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Colorectal Cancer: Epidemiology, Etiology, and Molecular Basis

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Epidemiology

Colorectal cancer (CRC) is a disease with a major worldwide burden. It is the fourth most frequently diagnosed malignancy in both sexes with almost 1 million people developing CRC annually.[1] CRC is the third most common cause of cancer death in the world, responsible for 630,000 deaths annually.[2] In the United States, CRC is the third most common cancer in men and women and the second most common cause of cancer death overall. CRC accounts for 11% of cancers diagnosed.[3] It is estimated that 147,000 cases will be diagnosed in the United States in 2004 and that there will be 57,000 deaths from the disease.[3]

The worldwide incidence of CRC is increasing; in 1975, the worldwide incidence of CRC was only 500,000.[4] In Western countries, some of the increase is attributable to the aging of the population; however, in countries with a low baseline rate of CRC, an increase in incidence after adjustment for age has been found. Before 1985, the age-adjusted incidence of CRC in the United States had been increasing; however, since this time, the rates have declined an average of −1.6% per year[5] (Figure 23-1). This reduction has been mainly confined to the Caucasian race and is largely limited to a decrease in the incidence of distal cancers. Therefore, the recent decrease in incidence in the United States may be attributable to screening, specifically screening with flexible sigmoidoscopy,[6] although other factors are likely to have influenced this trend. The incidence of proximal cancers has remained relatively stable over the same time period.[5,6] Currently, the overall probability of an individual developing CRC in United States over a lifetime is almost 6%.[3]

From a population perspective, age is the most important risk factor for CRC. CRC is predominantly a disease of older individuals; 90% of cases are diagnosed over the age of 50.[3] The risk of CRC continues to increase with age (Figure 23-2). The incidence per 100,000 people aged 80–84 is more than 7 times the incidence in people aged 50–54. However, CRC can occur at any age and the incidence of CRC occurring in patients younger than age 40 may be increasing.[7]

In the United States the risk of CRC differs by gender. The incidence of CRC is more than 40% higher in men than women.[5] Overall, the incidence of CRC in men is 64 per 100,000 males as compared with 46 per 100,000 females.[3] In addition, the ratio of colon to rectal cancer differs in the United States by gender; the ratio of colon to rectal cases for women is 3:1 as compared with 2:1 for males.[3]

Race and ethnicity influence CRC risk; Ashkenazi Jewish individuals seem to be at a slightly increased risk of CRC.[8] At least part of this increased incidence may be attributable to a higher prevalence of the *I1307K* mutation of the adenomatous polyposis gene, a mutation that confers an increased risk of CRC development. The *I1307K* mutation is found in 6.1% of unselected Ashkenazi Jewish individuals and 28% of Jewish individuals with CRC[9] whereas the mutation is rare in other populations.[10] In the United States, the incidence of CRC is higher in African-Americans of either gender as compared with Caucasians. Asian American/Pacific Islanders, Native Americans, and Hispanic Americans experience a lower incidence of CRC than Caucasians[3,11] (Table 23-1). African-Americans have not experienced the substantial reduction in incidence of CRC found to have occurred in Caucasians; before 1980, incidence in African-Americans was actually lower than in Caucasians. In African-Americans, the increased rate of cancer is predominantly attributable to a higher rate of proximal cancers.[12–14]

The Surveillance Epidemiology and End Results registry (a National Cancer Institute population-based cancer registry representing 14% of the population in the United States) reports cancer incidence and stage over time (Table 23-2). Between 1992 and 1999 for all patients diagnosed with CRC, 38% of patients were diagnosed with localized disease, 38% with regional disease, and 19% with metastatic disease. Five percent of patients were unstaged. As a proportion of total cases, African-Americans were more likely to present with advanced disease; 24% of African-Americans have metastatic

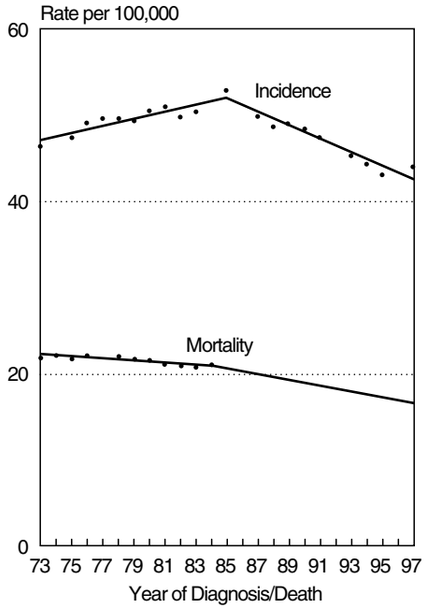

FIGURE 23-1. CRC incidence and death rates in the United States 1973–1997. (From Ries et al.[5] Copyright © 2000 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

