COLORECTAL CANCER: UPDATE ON RECENT ADVANCES AND THEIR IMPACT ON SCREENING PROTOCOLS

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As the third leading cause of cancer cases and deaths in the United States, colorectal cancer has been an area of intense interest. The objectives of this article are, through a review of the literature published between 1995 to 1998, to examine current trends in the epidemiology of colorectal cancer, new information on genetic, dietary, and other risk factors; to evaluate the effectiveness of current screening guidelines for various populations; to review information on chemoprevention; and finally to examine new concepts on the horizon in the area of colorectal cancer research. Much of the recent research in the field has focused on etiology, dietary, and other risk factors. Many genetic factors have been discovered, which serve to elucidate the mechanism of pathogenesis of colorectal cancer as well as offer possible targets for treatment strategies. Dietary and risk factors for colorectal cancer may pave the way for chemoprevention. In light of the most recent information on colorectal cancer, one is able to more accurately assess current screening guidelines for their effectiveness in all populations based on epidemiologic data, as well as evaluate more novel screening strategies for their possible utility in the future. In addition to a review of the most up-to-date literature, the authors also provide their recommendations for screening based on the evidence in which the review of the literature provides. Finally, current and future treatment options are discussed. It is our hope that the physicians will find this review useful in the evaluation and care of patients at risk of developing colorectal cancer. (*J Natl Med Assoc.* 2000;92:222–230.)

Key words: cancer ♦ colorectal ♦ cancer screening

The field of colorectal cancer research has seen many advances over the past decade in the characterization of the disease through its epidemiology, possible etiologies, and molecular genetics. These new advances will necessarily affect previously accepted views on treatment and screening guidelines for colorectal cancer. Although the efficiency and cost effectiveness of various screening modalities is still being debated, this article will approach the subject through a review of the most recent findings in this area of research. Our goals are to objectively examine current trends in the epidemiology of colorectal cancer, new information on genetic, dietary and environmental risk factors, effectiveness of current screening guidelines for various populations, the possible role of chemoprevention, and finally what is on the horizon in the field of colorectal cancer research. It is our hope that this article will provide the primary care physician with a thorough

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review of the pertinent information that will enable him or her to arrive at a diagnosis, treatment, subsequent counseling, and follow-up plan that is most appropriate for an individual patient.

EPIDEMIOLOGY

Colorectal cancer is estimated to be the third leading site of new cancer cases, preceded by prostate and lung in men, and by breast and lung in women.[1] This translates to 131,600 predicted cases of colorectal cancer in 1998; 95,600 due to cancer of the colon and 36,000 due to cancer of the rectum.[1] These numbers reflect a decrease in incidence from 53 per 100,000 in 1985 to 44 per 100,000 in 1994.[1] Demographic data suggest that colorectal cancer is primarily a disease of older populations (>55) except in cases of familial syndromes in which patients may present in their 30s or younger, such as hereditary nonpolyposis colorectal cancer (HNPCC), which accounts for approximately 4% to 6% of colorectal cancers.[2,3] It has been shown that incidence of colorectal cancer is directly related to increases in body mass index (BMI).[4] There are also anatomic, race, and gender variations in the incidence and distribution of colorectal cancer that may have a significant impact on future screening practices and recommendations. Blacks and women are more likely to develop disease proximally, whereas Asians have a predominance of rectal lesions and whites and non-white Hispanics have a large proportion of left-sided lesions.[5–7] In the United States, black men have the highest incidence (per 100,000) of colorectal cancer at 523.2 followed by white men at 427.2, white women at 334.5, and black women at 322.5.[1]

