonography likely will be an acceptable screening option once issues of training, availability, and cost are resolved.
- Compared to colonoscopy, CT colonography examination time is shorter and i.v. sedation is not needed. However, reading the scans takes ~25 minutes.
- CT colonography requires a thorough bowel prep, a somewhat uncomfortable gas distention of the colon, and a subsequent colonoscopy if positive, all of which may limit patient acceptance.
- Visualization of small polyps and flat lesions with CT colonography is poor though the clinical significance of this limitation relative to polyps 6 - 9 mm in size is controversial.
- When used alone, the current commercially available stool DNA test has a moderate sensitivity (though its specificity is high).
- Though DNA-based stool testing is promising, its place in CRC screening and surveillance requires further study.

resolution CT imaging of the bowel. These images can be rotated for different views and even combined for a complete three-dimensional view of the colon that then can be rapidly "flown through", thus simulating conventional, optical colonoscopy.

At the present time a thorough purging bowel cleansing preparation is required prior to the CT colonography procedure. Immediately before obtaining the CT scans, a rectal tube is inserted and the colon is insufflated with room air to the maximum level tolerated by the patient. Gas distention of the bowel is essential because interpretation is not possible when the bowel is spastic or collapsed. Scans then are obtained in both the supine and prone positions during a breath hold in order to redistribute the air into all parts of the colon and to help differentiate retained fluid (that will shift in location) from fixed filling defects. Increasingly, multidetector CT scanners are being employed for virtual colonoscopy because they scan faster and use thinner reconstruction intervals and collimations that allow for finer resolution of anatomic structures.

Most radiologists have relied mainly on two-dimensional images displayed on the workstation to identify abnormalities. Three-dimensional views of the same area then are scrutinized to confirm findings. As discussed below, some centers now utilize new special software that allows them to perform an initial rapid fly through of reformatted three-dimensional reconstruction of the colon and confirm any endoluminal findings with corresponding two-dimensional images.

Advantages and disadvantages of virtual vs. conventional colonoscopy

There are several proven and potential advantages of virtual colonoscopy over conventional colonoscopy. Examination time is substantially shorter and there is no need for pre-procedure sedation with its attendant risk, inconvenience, and recovery time. To date no serious morbidity or mortality has been reported with virtual colonoscopy while diagnostic conventional colonoscopy results in perforation of the colon in about 0.05% of reported cases. Precise localization of lesions is possible with virtual colonoscopy, while, except in the rectum and cecum,

intraluminal landmarks often are not sufficiently distinct to precisely identify a lesion's location during colonoscopy. The radiologist, using a number of static and dynamic display options, can examine and re-examine segments of the colon long after a scan has been performed. Lastly, virtual colonoscopy can be used to examine the proximal colon when an obstructing left-sided cancer prevents passage of a colonoscope, or it can complete a large bowel examination when colonoscopy is incomplete.

Current limitations of virtual colonoscopy compared to conventional colonoscopy include the need for a very thorough bowel cleansing preparation and for the somewhat uncomfortable pre-procedure gas distention of the colon. Colonic spasm or retained fecal debris or liquid may severely interfere with the accuracy of readings. Substantial time is required for radiologists to become proficient at interpreting scans (long learning curve), and each case may require 20-30 minutes of reading time. In most reported studies, accuracy is poor for smaller polyps and for flat lesions that are flush with the colorectal mucosal contour. If scans need to be repeated at relatively short intervals, radiation exposure also may be a concern. Lastly, as is the case with barium enema, the procedure is diagnostic only. A positive scan must usually be followed by a conventional colonoscopy at a different sitting with an additional bowel purging preparation.

Clinical studies of virtual colonoscopy

Initial studies of virtual colonoscopy performed in populations with a high-prevalence for colorectal neoplasia demonstrated sensitivity for detecting polyps >1 cm approaching 90% (Table 6), although sensitivity and specificity for detecting smaller polyps was poor.