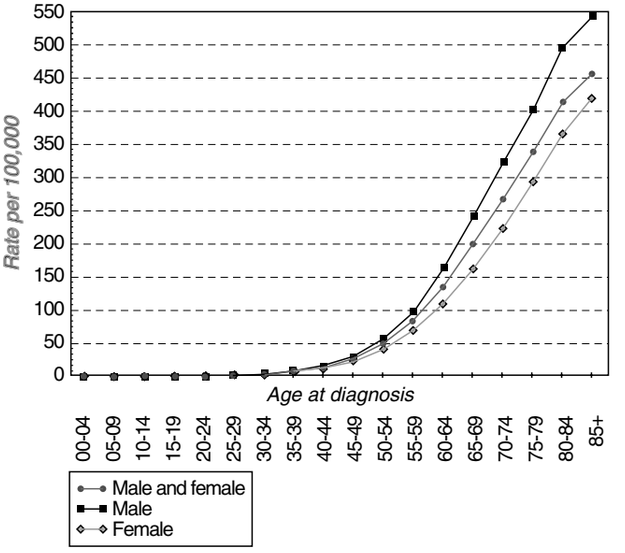

FIGURE 23-2. Age-specific incidence rates in the United States. Age-specific incidence both genders—circles. Age-specific incidence in males—squares. Age-specific incidence in females–diamonds. [Generated from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Public-Use, Nov 2002 Sub (1973-2000), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the November 2002 submission.]

disease at presentation.[11] Rates of metastatic disease have fallen over time, most notably for CRC of the distal colon and rectum in Caucasians.[14]

There is substantial geographic variation in the incidence of CRC, with relatively high rates in North America, Western Europe, and Australia and relatively low rates in Africa and Asia[15] (Figure 23-3). Such observations led to Burkitt's[16] hypothesis—that dietary differences, specifically fiber and fat intake, between populations were responsible for the marked variation in rates of CRC found around the world. Burkitt observed that populations in low-risk areas of the third world had greater stool bulk, a faster colonic transit time, and higher dietary fiber intake than populations in high-risk westernized regions. Although such ecologic studies are confounded by numerous factors (for example, variations in average life expectancy, cancer detection methods, etc.), environmental factors (most prominently dietary factors) are still considered to have a major role in this disease. This argument is supported by studies of migrants from low prevalence areas to high prevalence areas. Such studies generally demonstrate that the incidence of CRC in the migrants increases rapidly to become similar and in some cases to exceed the incidence of the high-risk area.[17] Interestingly, there is less variation in the incidence of rectal cancer between countries as compared with the incidence of colon cancer.[18,19]

Mortality from CRC is declining in the United States as age-adjusted CRC death rates peaked in the 1940s at 35 per 100,000. Rates in women have steadily decreased since this time and in 1998, the CRC death rate in women was 18.6 per 100,000. In men, death rates changed little until the 1980s and 1990s then decreased significantly; in 1998, the CRC death rate was 26.1 per 100,000 for men.[19] Improvements in surgical and medical treatments likely explain some of the change particularly that identified before 1985. More recently, the

TABLE 23-1. Incidence and mortality rates* for CRC by site, race, and ethnicity, United States 1996–2000

		Caucasian	African-American	Asian American and Pacific Islander	American Indian/Alaska Native	Hispanic/Latino
Incidence	Male	64.1	72.4	57.2	37.5	49.8
	Female	46.2	56.2	38.8	32.6	32.9
Mortality	Male	25.3	34.6	15.8	18.5	18.4
	Female	17.5	24.6	11.0	12.1	11.4

*Per 100,000 age-adjusted to the 2000 United States standard population.
Source: Adapted from Jemal et al.,[11] with permission from Lippincott Williams & Wilkins.