It is expected that 56,500 will die of colorectal cancer in 1998, which places the disease third in leading sites of cancer death in both men and women and represents a 25% decrease in mortality for women and a 13% decrease for men.[1] This rate, however, does not apply to all groups. Although blacks in the United States are more likely to die from cancers in general than any other group,[1] this does not appear to be the case in colorectal cancer. In fact, according to the American Cancer Society, there are no differences between whites, blacks, and Asian and Pacific Islanders in America.[1,7] However, when adjusted for age there are some differences. Age-adjusted mortality by race in the United States (per 100,000) is approximately 27.6 for black men, 24.2 for white men, 20.8 for black women, and 16.4 for white women.[2] According to Gore,[2] this suggests three levels of cancer risk, the highest being comprised of African-Americans, whites, and Japanese Americans, the intermediate level being comprised of Chinese and Filipino Americans, the lowest level being comprised of Mexican and Native Americans. Gore's premise[2] is supported by the ACS.[1] The ACS predicts an increase in incidence and mortality due to colorectal cancer in women compared to men.[1] This is in contrast to information presented by Breivik et al.,[8] which suggests that post-menopausal hormone replacement therapy (PMHRT) is protective and leads to a decreased incidence in women who are taking PMHRT. However, it must be noted that the final data regarding colorectal cancer incidence and PMHRT has not yet been definitively interpreted. Understanding the changes in the epidemiology of colorectal cancer is an integral component in the decision-making process when setting guidelines and recommendations.

ETIOLOGY, DIETARY, AND RISK FACTORS

Genetic Factors and Polyposis Syndromes

Many genetic factors and polyposis syndromes have been implicated in the etiology and pathogenesis of colorectal cancer. Foremost among the genetic factors thought to play a role in the development of colorectal cancer are the *p53* tumor suppressor gene, the gene deleted in colorectal cancer (*DCC*), and the proto-oncogene K-*ras*. It is believed that functional loss of *p53* by any mechanism leads to a loss of the ability of the cell to self-destruct in response to damages to DNA. This results in unchecked mitosis of damaged cells.[9] According to Goh et al.,[10] *p53* mutations are found in approximately 50% of colorectal cancers. Additionally, distal cancers seem to be more likely to have a *p53* mutation than cancers located in other areas of the colon or rectum.[8] *DCC* is a tumor suppressor gene that codes for a cell adhesion molecule. Loss of this gene may thus promote metastases and indicates a poor prognosis.[3,9,11] The proto-oncogene K-*ras* is also implicated in the formation of colorectal cancer. K-*ras* is a member of the *ras* gene family, which includes several genes, but K-*ras* is the most associated with colorectal cancer. This gene produces a GTP-binding protein utilized in the signal transduction pathway for growth receptors.[9] According to Blum,[11] K-*ras* mutations are the most frequent of all

mutations found in colorectal cancers and the frequency of K-*ras* mutation positively correlates with the size of the lesion and amount of dysplasia. Support for this growth hormone/receptor mechanism can be found in such evidence as the increased incidence of colorectal cancer in patients with acromegaly, a disorder in which response to growth hormone by growth receptors is altered leading to abnormally rapid and prolonged growth.[3]

In addition to *p53*, *DCC*, and K-*ras*, there are two gene families associated with familial syndromes. These genes are the mismatch repair genes *hMSH2*, *MLH1*, *PMS1*, and *PMS2* and the adenomatous polyposis coli gene (*APC*). Mutations in the mismatch repair genes are believed to be responsible for the two forms of hereditary nonpolyposis colorectal cancer (HNPCC), Lynch syndromes I and II, by causing phenotypic microsatellite instability.[3,9,12] Lynch syndrome I is characterized by development of proximal colorectal cancer at a mean age of 44 years, whereas Lynch syndrome II is also characterized by early onset of proximal colorectal cancer as well as cancer of the endometrium, ovaries, and other organs.[3] According to a study by Voskuil et al.[12], HNPCC families have an increase in relative risk over successive generations, which highlights the familial and genetic nature of this condition. The *APC* gene produces a β-catenin binding protein, the loss of which may cause disturbances in cell cycle regulation and apoptosis.[9] *APC* is implicated in development of the familial syndromes FAP (familial adenomatous polyposis, also known as Gardner's syndrome) and Turcot's syndrome.[3] FAP is characterized by autosomal dominant transmission and inevitable colorectal cancer between 34 and 43 years of age.[3] Turcot's syndrome is a variant of FAP, which is associated with medulloblastomas.[3] Other polyposis syndromes include Peutz–Jeghers, Juvenile Polyposis Coli, Ruvalcaba's, and Cronkhite–Canada. All except for Peutz–Jeghers syndrome are characterized by juvenile polyps and a high incidence of colorectal neoplasia. Peutz–Jeghers syndrome is characterized by hamartomous polyps primarily in the small intestine but also less frequently in the stomach and colon. Although there are other genes that may be involved in the development of colorectal cancer, *p53*, *DCC*, K-*ras*, the mismatch repair genes, and *APC* represent those most cited as possible or known etiologies in our review of the recent literature.