Table 6. Sensitivity of Virtual Colonoscopy for Detecting Large (≥1cm) Polyps

Type of Study Author, year	Total patients in study	Total patients with polyps ≥ 1 cm in diameter	Sensitivity for polyps ≥1 cm in diameter	
			By polyp	By patient
Studies in patient referred for colonoscopy				
Fenlon, 1999	100	22	91%	96%
Yee, 2001	300	82	90%	100%
Pineau, 2003	205	27	78%	90%
Studies in average risk screening patients				
Pickhardt, 2004	1337	51	92%	94%
Cotton, 2004	600	42	52%	55%

The Pickhardt study, a recent large study performed in three military hospitals in a low-prevalence, largely average-risk population of 1233 asymptomatic adults may represent an important break-through in the development of virtual colonoscopy, and the results appear to predict a positive future for this new modality. In this large comparison of virtual and conven-

tional colonoscopy, six experienced radiologists used a commercially available CT three-dimensional colonographic computer system (Viatronix, Stony Brook, NY) that creates a three-dimensional endoluminal display for the initial detection of polyps, followed with rapid confirmation of findings with corresponding two-dimensional images. Patients underwent a standard 24-hour colonic preparation and then they also consumed 500 ml of barium for solid-stool tagging and 120 ml of diatrizoate solution for opacification of retained luminal fluid. This preparation allowed the computer program to differentiate between retained stool and polypoid defects, and for electronic fluid cleansing. All scans were performed with multidetector helical CT scanners. Colonoscopy that was performed by 17 experienced endoscopists blinded to the results of the virtual examination was complete to the cecum in 99.4% of participants.

Remarkably, the sensitivity of virtual colonoscopy in this study was 93.8% for adenomatous polyps at least 1 cm in diameter, 93.9% for polyps at least 8 mm in diameter, and 88.7% for polyps at least 6 mm in diameter. The sensitivity of optical colonoscopy for polyps of these sizes was 87.5%, 91.5%, and 92.3%, respectively. Of two malignant polyps detected by virtual colonoscopy, one was missed by conventional colonoscopy. Virtual colonoscopy specificity for these three sizes of polyps also was high (96%, 92.2%, and 79.6%, respectively). The negative predictive value for polyps of at least 8 mm was more than 99%. The authors concluded that CT virtual colonoscopy, using the more advanced methodology employed in this study, is as accurate as conventional colonoscopy for the detection of clinically important colorectal polyps (>6 mm) in asymptomatic, average-risk adults.

A subsequent study more representative of current community practice compared colonoscopy and virtual colonoscopy in 615 participants referred for routine clinically indicated colonoscopy in 9 major hospital centers. The sensitivity of virtual colonoscopy for polyps = 10 mm was 55% and for lesions = 6m was 39%. Virtual colonoscopy missed 2 of 8 cancers. The authors concluded that virtual colonoscopy was not yet ready for widespread clinical application. This large study, however, has been criticized for having very poor quality control between centers. There was considerable variability in the training and experience of radiology investigators at the start of the trial that resulted in an unacceptable range of results (sensitivity for large polyps ranged from under 10% to 87%).

Unresolved issues

Most gastroenterologists now agree that missing diminutive polyps (<5 mm) has very little clinical importance . Currently, however, the controversial area has to do with adenomas of intermediate size (6-9 mm). Although such polyps pose a low immediate cancer risk, most clinicians and many patients may not be willing to have such lesions regularly missed unless they know that repeat screening will be carried out within 3-5 years. Increasing the frequency of screening virtual colonoscopy, of course, greatly increases the cost of this as a screening option, and may not allow it to compete with the option of doing direct colonoscopy screening every 10 years as is now recommended. Frequent CT scanning also raises concerns about cumulative radiation exposure.

Like conventional colonoscopy, virtual colonoscopy is expensive. Current charges for screening virtual colonoscopy (which yet are not covered by most health payers) are similar to that of an

abdominal/pelvic CT scan. However, if the indication for an examination is screening, additional colonoscopies will be needed in at least 10%-20% of patients to assess findings or resect polyps. In these cases, a more cost-effective approach may be just to do an initial colonoscopy that is both diagnostic and therapeutic in a single sitting with a single bowel preparation.

A cost-effectiveness analysis showed conventional colonoscopy to be the more cost-effective screening approach. Only when the cost of virtual colonoscopy was assumed to be < 55% of that of colonoscopy, or the compliance rate was assumed to be 15% - 20% higher, did virtual colonoscopy become the more cost-effective option.

Conventional colonoscopy requires sedatives, is expensive and has some risks. Many, therefore, are attracted to the concept of a "virtual" examination. However, when patients learn that they first must undergo a vigorous cathartic prep and then be subjected to rectal instillation of gas, their acceptance decreases. In studies of back-to-back comparisons of virtual and conventional colonoscopy, there have been at least six surveys of patient preference. In three of these, patients preferred virtual colonoscopy and in three they preferred conventional colonoscopy. However, when later asked which test they would want for repeat screening, virtual colonoscopy was selected as a preference in five of six surveys. The development of "electronic cleansing" would likely greatly increase the acceptance of virtual colonoscopy.