TABLE 23-2. Stage at diagnosis

	Caucasians	African-Americans
Localized	38	34
Regional	38	36
Distant	19	24
Unstaged	5	7

reduced mortality rate is likely secondary to the reduced incidence of CRC. In fact, no improvement in case fatality has been identified since 1986[20] indicating the trends in mortality are likely complex, particularly given the gender differences. African-Americans have the highest mortality rate from CRC in the United States (Table 23-1). The reasons for the higher mortality rate are likely multifactorial including the higher incidence of CRC, and the differences in stage distribution. However, African-Americans had worse 5-year survival for all stages of disease, and the difference in 5-year survival rates between Caucasians and African-Americans has actually increased over time; from an absolute difference of 5% in the 1970s (51% versus 46%) to an absolute difference of 13% in the 1990s (63% versus 53%).[11,21] Differences in incidence, stage distribution, and survival of CRC between Caucasians and African-Americans are in part attributable to differences in socioeconomic status, screening rates, and treatment[22]; however, the differences may also be attributable to genetic and environmental factors that have yet to be elucidated.[23]

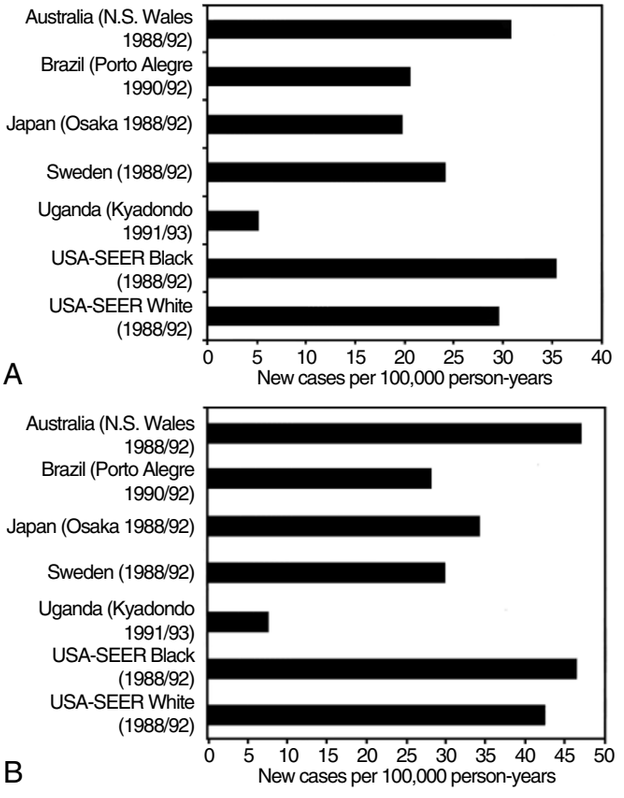

FIGURE 23-3. **A** Age-standardized (to the world population) incidence rates of cancer of the large bowel among females. **B** Age-standardized (to the world population) incidence rates of cancer of the large bowel among males. (Reprinted from Lagiou.[15] Copyright © 2002 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.)

Because CRC is a survivable cancer, with 5-year survival rates adjusted for life expectancy of 63%,[3] the prevalence of people living with a diagnosis of CRC in the population is substantial. In 1996, more than 380,000 Americans older than 65 years of age received some type of CRC care (treatment or follow-up).[24] In total in 2004, more than 1 million living Americans have had a diagnosis of CRC.[25]

Etiology

Dietary Constituents and Supplements

The colon is constantly exposed to the substances we ingest and the byproducts of ingestion. Thus, the role of diet in the pathogenesis of CRC has long been speculated. However, the relationship between diet and CRC risk is at best unclear. Studies in this area are difficult to conduct, because exposures tend to be multifactorial and change over time with our diet. In addition, because colorectal carcinogenesis is a multistep process, a number or combination of exposures may be necessary, and genetic susceptibility is likely to have a role. In addition, in most cases, randomized trials are not feasible, and therefore studies must be observational in nature. When intervention studies are possible, follow-up is relatively short term (compared with the long-term exposure that may be necessary for cancer development), and single dietary components are generally selected for evaluation although the influence of diet may depend on complex interactions between dietary constituents. In addition, to reduce sample size, some studies are conducted on patients with a history of adenomatous polyps. Some interventions in these patients may not be effective, because such patients may have already acquired numerous genetic alterations in normal-appearing colonic mucosa. Some interventions may need to be instituted before development of polyps. Although it can be stated that an individual with no other risk factors for CRC who ingests a diet that is high in fiber, fruits, and vegetables and low in animal fat and red meat will be on average at lower risk of CRC than an individual who eats a diet low in fiber, fruits, and vegetables and high in animal fat and red meat, it is difficult to determine with certainty which dietary components or combinations are responsible for the decreased risk.