Diet and Chemoprevention

Although much of the theory supporting the chemopreventive properties of certain nutrients is sound, the degree to which these nutrients independently play a role in the prevention of colorectal cancer has not been completely elucidated. There are several possible mechanisms cited as predisposing factors for the development of colorectal cancer. It has been proposed that bile acids, which are produced through the metabolism of dietary fat, may be tumorigenic. According to some researchers, these bile acids can be complexed with calcium and vitamin D to form insoluble compounds that would inhibit the tumor-producing effects of dietary fat.[13,14] This assertion is supported by data that suggest that increasing distance from the equator, and thus decreased exposure to sunlight and vitamin D production by the body, is directly related to increasing incidence of colorectal cancer.[15] In addition, the majority of the studies on this relationship reviewed by Kroser et al.[15] show a statistically significant inverse association between calcium and vitamin D intake and colorectal cancer.

Another possible mechanism for the development of colorectal cancer is the production of damaging free radicals by colonic bacteria. It has been proposed that antioxidants, such as tocopherol (vitamin E) and carotenoids may reduce these free radicals thus eliminating their cancer-causing effects.[14,16] There is further evidence that γ-tocopherol, which is preferentially secreted into fecal material, may have a more protective effect than α-tocopherol, which is secreted mostly into the plasma.[16] Both α- and γ-tocopherol are vitamin E, however they have different stereochemistry, which accounts for their slightly varied chemical effects. Although a large prospective study on women[17] did not discriminate between α- and γ-tocopherol, it did show that vitamin E intake (regardless of stereochemistry) is inversely related to colorectal cancer.[16] A theory with the same basic premise implicates iron as the cause of free radical generation, and data support the notion that an increase in iron intake from pharmacological sources may be related to an increase in colorectal cancer in animal models.[14,16]

The amount and type of fiber in the diet has long been suspected to play an important role in the pathogenesis of colorectal cancer and is one of the most consistently observed inverse associations to

colorectal cancer.[15] For instance, there is believed to be a difference between the fiber provided by cruciferous vegetables, such as spinach and cabbage, and that provided by fruits, other vegetables, grains, and starches. The exact mechanism of this difference in types of fiber has yet to be determined. There are several proposed mechanisms as to how increased fiber intake may alter risk profiles. Fiber may bind bile acids, which have been suspected of promoting neoplasia. Fermentation of fiber by bacteria may produce the short-chain fatty acids believed to be protective against colorectal cancer, have a dilutional effect on carcinogens by increasing bacterial mass, or alter gut pH. Fiber may also increase fecal transit time thus reducing duration of exposure to carcinogens.[3,13,15] There is also evidence that cruciferous vegetables (spinach and cabbage) may have extra benefit outside of that provided by their bulk-increasing effect.[3]