Conclusions and Recommendations
Virtual colonoscopy screening has a promising future. If the results of the study by Pickhardt et al are reproducible on a larger scale, and if issues of size threshold for polyps, cost, availability, and compliance are satisfactorily addressed, the future addition of virtual colonoscopy to the menu of screening options appears certain, and this should help improve overall screening compliance and favorably impact colorectal cancer control.

Stool-Based DNA Tests
As adenomatous polyps develop, grow, acquire advanced histologic features, and eventually turn cancerous, they acquire an increasing number of genetic alterations. It was shown many years ago that DNA from cancers and polyps is shed into the colonic lumen continuously via the exfoliation of neoplastic cells. Very small quantities of sloughed DNA remain chemically stable in stool and can be isolated and analyzed for relevant DNA abnormalities. One difficulty is the presence of substantial DNA from normal colonic epithelial cells, from residual consumed biologic foodstuffs and from normal flora bacteria. Nonetheless techniques have been developed to isolate DNA from stool and examine it for mutations and changes that occur in adenoma and cancer cells.

Colorectal neoplasms are genetically heterogeneous and no single mutation has been found that is expressed by all advanced polyps and cancers. An assay system was developed that analyzed DNA isolated from stool for a panel of 15 point-mutations on K-ras, p53, and APC genes, Bat-26 (a microsatellite instability marker), and highly amplifiable DNA ("long DNA") that occur in colorectal neoplasia (Exact Sciences, Marbourough, MA). In a demonstration study using this panel freezer-archived stools were analyzed from 22 patients with colorectal cancer,

from 11 with large (>1 cm) adenomas, and from 28 with endoscopically normal colons. The sensitivity for the assay was 91% and 82% for cancer and large adenomas, respectively, with a specificity of 93%.

Clinical studies of the stool DNA panel assay
Several studies have been carried out in selected patients to determine the clinical sensitivity and specificity of the multitarget DNA assay panel for the detection of advanced colorectal neoplasia (see Table 7). A preliminary report from a prospective study performed in several Boston area hospitals of 38 patients who were already scheduled for subsequent colonoscopy showed

Table 7. Sensitivity and Specificity of the Multitarget DNA Assay Panel for the Detection of Colorectal Cancer

		Sensitivity	Specificity
Ahlquist, 2000*	22 patients	91%	93%
Syngal, 2002	38 patients	68%	——
Tagore, 2003	80 patients	62%	96%
Imperiale, 2003#	2507 patients	52%	95%

* Retrospective feasibility study using archived stool samples
\# Multicenter prospective trial in average-risk patients

that the sensitivity of the assay for detecting 28 invasive carcinomas was 68%. Sensitivity for detecting high-grade and low-grade dysplasia was 40% and 20%, respectively. In 21 patients who had repeat stool DNA tests after surgical resection of their cancers, 18 had no detectable DNA abnormalities. In another study of 80 patients with advanced colorectal neoplasia and 212 control subjects performed in Sacramento, CA, the sensitivity and specificity of the DNA stool assay for detecting cancer was 63.5% and 96.2% .

The Multitarget assay panel developed for average-risk screening (PreGen-Plus®, Exact Sciences, Marborough, MA) was marketed commercially last year. The assay tests for point mutations in the APC, K-ras, p53, and Bat-26 genes, plus a DNA integrity assay (a marker for abnormal apoptosis). According to the manufacturer, these markers constitute 65-70% of the mutations associated with advanced colorectal neoplasia. Not coincidently, this approximately equals the average sensitivity of the test in six clinical trials completed to date in selected patients. Currently, clinical stool samples are couriered for analysis to a laboratory in Burlington, NC and results return in 2-3 weeks, at a cost of $599 per case.

Prospective trials in average-risk populations
There is currently a National Cancer Institute-sponsored multicenter study of the PreGen-Plus assay versus FOBT, flexible sigmoidoscopy and colonoscopy. Results from this large trial are expected next year. Results from an Exact Sciences-sponsored prospective, double blinded multicenter study of 2,507 previously unscreened, average risk patients were recently reported. The study was designed to compare colorectal cancer screening with the PreGen-Plus assay with one time screening with a guaiac-based FOBT, Hemoccult II (Beckman-Coulter, Palo Alto,

CA), with results at subsequent colonoscopy as an endpoint. Of 31 cancers detected with colonoscopy, 16 (51.6% sensitivity) and 4 (12.9% sensitivity) were detected by the DNA assay and the FOBT, respectively. Sensitivity for detecting advanced adenomas for the DNA assay and the FOBT was 15.1% and 10.7%, respectively. The specificity for advanced neoplasia was similar for both tests at about 95%.