Dietary Fat

Dietary fat, particularly saturated animal fat has been implicated in carcinogenesis in the colon and rectum. Early research using animal models demonstrated a carcinogenic effect of dietary fat on colonic mucosa,[26–28] and ecologic

studies found parallels between CRC rates and dietary fat consumption. Countries with populations eating a high fat diet had higher CRC rates than countries with populations eating a lower fat diet.[29] However, dietary fat consumption is related to a number of other factors that may influence cancer risk, including other dietary factors such as dietary fiber and micronutrient consumption, as well as life-style factors such as exercise and alcohol consumption. Therefore, ecologic comparisons between countries are subject to a substantial risk of confounding.[30]

More than 13 case-control studies have been conducted to evaluate the relationship between dietary fat intake and the risk of CRC. These have been quantitatively summarized by Howe et al.[31] and include 5287 cases with CRC and 10,470 controls. Although positive associations were identified for total energy intake and CRC in almost all of the studies, there was no energy-independent relationship between dietary fat intake and CRC risk. After controlling for total energy intake, the odds of development of CRC in subjects with the highest dietary fat intake as compared with those with the lowest intake was 0.90 [95% confidence interval (CI), 0.72–1.13]. Overall, there was no evidence for any association of total dietary fat intake and development of CRC. A small but consistent relationship between cholesterol intake and CRC was identified.

At least six cohort studies have been conducted to evaluate the relationship between dietary fat and CRC.[32–37] Only one study[36] identified an association between dietary animal fat and development of CRC, with a twofold increase in CRC in the highest consumers of animal fat as compared with the lowest consumers. A separate analysis of this same cohort indicated that regular intake of red meat was associated with a 2.5-fold increase in CRC risk as compared with infrequent consumption.[38] In fact, the evidence that red meat consumption is associated with CRC is in general more compelling than the evidence of an association with dietary fat. Given the lack of evidence for an independent association of dietary fat with CRC, it is unlikely that the animal fat in red meat is responsible for the association between red meat and CRC.

Red Meat

There are a number of potential carcinogenic mechanisms unrelated to fat content that may result in a causal relationship between red meat ingestion and CRC. Red meat is high in iron, a prooxidant. Dietary iron may increase free-radical production in the colon, and these free radicals may cause chronic mucosal damage or promote other carcinogens. In humans, red meat ingestion stimulates production of N-nitroso compounds in a dose-response manner.[39] Because many N-nitroso compounds are known carcinogens, this is a potential mechanism for an association between red meat and CRC. Formation of heterocyclic amines and polycyclic aromatic hydrocarbons in meat by cooking over an open flame or cooking until well done may be an important factor because these compounds are carcinogenic in animal models.[40]

Many epidemiologic studies have been conducted to determine the effect of ingestion of red meat on CRC risk. Two metaanalyses have been published,[41,42] one combining the results of 13 cohort studies,[41] the other combining 21 case-control studies and six cohort studies.[42] In the two studies, the pooled estimate for the increase in the risk of CRC caused by meat consumption was similar; the pooled estimate for the odds of development of CRC in the highest meat-consuming groups as compared with the lowest was 1.14. A daily increase of 100 g of red meat (3.5 ounces) was associated with a 12%–17% increased risk of CRC. The risk was substantially higher with the ingestion of processed meat. Of note, individuals that consume diets high in red meat generally consume diets low in other dietary factors,[43] such as antioxidants that may themselves be important in colorectal carcinogenesis. It is therefore difficult to rule out the possibility that the apparent effect of red meat on development of CRC may be confounded or modified by other dietary or lifestyle factors.