The largest body of new information on chemoprevention, however, involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The antineoplastic property of NSAIDs has been recognized since 1980, and its association with reduced risk for colorectal cancer has been reported since Kune et al.'s 1988 study.[18,19] The proposed mechanism for NSAID reduction in risk of colorectal cancer and adenomas is centered around the inhibition of the cyclooxygenase (COX) pathway in prostaglandin production.[18,20–22] It has been shown that, after undergoing neoplastic change, colonic mucosa produces increased levels of several prostaglandins, notably PGE_2.[18,20–22] Along with the COX inhibition, NSAIDs may also decrease cell proliferation, induce apoptosis, and increase immune surveillance, according to Shiff et al.[18,23–30] The Physician Health Study shows no association with colorectal cancer after 5 years of aspirin use, but other data suggest that aspirin or NSAIDs must be taken for at least 9 years before the decrease in risk is observed.[18,31] In a study by Ruffin et al.,[20] it was determined that 81 mg of aspirin taken daily substantially reduced colorectal mucosa prostaglandins. Along with increasing knowledge on the role of diet in the pathogenesis of colorectal cancer, the possibility of NSAID prophylaxis may soon offer the clinician an opportunity to help those most at risk for developing this form of cancer.

Risk Factors

Although genetics play a large part in the development of colorectal cancer, there are several groups at increased risk secondary to lifestyle and environmental factors. Among those factors shown to increase risk are weight or BMI, smoking, alcohol use, physical activity, occupation, and infection with certain microorganisms. According to a study by Caan et al.,[4] increased weight and BMI are significantly associated with colorectal cancer in men >55 years and women <70 years of age. A comparison of the highest and lowest quintiles for BMI and weight shows an odds ratio of 2 in men and 1.5 in women.[4] A lack of physical activity has been linked to an increased incidence of colorectal cancer that is independent of weight or BMI.[15] There appears to be a weak association between smoking and the risk for colorectal adenomas. Although not statistically significant, smoking is associated with decreased levels of folate, which may aid fruits and vegetable in their protective effects.[32] According to an article by Kroser et al.,[15] the smoking of cigars and pipes has been found more often in cases than controls in most studies, possibly due to a tendency to swallow more carcinogens with cigars and pipes than cigarettes. A study by Giovannucci et al.[33] shows a stronger correlation with a threefold increase in risk when comparing smokers to nonsmokers. Unlike smoking, alcohol has been associated with increased risk of colorectal adenomas, more so than colorectal cancer.[32] The proposed mechanisms are a reduction in folate caused by alcohol and its metabolites, alteration of bile acid composition, increased proliferation of colonic mucosa, and/or generation of carcinogens by the liver such as acetaldehyde metabolites.[3,15,32] Occupational exposure to asbestos has been linked more to rectal than colon cancer.[15] There is also a weaker association with pesticides and herbicides.[15] Finally, one article of those reviewed mentioned that *Streptococcus bovis* infection has been linked with colorectal cancer. Gore[3] proposes that any patient presenting with *S bovis* endocarditis or bacteremia should be evaluated for colorectal changes after the infection has been treated; however, the author does not provide any specifics on timing of treatment or follow-up screening.

SCREENING

Screening Methods

There are five criteria to justify screening for a disease:

1. The disease must have a significant impact on the quantity or quality of life.

2. The frequency of the disease must be sufficient enough to justify the cost and risk of screening.
3. Acceptable methods of treatment must be available.
4. The disease must have an asymptomatic phase, and treatment during this phase must yield results superior to those obtained by delaying treatment until symptoms appear.
5. Tests must be available at a reasonable cost and risk to detect the disease in the asymptomatic phase. The fifth criteria is the cause of much debate.

There are currently four widely used and accepted diagnostic methods capable of detecting colorectal adenomas and cancer:

1. The fecal occult blood test (FOBT).
2. Flexible sigmoidoscopy.
3. Barium enema examinations.
4. Colonoscopy.

We will evaluate all of these methods for cost, risk, and effectiveness.