Unresolved issues

At the present time, pending the results of the second large average-risk trial, it is uncertain how the current DNA assay should be used for screening. When used alone, its sensitivity of the current assay for detecting cancers and advanced adenomas is inadequate as a one-time test. Some have suggested that the first wide use of the test may be in populations at high risk for colorectal cancer, followed by those with an intermediate-level risk such as Ashkenazi Jews, in whom APC mutation is thought to be more common in those who develop colorectal cancer. Another possible use for the test would be to combine it with other methods of screening in order to detect interval cancers that occasionally occur. For example, if direct colonoscopy screening is negative and repeat screening isn't recommended for 10 years, a check with the DNA assay might be performed at five years for additional reassurance that the patient is not developing an interval advanced neoplasm. Since the specificity of the test is high, false positives are unlikely in this setting.

Conclusions and Recommendations

The development of a very specific DNA-based stool screening test for colorectal neoplasia is one of the important clinical advances resulting from the remarkable molecular-genetic studies of colorectal cancerogenesis carried out over the past two decades. A commercially available multitarget genetic panel assay currently appears capable of detecting up to about 60% of colorectal cancers and many advanced adenomas according to several individual trials in selected patients and one large multicenter trial in an average risk population. The results of a second similar trial are pending. The place of stool DNA testing in the scheme of colorectal cancer screening and surveillance requires further consideration from clinicians, guideline panels, and policy makers. However it offers an additional stool test option for people unwilling to undergo colonoscopy.

DIETARY AND ENVIRONMENTAL FACTORS AND COLORECTAL CANCER PREVENTION

Colorectal cancer is a preventable disease. When people migrate from low incidence countries, such as Japan or Africa, to a high incidence country such as the United States, the rates of disease among their offspring increase to those of their adopted country. This indicates that there is something in the environment that is responsible. There is about a 9-fold difference in the incidence of colorectal cancer in the highest risk countries compared to the lowest risk countries. Based on these differences in incidence and the experience of migrants, experts have estimated that as much as 80% of colorectal cancer might be explained by environmental factors. The term "environment" in this instance does not refer to air or water pollution, but rather to dietary and lifestyle factors that are part of our environment. Although the environment is central to the etiology of most colorectal cancers, individual genetically

KEY POINTS & RECOMMENDATIONS

- Epidemiological evidence indicates that much of CRC is due to dietary and lifestyle factors.
- Red meat intake is associated with increased risk of CRC though the reasons are unclear.
- Though the evidence is mixed, a high fiber diet appears to reduce CRC risk and has other benefits to the gastrointestinal system.
- Whole fruits and vegetables are protective against CRC.
- Calcium supplements, in the presence of adequate levels of vitamin D, help protect against CRC.
- With the exception of calcium and folate, there is little reason to recommend supplements (e.g., anti-oxidant vitamins, trace metals) as a means to reduce CRC risk.
- Smoking increases CRC risk; however, there are numerous other reasons to avoid smoking.
- Alcohol increases the risk of CRC particularly in the presence of low folate levels.
- Physical activity reduces CRC risk while obesity increases it; the interaction between diet-exercise-obesity and CRC is complex.

determined susceptibility is also important. We are beginning, for the first time, to understand gene-environment interaction as it relates to colorectal cancer risk.

The implications of an environmental cause of colon cancer are clear. If we could identify and modify the relevant environmental factors, we could prevent most colorectal cancer. The challenge is to discover the environmental factors that are responsible and to change them.

Diet

Diet has received the greatest attention for obvious reasons - diet is a factor that changes markedly with migration and acculturation. Moreover, what we eat ends up in our colon, in one form or another. There have been a large number of studies of diet and colon cancer. As a consequence of a number of carefully conducted studies, we are beginning to reach some clarity on aspects of the diet that are associated with colorectal cancer. Table 8 summarizes the information on dietary and lifestyle factors that have been linked with colorectal cancer with a qualitative and subjective rating of the strength of the evidence. In almost all cases the evidence comes from large cohort studies.