Fruit and Vegetable Intake

The effect of dietary intake of fruit and vegetables on CRC risk has been extensively evaluated. Fruits and vegetables are a source of antioxidants, including carotenoids and ascorbate. Other bioactive constituents in fruits and vegetables that may protect against carcinogenesis include the indoles and isothiocyanates. Previous research, including results from 22 case-control studies and four prospective cohort studies, has provided substantial support for the hypothesis that vegetable intake reduces the risk of CRC, whereas intake of fruit did not seem to have an effect.[44] More recent data, however, have not demonstrated a convincing link between vegetable or fruit intake and a reduced risk of CRC. In four large prospective cohort studies (the Nurse's Health Study of 121,700 women, the Health Professionals Follow-up Study of 51,529 men, the Netherlands Cohort Study on Diet and Cancer including 120,852 men and women, and the Cancer Prevention Study II Nutrition Cohort, including 133,163 men and women),[45–47] fruit and vegetable intake was not statistically significantly associated with a reduced risk of CRC. Of note, participants in the Nurse's Health Study and the Health Professionals Follow-up Study had a higher consumption of fruits and vegetables and a higher prevalence of multivitamin use than the general United States population.[48] The Netherlands study did show a trend toward a reduced risk of colon cancer in women eating large amounts of fruit and vegetables, particularly the brassica vegetables (cabbages, kale, broccoli, Brussels sprouts, and cauliflower) and cooked leafy vegetables. The Cancer Prevention Study II[47] also demonstrated a non–statistically significant trend for a higher colon cancer risk in men with the lowest vegetable consumption and women with the lowest fruit consumption.

Two additional studies have recently evaluated the effect of fruit and vegetable consumption in cohorts of women enrolled

in breast cancer screening studies.[48,49] In the first study[48] of 61,463 women enrolled in the Swedish Two Counties randomized trial of screening mammography, fruit and vegetable consumption was associated with a decreased risk of CRC. Individuals consuming greater than 5.0 servings per day had a relative risk (RR) of CRC of 0.73 compared with individuals consuming less than 2.5 servings. The second study[49] included 45,490 women who participated in the Breast Cancer Detection Demonstration Project, a National Cancer Institute–sponsored breast cancer screening program. These women completed a food frequency questionnaire and were followed for 386,142 person-years. No association between fruit and vegetable intake and CRC risk was identified, even after adjustment for other potential confounders. In addition, a dietary intervention trial has been conducted; the Polyp Prevention Trial, randomized 2079 people with colorectal adenomas to either intensive dietary counseling with assignment to a diet low in fat and high in fruits, vegetables, and fiber or control.[50] No difference in adenoma recurrence rate was found in the intervention group as compared with the control group.

Overall, the evidence for an association between fruit and vegetable intake and the risk of CRC is inconsistent. Given this lack of concordant data, it is unlikely that a large number of cases of CRC can be attributed directly to a lack of fruit or vegetables, or that major additional interventions to increase consumption would lead to a substantial reduction in the incidence of CRC.

Fiber

Dietary fiber was one of the first dietary components thought to have a protective role in carcinogenesis. An association of a high fiber diet with a decreased risk of CRC was first theorized in 1969 by Burkitt[16]; however, the data regarding the association between fiber and CRC risk are conflicting. Several mechanisms have been proposed for the protective effects of fiber: fiber may increase intestinal transit and therefore reduce the length of exposure of the colon to carcinogens, and fiber may dilute or absorb various potential carcinogens, particularly bile salts. In addition, products of fiber degradation and fermentation in the colon (such as butyrate) may also have a role.[51] Overall, there has been little consistent evidence that a high fiber intake is associated with a decreased risk of CRC.[51] Two large American cohort studies, the Nurses Health study[52] and the Health Professionals' Follow-up Study,[35] found no evidence of benefit of fiber on CRC risk.

However, two recent studies have reopened the debate. In the Prostate, Lung, Colorectal and Ovarian Screening Trial,[53] a nested case-control study of more than 37,508 people undergoing flexible sigmoidoscopy was performed using food frequency questionnaires. People who reported the highest amounts of fiber in their diets had the lowest risk of colorectal adenomas, 27% less than people who ate the least amount of fiber. The strongest association was found for fiber from grains, cereals, and fruits but not for fiber from legumes and vegetables. When colonic and rectal adenomas were evaluated separately, the effect of fiber was seen only in colonic adenoma. In a second study, a prospective cohort study comparing the diet of more than 500,000 people in 10 European countries, investigators in the European Prospective Investigation into Cancer and Nutrition[54] found that people who ate the most fiber had a 25% lower incidence of CRC than those who ate the least fiber. Again, the protective effect was highest for colon and least for rectum.