The FOBT is the least expensive of all colorectal screening tools, which makes it the most widely used in asymptomatic, low risk populations.[34,35] However, there are problems with the FOBT that make it a poor choice, regardless of the cost. Modifications must be made in the manner in which the test is administered to make it more accurate. One weakness of the FOBT is its high false-positive rate, which can, in part, be attributed to ingestion of red meat, certain vegetables, and aspirin before the test.[34] This situation is easily remedied by placing the patient on dietary restriction several days before the test. A dilemma not so easily rectified is false results due to bleeding from sources other than colorectal polyps or cancers such as hemorrhoids, peptic ulcers, and diverticulitis.[36] Another weakness of the FOBT is the trend of widely varying reports on sensitivity, anywhere from 26%–92% depending on the study.[36] The higher sensitivity is obtained by rehydrating the test with a drop of deionized water before applying the reagent.[36] However, according to Levin et al.,[35] increasing the sensitivity in this way leads to a 2.5-fold decrease in the positive predictive value and thus a decrease in specificity from 97.7% to 90.4%. This decrease in specificity inevitably will lead to an increase in follow-up costs. Yet a third drawback of this guaiac-based test is the fact that colorectal polyps and cancers do not bleed continuously. Hence, a negative FOBT result does not mean that there is not a polyp or even a colorectal carcinoma, just that it is not bleeding at the time of the test.[34] For these reasons, even though the specificity and sensitivity of some brands of fecal occult tests is acceptable,[35] the FOBT cannot be used as the only preliminary test.[34] An alternative to the FOBT, as it is currently administered, would be an immunochemical version. Immunochemical tests only detect immunoreactive globin and hemoglobin. Furthermore, the immunochemical version is not affected by diet and generally requires only a single test.[36] Data indicate a sensitivity and specificity of 70%–90% and 95%, respectively.[36] Some researchers have even proposed using the immunochemical test to confirm a positive guaiac in order to provide acceptable sensitivity and specificity.[37]

Flexible sigmoidoscopy is another option for screening. It enables visual examination of the rectum and distal colon and is the least expensive of the visual methods.[34] Flexible sigmoidoscopy is currently a component of the ACS guidelines for colorectal cancer screening.[1,38,39] There is evidence to suggest that screening by flexible sigmoidoscopy can decrease mortality due to left-sided colorectal cancer and that the sensitivity for patients with adenomas is approximately 50%.[38] The unit cost of flexible sigmoidoscopy is $80 and the cost per added year of life is $11,947, if the procedure is performed alone every 5 years and $13,639 if performed once every 5 years with the FOBT as recommended by the ACS.[1,34,40] There are several drawbacks to this screening procedure such as its inability to detect proximal cancers, its low sensitivity, its invasiveness, and the frequent failure to visualize the entire sigmoid colon during the procedure.[38]

The barium enema examinations, single and double contrast, are also visual examinations that enable the examiner to see the entire colon while being minimally invasive.[34] The double contrast barium enema is part of the ACS recommendations for screening for colorectal cancer, and according to Glick et al., the test has a sensitivity of 70% and a specificity of 90% for polyps and cancers.[1,40] The median sensitivity according to Gelfand is 94%, but the author qualifies that the sensitivity varies by institution according to the experience of the examiner.[34] For this reason, unlike flexible sigmoidos-

copy, double contrast barium enema can be used alone as a screening method once every 10 years according to the ACS.[1] The unit cost of the double contrast barium enema is $131 and the cost per added year of life is $21,887 if performed every 10 years.[40] The major disadvantage to the enema examination is allergic reaction to the contrast material. Even after taking allergic reactions into consideration, the double contrast barium is the safest method for viewing the colon and rectum.[34] One question that has been raised is the possible danger of radiation exposure over a lifetime; however, this complication appears to be minimal and does not contribute significantly to an increase in secondary cancers due to radiation exposure.