Red meat

The majority of studies have shown an increased risk of colorectal cancer with high intakes of red meat. In the past, investigators reasoned that the risk from eating meat derived from the high fat content in meat. Recent studies in humans, however, have not shown a clear association with fat in the diet, although there is some preliminary evidence that transfatty acids (found in soft margarine and baked goods) might be associated with colorectal neoplasia. Currently, there

Table 8. Evidence for dietary and lifestyle risk factors for colorectal cancer

Strength of Evidence	Decreased Risk	Increased Risk
Convincing	**Physical activity** **Calcium***	**Obesity**
Probable	**Vegetables**	**Red meat** **Alcohol** **Cigarette smoking** **Heavily cooked meats**
Possible	**Fiber*** **Folate** **Selenium** **Vitamin D**	**Total fat** **Saturated fat** **Transfatty acids** **Tall stature**
Insufficient evidence	**Vitamins C, E**	**Beta carotene**

* Evidence available from randomized controlled trials

has been speculation that the risk associated with red meat is a consequence of the manner in which meat is prepared. Heterocyclic amines and polyaromatic hydrocarbons are produced when red meat is cooked at high temperature. These compounds may be carcinogenic.

Fiber

The fiber hypothesis has been popular since the 1970's when Denis Burkitt observed that African natives consumed a high fiber diet and had low rates of colorectal cancer. There were a number of possible biological explanations for a protective effect of fiber. For example, unabsorbed fiber can dilute potential carcinogens providing them less contact with the mucosa. Fiber can also bind to certain agents within the gut to decrease their absorption.

Recent studies have cast doubt on the cancer-preventing effects of fiber. A large, carefully conducted cohort study of nurses found no protective effect of fiber. The study is particularly credible because of its large size, prospective design, and ability to distinguish fiber from various sources including cereals, fruits, or vegetables. Two randomized trials of fiber also did not show that fiber prevented adenomas of the colon. However, a cohort study conducted in 10 European countries showed a clear protective effect of fiber with a consistent dose response relationship. Individuals in the highest category of fiber intake were about 40% less likely to develop colorectal cancer compared to individuals in the lowest category of fiber intake. The differences between the negative cohort studies and clinical trials in the United States and the positive cohort study in Europe could be due to basic differences in the overall diet or to the fact that the range of dietary fiber intake in Europe is broader. Based on the strong results of the European cohort study there are still reasons to think that eating a high fiber diet may be protective. Importantly, there are few downsides to a high fiber diet. High fiber may protect against constipation,

hemorrhoids and possibly diverticulosis. Soluble fibers may decrease cholesterol.

Fruits and vegetables
Some of the most compelling evidence suggests that vegetables can prevent colorectal cancer. Virtually all of a large number of studies of fruits and vegetables demonstrate a moderate protective effect. But not all of the studies are positive. The Nurses Health Study, for example, did not find a protective effect against colon or rectal cancer. There are a large number of chemicals from the plant kingdom that have been found to be anti-carcinogenic, anti-promotional, or anti-mutagenic in test systems. These chemicals operate at a number of different sites in the carcinogenic pathway.

Calcium and vitamin D
There is a large body of epidemiological evidence that supports a protective effect of calcium against colorectal cancer. The strongest evidence supporting a protective effect of calcium comes from a large US randomized controlled trial in which subjects were randomized to 1200 mg per day of calcium, in the form of calcium carbonate, or placebo to determine whether calcium supplements would decrease the incidence of recurrent colorectal adenomas. The study showed a 19% reduction in the overall development of new adenomas and a 24% reduction in the number of new adenomas in the calcium group compared to placebo. Very similar findings were reported from a smaller European trial in which calcium supplementation (2 gm/day) conferred a 25% (95% CI -29% to 57%) reduction in risk.

The mechanism for protection by calcium is not known. The US study showed that the effect of calcium was only found in subjects with higher levels of vitamin D suggesting that both calcium and adequate levels of vitamin D are necessary for the effect. Calcium in recommended amounts is virtually without side effects, and most people in the United States do not achieve the recommended daily allowance for calcium. For those reasons, physicians can recommend calcium supplements with the expectation that doing so will improve colon health and bone health. A variety of calcium compounds and dosage forms are available; selection is largely a matter of patient preference.

A possible protective effect of vitamin D on colorectal cancer was first proposed more than twenty years ago when it was observed the colorectal cancer rates were inversely related to sunlight exposure. In vitro and in vivo studies have shown that vitamin D and vitamin D analogs can inhibit colonic epithelial cell proliferation, induce differentiation and promote apoptosis. Many animal studies and epidemiological reports also support a protective effect of vitamin D.