Dietary interventions to increase fiber intake have proven unsuccessful in reducing the risk of colorectal neoplasia. A metaanalysis has evaluated the effect of five intervention trials.[55] These studies randomized a total of 4349 individuals to some form of fiber supplementation or high fiber dietary intervention.[50,56–59] When the data were combined, there was no difference between the intervention and control groups for the number of subjects developing at least one adenoma [RR = 1.04 (95% CI, 0.95–1.13)]. The authors concluded that there is currently no evidence from randomized studies to suggest that increased dietary fiber intake will reduce the incidence or recurrence of adenomatous polyps within a 2- to 4-year period.

Currently there is no single accepted definition of fiber. Many different types of fiber exist (soluble/nonsoluble, polysaccharides/nonpolysaccharides) and these differences may influence CRC risk. In addition, fiber intake itself may not be protective but may be correlated with other healthy lifestyle choices as well as other components of a healthy diet (for example, high vegetable, low fat, and low meat). The lack of effect found in randomized trials as compared with observational studies indicates this may be the case. However, the intervention trials may have been too short in duration to be able to demonstrate an effect.

Calcium

Substantial epidemiologic and experimental evidence exists to support the beneficial effect of calcium on the prevention of colorectal neoplasia. Calcium has the capacity to bind and precipitate bile acids and may directly influence mucosal cell proliferation. Most, although not all, of the observational studies evaluating the influence of dietary calcium have demonstrated a protective effect of calcium on risk of CRC. Particularly compelling, two randomized double-blind placebo-controlled intervention trials of calcium for the prevention of adenoma recurrence that included a total of 1346 subjects[57,60] have demonstrated that the use of calcium supplementation (1200 mg daily for a mean duration of 4 years or 2000 mg daily for a mean duration of 3 years) was associated with a reduction in the recurrence of colorectal adenoma, although only one study[60] achieved statistical significance. In a metaanalysis of the two studies, the overall odds of developing recurrent adenomas was 0.74 for patients randomized to receive calcium as compared with placebo.[61]

The effect of calcium on a non–high-risk cohort is less clear. A metaanalysis of available studies conducted in 1996[62] concluded that the evidence to support the benefit of calcium intake on reduction of colorectal neoplasia was not consistent with a substantial effect. More recently, large observational studies have supported a modest effect of calcium in the prevention of CRC, particularly calcium supplementation. In a study of 87,998 women from the Nurses' Health Study and 47,344 men from the Health Professionals Follow-up Study, an RR of distal CRC of 0.73 was found for those ingesting more than 700 mg of calcium per day. No association was found for proximal cancers.[63] In the Cancer Prevention Study II, Nutrition Cohort Study, 60,866 men and 66,883 women completed a detailed dietary questionnaire and were followed for 5 years. Total calcium intake (from diet and supplements) was associated with marginally lower CRC risk in men and women (RR = 0.87; 95% CI, 0.67–1.12, highest versus lowest quintiles, *P* trend = .02).[64] A pooled analysis of 10 cohort studies including 534,536 individuals[65] evaluating the influence of dairy foods and calcium on CRC confirms a consistently decreased risk of CRC for those with the highest intake of dietary calcium as compared with those with the lowest intake. Although the effect of calcium may be modest, given that CRC is a common disease, the overall impact of optimizing calcium intake from a population standpoint could be substantial.

Folate

Folate, a B vitamin, is important for normal DNA methylation. Methylation is important in the regulation of cellular gene expression. Folate deficiency may lead to cancer through disruption of DNA synthesis and repair, or loss of control of proto-oncogene activity.[66] In 15 retrospective epidemiologic[67] studies evaluating the association between folate and CRC risk, most demonstrate a statistically significant or trend toward a significant relationship between higher intake of folate and a reduced risk of CRC or adenoma formation. There are 11 prospective studies that have evaluated the influence of folate on CRC risk in North American and European populations.[67] In an unpublished metaanalysis of these data, a 20% reduction in the risk of CRC was found in those with the highest folate ingestion as compared with those with the lowest level of ingestion.[68] Although the relationship between folate and CRC in epidemiologic studies is generally consistent, it is not uniform, and there are no large-scale randomized trials evaluating the effect of folate supplementation on CRC or adenoma risk in the general population. Of note, since 1998, the United States Food and Drug Administration has required folate fortification of all flour and cereal grain products in the United States,[69] and thus folate consumption in the population is likely increasing.