Colonoscopy is generally considered the gold standard for detection of colorectal polyps and cancer and is also used to perform a biopsy or to remove polyps during the procedure.[34] The sensitivity and specificity of colonoscopy is estimated to be 90% and 100%, respectively.[40] However, in cases where the double contrast barium enema is used as the gold standard, it has been determined that colonoscopy misses 10%–20% of all lesions detected by the enema study.[34] The cost of colonoscopy is $285, $434 with polypectomy, and the cost per added year of life is $22,171 if the test is performed once every 10 years as recommended by the ACS.[1,40] Several complications associated with colonoscopy, such as perforation, hemorrhage, and contamination of the colonoscope with transmission of colonic bacteria to patients, all of which would alter the cost per added year of life, have brought forth serious criticisms of the procedure.[34]

In short, a review of the literature shows that, although the FOBT is the least expensive and does indeed reduce mortality due to colorectal cancer, it is hardly the most effective method of screening.[34,41] In fact, according to Eddy's analysis of the cost effectiveness of various screening techniques using mathematical modeling, examinations that allow for a full examination of the colon, such as colonoscopy or double contrast barium enema, are the most effective.[41] The increase in cost is balanced by the fact that the tests need only be employed once every 10 years in an average risk population according to ACS guidelines.[1]

Organizational Recommendations

Many organizations have set forth their guidelines and recommendations for the screening of colorectal cancer. The ACS recommends that, beginning at age 50, men and women have either FOBT yearly plus flexible sigmoidoscopy (FSIG) every 5 years *or* colonoscopy every 10 years *or* double contrast barium enema every 5 to 10 years. A digital rectal examination (DRE) should be done with the sigmoidoscopy, colonoscopy, or double contrast barium enema. The ACS further states that those at increased risk for developing colorectal cancer, such as those who have had colorectal cancer in the past, those with inflammatory bowel disease or polyps, those who have a first degree relative with or a strong family history of colorectal cancer or polyps, or those who are members of families with hereditary colorectal cancer syndromes should undergo the previously mentioned screening procedures earlier than 50 years of age (although they do not state how much earlier).[1]

The National Cancer Institute (NCI) recommends a DRE at regular checkups, and beginning at age 50 an annual FOBT and FSIG every 3 to 5 years.

The American Gastroenterology Association (AGA) suggests an FOBT each year and an FSIG every 5 years with biopsy of polyps <1 cm for people at average risk. If adenomatous polyps, polyps >1 cm or cancers are found, the patient should be recommended for colonoscopy with polypectomy and/or biopsy. Those with tubular adenomas should consult their physician. FOBT and FSIG can be combined in the manner mentioned above. Double contrast barium enema (DCBE) can be offered every 10 years and colonoscopy every 10 years (unless otherwise indicated by abnormal findings on FSIG as described above).[42] The AGA's guidelines state that for those who have a first degree relative with or a strong family history of colorectal cancer or polyps, screening should be the same as that for average risk groups but begin at age 40 instead of age 50. For those who are members of families with hereditary colorectal cancer syndromes, such as FAP or HNPCC, should receive genetic testing and counseling to determine their gene status. In the case of FAP, gene carriers or indeterminant cases should receive FSIG annually beginning at puberty and if polyps are found consider colectomy. In the case of HNPCC, patients should have an examination of the entire colon every 1 to 2 years between 20 and 30 years of age and annually after age 40. Patients in whom large or multiple adenomatous polyps have been found and removed should have an examination of the colon 3 years after removal

and every 5 years subsequently. Those with a personal history of colorectal cancer should have a complete examination within 1 year of resection then again 3 years after and, if normal, every 5 years subsequently. People with inflammatory bowel disease should have a surveillance colonoscopy at a frequency consistent with the extent and duration of disease.[42] The AGA screening guidelines have been endorsed by the ACS, the American College of Gastroenterology, the American Gastroenterological Association, the American Society of Colon and Rectal Surgeons, the American Society for Gastrointestinal Endoscopy, Crohn's and Colitis Foundation of America, the Oncology Nursing Society, and the Society of American Gastrointestinal Endoscopic Surgeons.