Selenium
A large, randomized trial of selenium to prevent skin cancer found that colorectal cancer deaths were 60% less frequent among individuals who were assigned to selenium. The individuals randomized to selenium also had a decreased risk for lung, prostate and esophageal cancer. The results need to be confirmed. Iron is a proxidant leading to speculation that dietary iron or total body iron could increase the risk of colorectal cancer.

Micronutrients
Because fruits and vegetables are associated with lower risk of colorectal cancer, one might speculate that the protective effect could be due to vitamins, particularly the anti-oxidant vitamins A, C and E.

Anti-oxidants can inhibit free-radical reactions and thereby prevent oxidative damage to DNA. Unexpectedly, clinical trials of anti-oxidant vitamins have not shown a protective effect against colonic neoplasms. Additionally, there are randomized studies that show that individuals randomized to beta carotene may actually have higher rates for certain cancers. There is little reason to recommend anti-oxidant vitamins to prevent colorectal cancer. On the other hand, a daily multivitamin tablet has been recommended as a health promoting measure for people who may not be getting sufficient vitamins in their diet, although there is not yet strong evidence supporting this recommendation from randomized trials.

There are a number of studies that suggest that low dietary folate or low levels of folate measured in the blood might increase the risk for colorectal cancer. In the large Nurses' Cohort, for example, women who took multivitamins that contained folic acid for at least 15 years were about 75% less likely to develop colon cancer than women who never took supplements. Protection required supplement use for 15 years or more - shorter duration of use conferred no protection. The protective effect seen in the Nurses' study was primarily due to the folic acid component of the multivitamins, rather than the anti-oxidant vitamins.

The mechanism of protection by folic acid is not known, but folic acid serves as a methyl donor, and methyl groups may be involved both with DNA synthesis and repair.

Lifestyle

Smoking and alcohol

The majority of studies demonstrate an increased risk of colorectal cancer and adenomas with cigarette smoking. Information from large cohort studies of nurses and male health professionals have demonstrated significantly increased risks among smokers who had been smoking for at least 35 years. According to the International Agency for Research on Cancer, cigarette smoke contains over 60 carcinogens for which there is sufficient evidence of carcinogenicity in either laboratory animals or humans. While the precise explanation for the increased risk with cigarette smoking is not known, the public health implications of the finding are negligible since there are numerous other reasons why people should not smoke cigarettes.

Alcohol has been linked with an increased risk for both adenomas and cancer. The data are more consistent for adenomas, but the majority of studies also support an association between alcohol and cancer. The risk is increased for both men and women, and the risk extends to moderate drinkers, e.g. one drink per day.

Physical activity

Physical activity has been consistently shown to protect against colorectal cancer. Both leisure-time and occupational activities appear to be important. Lower rates of physical activity levels could help explain higher colorectal cancer incidence rates in industrialized countries. The mechanism responsible for the protective effect of exercise is not known. Some have speculated that increased physical activity increases propulsive activity in the large bowel providing less contact time between luminal carcinogens and the colonic mucosa. When diet is held constant, however, physical training has no

consistent effect on large bowel function. There is a complex relationship between diet, obesity and physical activity that is not fully understood. Fortunately, increased physical activity appears to protect not only against colorectal cancer, but also against cardiovascular disease, an even more common cause of mortality.

Obesity and insulin resistance

The amount of food, rather than the type, may also be important. Obesity has been linked to colon cancer in both men and women. Recent cohort studies have shown that obese women are 50% more likely to develop colon cancer, and obese men 80% more likely. The type of obesity may be important. When men become obese they tend to accumulate fat in the abdominal area, in contrast to women who accumulate fat in the hips and thighs. Abdominal obesity, in particular, is associated with insulin resistance and higher circulating levels of insulin. There is a growing literature that has linked insulin and insulin resistance with colorectal cancer incidence. Tall stature has also been shown to be a risk factor for colorectal cancer, even after controlling for body weight. Achieved adult height is importantly influenced by adolescent nutrition.

Constipation

There has long been speculation that constipation might be responsible for large bowel cancer due to more prolonged contact with the mucosa by carcinogenic substances in stool. The majority of studies show a small increase in risk, but individual studies suffer from small sample size, wide confidence intervals, and varied definitions of constipation. Neither constipation nor the use of laxatives appears to be important risk factors for colorectal cancer.