Alcohol

Alcohol ingestion has a possible role in colorectal carcinogenesis. Alcohol may alter folate absorption, increasing CRC through reduction of folate bioavailability. Acetaldehyde, a product of alcohol metabolism may have a role, and alcohol may also contribute to abnormal DNA methylation directly. A metaanalysis of five follow-up studies and 22 case-control studies published in 1990[70] demonstrated only a weak association between alcohol and CRC, although the effect was stronger when only rectal cancer was considered. A more recent pooled analysis[71] of eight cohort studies examining the relationship between alcohol intake and CRC including a total of 489,979 people in five countries has been conducted. An increased risk of CRC was identified in persons with an alcohol intake of two or more drinks per day (an amount consumed by only 4% of women and 13% of men in these studies). For those individuals who drank two to three drinks per day, the RR of CRC as compared with nondrinkers was 1.16. For those people who drank three or more drinks per day, the RR (1.41) was greater. The association was found for all sites in the colon and rectum and for both women and men. No clear difference was seen in the risk attributable to specific types of alcohol (beer versus wine versus spirits). Of note, these cohort studies were limited to a single measure of alcohol consumption at baseline and thus could not assess duration of alcohol use or lifetime alcohol exposure. However, the findings of an association with alcohol intake are consistent, and there are no studies that demonstrate a protective effect of higher alcohol consumption.[72] Thus, the totality of the evidence indicates that a high level of alcohol intake (two or more drinks per day) is associated with an increased risk of CRC.

Aspirin and Nonsteroidal Antiinflammatory Drugs

There is considerable observational evidence that the use of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) has protective effects at all stages of colorectal carcinogenesis (aberrant crypt foci, adenoma, carcinoma, and death from CRC).[73] The mechanism of antineoplastic action of NSAIDs is incompletely understood but it is believed that both cyclooxygenase (COX)-dependent and COX-independent pathways may be important.

At least 30 observational studies have been conducted to evaluate the influence of NSAID (primarily aspirin) use on development of CRC and colorectal adenoma. A consistent reduction in the risk of colorectal neoplasia in NSAID users is identified in these studies of various design, that use various methods of controlling for potential confounders.[73] In a pooled analysis of studies evaluating the effect on colorectal adenoma, the summary RR for colorectal adenoma in aspirin users was 0.7 and in NSAID users was 0.6, indicating a statistically significant reduction in risk in aspirin and NSAID users.[74] In the pooled analysis of the effect of aspirin and NSAIDs on CRC risk, the results were virtually the same.[75] Overall, the data evaluating the effect of nonaspirin NSAIDs is more limited than that for aspirin.[76]

Several intervention studies have been conducted, and a Cochrane review of the results of the randomized controlled

intervention trials has been published.[77,78] The authors of this metaanalysis reviewed one population-based prevention trial (including 22,071 people),[79] three secondary prevention trials in people with sporadic polyps (including 2028 patients),[80–82] and four trials in 150 patients with familial adenomatous polyposis (FAP).[83–86] The authors conclude based on data from these high-quality trials that there is some evidence for the effectiveness of intervention strategies using NSAIDs for the prevention of colorectal adenoma. However, the single primary prevention trial reviewed[79] did not demonstrate a decreased incidence of CRC in the intervention group. Therefore, the results of ongoing trials evaluating the effects of NSAIDs on CRC development are necessary before the widespread usage of NSAIDs as a chemopreventive agent for this disease. Serious gastrointestinal complications occur in regular users of aspirin and NSAIDs. Although events are rare, hospitalizations for gastrointestinal complications occur in 7 to 13 per 1000 chronic users of NSAIDs per year.[87,88] Because chemopreventive agents must be used in the general population to substantially reduce the burden of disease, the risks of chemoprophylaxis with aspirin or NSAIDs may outweigh the benefits. Some recent studies have evaluated the role of COX-2 inhibitors in the prevention of CRC.[89,90] However, in comparison to aspirin, the research evaluating COX-2 inhibitors is limited. In addition, because there are potential cardiotoxic effects of COX-2 inhibitors, their use in chemoprevention cannot be supported.[91] A number of authors have evaluated the cost-effectiveness of chemoprevention of CRC with NSAIDs[92,93] or COX-2 inhibitors[94,95] and found that chemoprophylaxis with these compounds is not cost effective.