Authors' Recommendations

After a thorough review of the current literature, the authors' propose, for those patients at average risk, screening with a rehydrated version of FOBT annually plus FSIG every 5 years *or* DCBE every 5 years. DCBE is preferred because it allows for viewing of the entire colon without the risk associated with colonoscopy. Additionally, use of DCBE can be considered adequate screening for those populations, such as blacks and women, in which proximal or right-sided lesions predominate. Re-evaluation of the immunochemical test for occult blood should occur as data on sensitivity and specificity become available. For high risk populations as defined by the ACS, the recommendations outlined by the AGA above are found to be more than adequate.

Concepts on the Horizon

As we gain more knowledge about the etiology, molecular genetics, and risk factors for colorectal cancer, we are able to develop new approaches to screening and predicting the prognosis for this particular cancer. These novel approaches use antigens, enzymes, and DNA to determine who has primary colorectal cancer, a recurrence, or even the prognosis of a patient. Fecal carbonic anhydrase II is an enzyme in the mucosa of the large bowel responsible for the conversion of CO_2 and H_2O to bicarbonate. It has been found that malignant mucosa expresses much less of this enzyme than normal colonic mucosa and that reduced levels may be particularly associated with the promotion stage of carcinogenesis.[43] Carcinoembryogenic antigen (CEA) is an antigen shed from tumor cell surfaces, and, although it is often found to correlate with colorectal cancer stage, it is not specific for colorectal cancer.[3] For this reason, CEA is not yet considered appropriate as a screening tool, although it is still an excellent marker for recurrence. Mutations of the adenomatous polyposis coli (*APC*) gene are implicated in the development of FAP, Gardner's syndrome, and Turcot's Syndrome.[3] Blum[44] has determined that characterizing DNA from peripheral blood, stool, or intestinal biopsies would be a genetic approach to screening for this familial condition, which leads to colorectal cancer. Tominaga et al.[45] have suggested screening for truncated APC proteins found in colorectal cancer cells, because mutations in the gene lead to an abbreviated APC protein. It has been proposed that CA19-9, a carbohydrate antigen that may function in invasion and metastasis, may be detected in tumor tissue and serum and used to assess patients' risk of recurrence and death and possibly which patients will benefit from adjuvant therapy.[46] Indeed, the conclusion of Nakayama et al's. study is that detection of CA19-9 identified patients at high risk of cancer recurrence and death.[46] Yet another novel concept is to measure the amount of DNA present in the stool. There is evidence that neoplastic colonic mucosa sheds DNA fourfold in excess of what normal colonic mucosa produces.[47] This would allow detection of the carcinogenic process possibly before symptoms such as bleeding appear.

Although these ideas are still in their preliminary stages, they offer remarkable promise for a more efficient, accurate, and inexpensive way to screen for colorectal cancer and its precursor lesions.

TREATMENT

Although the primary focus of this article is new information on prevention of colorectal cancer, it is appropriate here to mention some of the strategies being employed to treat colorectal cancer. Surgery has been and remains the primary treatment for colorectal cancer. There is increasing emphasis on adjuvant and neoadjuvant chemotherapy in an effort to prevent recurrence and to improve survival.[48] As in all other areas of colorectal cancer research, the topic of treatment is enjoying as much growth in information and possibilities as the areas of etiology and chemoprevention. The mainstay of pharmacological therapy for the past 40 years has been 5-flu-

orouracil (5-FU).[48–51] Although 5-FU is still the foundation for chemotherapy, many new agents for colorectal cancer are being researched or are currently in trials. These new pharmacological agents include antifolates, topoisomerase inhibitors, platinum analogues, *ras* inhibitors (including K-*ras* and other genes in the *ras* gene family) and inhibitors of other signal transduction pathways, biological response modifiers such as recombinant interferon and recombinant interleukin-2, monoclonal antibodies, gene therapy, and even a colorectal cancer vaccine.[48–52] Although the goal is always prevention, there are many exciting treatments in the future for colorectal cancer.

CONCLUSION

The field of colorectal cancer research has seen many advances over the last decade and will continue to see many more in the decade to come. As we focus our attention on the prevention of colorectal cancer, it is important to continually consider not only the cost of prevention, but the quality of the lives that we affect by our policies.

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