Conclusions and Recommendations

Sensible modifications in diet and lifestyle could have a favorable impact on the development of colorectal cancer. (Table 9) Although prospective interventional trials have not been completed that demonstrate a beneficial affect in terms of cancer from these recommendations, the epidemiological and experimental data are sufficiently strong to justify provisional dietary and lifestyle recommendations. At the same time it is important to recognize that the benefits of screening for colorectal cancer completely dominate the effects of primary prevention. In discussing strategies for cancer prevention with our patients, it is very important to make this clear.

Table 9. Practical, evidence-based recommendations for primary prevention

1. Eat a sensible diet, high in vegetables and fruits; limit red meat (< 2 servings/week).
2. Avoid obesity (BMI < 26 kg/m2)
3. Engage in regular exercise - 30 minutes/day moderate or vigorous
4. Consider supplements with calcium (1200 mg/day) and folic acid (1 mg)
5. Limit alcohol consumption; don't smoke
6. Participate in regular screening
7. Avoid health claims and fads based on weak data

NSAIDS/COX-2 AND CRC PREVENTION

Epidemiologic studies have reported a consistent reduction in the incidence of colorectal adenomas and colorectal cancer, as well as decreased colorectal cancer mortality associated with the use of aspirin and other non-steroidal anti-inflammatory drugs. These findings have stimulated considerable interest in prospective clinical trials to evaluate the impact of these agents on colorectal adenoma and cancer incidence and on colorectal cancer mortality. Emerging information about the mechanisms of action of both selective and non-selective COX inhibitors has contributed to our understanding of how these compounds may be used optimally.

Chemoprevention is the use of specific chemical compounds to prevent, inhibit orreverse carcinogenesis prior to the development of invasive disease. Adenomatous polyps and inherited syndromes of colon cancer are often employed in studying chemopreventive agents because when cancer itself is the endpoint very large numbers of patients are needed and observation periods of 10 to 20 years are usually required. But although adenomas are well demonstrated to be the precursors of colon cancer, issues remain including the small fraction of adenomas that become malignant and the "miss rate" of adenomas on colonoscopy. Nonetheless the adenoma and syndrome models have provided compelling evidence of the effectiveness of aspirin and other chemopreventive agents to prevent colon cancer.

Chemoprevention Studies of Aspirin and NSAIDs

NSAIDs have been studied as chemopreventive agents since the 1970's when it was clearly demonstrated that NSAIDs inhibited carcinogen induced colorectal cancer in rodents. More recently the min mouse, the mouse equivalent of human FAP created by inserting mutations into the APC gene, has been a valuable model for the study of both conventional NSAIDs and selective COX-2 inhibitors. Both classes of agents have been shown to restore apoptosis and inhibit polyp development.

Clinical case-control and cohort have documented a 40-50% reduction in colorectal adenomas, colorectal cancer incidence and colorectal-associated mortality in individuals taking NSAIDs. In a prospective cohort of 662,424 patients enrolled in the ACS Cancer Prevention Study II, risk of colon cancer death decreased about 40% in both men and women for those who reported using adult dose aspirin = 16 times per month. In the Health Professionals Follow-up study of 47,900 men, the relative risk of colorectal cancer was reduced about 32% when regular aspirin was used (defined as = 2 times/week). In a study of over 11,000 men and women in Sweden with rheumatoid arthritis (and presumably ingesting NSAIDs), colon cancer incidence was 37% lower and rectal cancer incidence was 28% lower than predicted from cancer registry data. In the prospective cohort Nurse's Health Study, 1,368 cases of confirmed distal colorectal adenoma were diagnosed between 1980 and 1998. Women who regularly used = 2 standard [325mg] tablets of aspirin per week had a relative risk for adenoma about 25% lower than non-regular uses. There was a relationship to dose in that women who used more than 14 tablets per week had about a 50% reduction in adenoma risk.

Recent randomized, controlled intervention studies of adenoma formation post polypectomy have also been compelling, and have demonstrated up to 56% adenoma formation reduction, delay in adenoma formation and effectiveness for both 81mg and 325 mg dose of aspirin. Table 10.

Table 10. Summary of Recent Intervention Studies of the Efficacy of Aspirin and NSAIDs in the Prevention of Colorectal Neoplasia

Intervention	No of Subjects in Intervention Group	Dose per day	End-point: Adenoma Recurrence	Duration of Intervention	RR/OR vs. Placebo (95% CI)
Aspirin	372	325mg	Any Adenoma	3 years	0.96 (0.81-1.13)
			Advanced Adenoma		
Aspirin	377	81mg	Any Adenoma	3 years	0.81 (0.69-0.90)
			Advanced Adenoma		
Aspirin	259	325mg	Any Adenoma	3 years	0.65 (0.46-0.91)
Aspirin (soluble)	126	160mg or 300mg	Any Adenoma recurrence	1 year	0.73 (0.52-1.04)
			Adenoma > 5mm	1 year	0.44 (0.24-0.82)

Chemoprevention of Familial Adenomatous Polyposis (FAP)

Four randomized placebo controlled trials have determined that sulindac at a dose of 300-400mg for 4 to 6 months reduces the number and size of adenomas in the rectum of FAP patients by up to 70%. But sulindac resistant adenomas may develop during drug treatment and "breakthrough" can occur upon discontinuation. A recent randomized, double-blind placebo-controlled study failed to show an effect of sulindac on the development of adenomas in young FAP patients genotypically affected but who had not yet displayed adenomas.

The selective COX-2 inhibitor, celecoxib, at a dose of 400mg twice daily has been shown to reduce the mean number of rectal polyps in patients with FAP by 28%. This led to the approval by the US Food and Drug Administration of the use of celecoxib as a pharmacological adjunct for the reduction of polyp numbers in patients with FAP together with routine care including endoscopic surveillance and surgery. Several prospective randomized controlled studies are in progress on the effectiveness of selective COX-2 inhibitors (celecoxib, rofecoxib) in preventing the recurrence of sporadic colorectal adenomas, either when used singly or in combination with other compounds. These data should be available by 2006. The efficacy of these compounds will determine whether they will be useful in reducing the risk of colorectal cancer compared with periodic colonoscopy.

Safety

The safety threshold has to be very high for a chemopreventive agent if one is considering intervention in asymptomatic individuals. The adverse public health impacts of present aspirin and NSAID use are significant in view of an estimated 107,000 hospitalizations and 16,500 related deaths annually in the U.S. The most common adverse effect of NSAIDs is gastro-duodenal ulceration; it is estimated that significant gastrointestinal bleeding occurs in 1 in 100 people taking aspirin for over 2 years. The severity of gastrointestinal bleeding is correlated with increasing dose as is another serious adverse outcome, intracranial bleeding. Risk factors associated with the development of NSAID GI complications include advanced age, history of prior ulceration, concomitant use of corticosteroids and anticoagulants. Other adverse effects of NSAIDs include renal dysfunction, exacerbation of hypertension and hypersensitivity reactions.

The propensity by NSAIDs to cause peptic ulceration is largely attributed to COX-1 inhibition and possibly could be ameliorated by concomitant use of proton pump inhibitors at a significant increase in cost. The use of mildly selective (e.g. nabumetone) or highly selective COX-2 inhibitors (COXIB's) (rofecoxib, celecoxib) relative to COX-1, is associated with a lower risk of peptic ulceration. Of some concern with the use of COXIB's is their potential to inhibit prostaglandins without affecting TxA2. This effect could contribute to an increased predisposition to vascular thrombosis particularly in individuals with underlying atherosclerosis. Considerable attention is being focused on cardiovascular safety by Data and Safety and Monitoring Boards in prospective trials of celecoxib and rofecoxib.

Conclusions and Recommendations

Chemoprevention for colorectal neoplasia has the potential to reduce mortality from this disease especially when used in combination with beneficial lifestyle factors and periodic screening. The ideal agent would need to be safe, non-toxic and without significant side effects. As noted above, aspirin and NSAIDs have significant side effects although COX-2 inhibitors cause fewer side effects.

In approaching the issue of safety and efficacy, it is appropriate to cite the U.S. Preventive Services Task Force's position. It recommends the use of low-dose aspirin as primary prophylaxis against myocardial infarction only in those at high risk of coronary artery disease. However, recent studies suggest that the optimal doses for cardiovascular and colorectal neoplasia protection differs considerably. Substantially greater doses of aspirin may be needed for a significant degree of colorectal neoplasia protection although even with relatively low doses, a minor chemopreventive benefit in the large bowel may be observed. For the present, those at average risk should reply primarily on appropriate lifestyle, screening and surveillance methods to reduce colorectal neoplasia while awaiting the results of additional trials. Aspirin use may be indicated, however, for those at higher risk (previous colon cancer, advanced adenomas or a strong family history). Such individuals should be carefully screened to avoid those with a history of peptic ulcer or hemorrhagic stroke.

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