Hormone Replacement Therapy

Observational studies have demonstrated an association between hormone replacement therapy (HRT) in women and a reduction in both incidence and mortality from CRC. Possible mechanisms for the effect of HRT include a reduction in bile acid secretion (a potential promoter or initiator of CRC), as well as estrogen effects on colonic epithelium, both directly and through alterations in insulin-like growth factor with the use of estrogens. A metaanalysis of 18 observational studies of postmenopausal HRT demonstrated a 20% reduction in incidence of CRC in women who had taken HRT as compared with those that had never taken HRT.[96] The Women's Health Initiative was a randomized trial of estrogen plus progestin in postmenopausal women including 16,608 women. The study was discontinued early, because after a mean of 5.2 years of follow-up, it was determined that the relative risk of breast cancer in the treatment group exceeded the predefined stopping boundary and the overall risk of adverse outcomes exceeded the benefits.[97] At that time, there seemed to be a protective effect of HRT on incidence of CRC. With further follow-up, a total of 122 cases of CRC developed in this cohort[98]: 43 cases in the group receiving HRT and 72 cases in the group receiving placebo, indicating that relatively short-term HRT was associated with a significantly decreased risk of CRC. Interestingly, the women who developed CRC while on HRT were more likely to present at an advanced stage than women who developed CRC when on placebo. The frequency of screening for CRC was similar between the two groups.

Overall, there seems to be a consistent reduction in the risk of CRC with the use of HRT. However, given the potential adverse effect of HRT, this should not be used as a primary preventive strategy for CRC.[99] Interestingly, some authors have found that the influence of estrogen on CRC risk is related to microsatellite instability (MSI)—the presence of estrogen seems to protect against MSI whereas lack of estrogen in older women increases the risk of development of an MSI-positive tumor.[100]

Obesity

Obesity seems to increase the risk of colon cancer in men and premenopausal women. Case-control studies[101,102] and cohort studies[103–105] have demonstrated a strong association between a high body mass index and incidence of CRC, with a twofold increased risk of CRC found in the obese. One of the proposed mechanisms for the association is the relative insulin resistance found in many obese patients. Insulin resistance results in hyperinsulinemia and increased activity of IGF (insulinlike growth factor) peptides. High IGF-1 levels are associated with cell proliferation[103] and may increase the risk of colonic neoplasia. In the past, most studies have demonstrated a stronger association between obesity and CRC risk in men than in women. More recent evidence has demonstrated that in women, the association between obesity and CRC risk may be modified by estrogen. Several observational studies have demonstrated an increased risk of CRC in obese women; however, the association was limited to premenopausal women.[104,106,107] In postmenopausal women, the increased estrogen production associated with obesity was thought to mitigate the risk. Of note, not all observational studies have confirmed this relationship.[103]

Physical Activity

More than 50 studies have been conducted to evaluate the influence of physical activity on CRC risk. Overall, the literature is relatively consistent with respect to the effect: greater physical activity (occupational, leisure, or total activity) is associated with a reduced risk of CRC. The effect is relatively small; the estimated increased risk of colon cancer in the sedentary ranges from 1.6 to 2.0. (Of note, this figure compares to the increased risk of heart disease attributable to a sedentary lifestyle of 1.3 to 1.4.) The effect of physical activity on colon cancer is consistent in both case-control studies and cohort studies.[108] Although physical activity may be associated with a number of other healthy lifestyle factors, studies

controlling for such factors (diet, smoking, nonsteroidal use, body mass) show an independent protective effect of physical activity. The effect of physical activity on the risk of rectal cancer is somewhat less consistent; some studies demonstrate no effect, and in studies that do demonstrate an effect, it is weaker. The amount of physical activity required to have an effect is substantial—risk reduction is estimated to occur with 3.5–4 hours of vigorous activity (running) per week but requires 7–35 hours of moderate activity (walking at a brisk pace) per week.[108]

The biologic mechanisms that explain the relationship between physical activity and CRC risk are unclear. Increased physical activity leads to changes in insulin sensitivity and IGF levels, and both insulin and IGF have been demonstrated to potentially be involved with colorectal carcinogenesis.[109–111] Additional proposed mechanisms include effects of physical activity on prostaglandin synthesis, effects on antitumor immune defenses, and the reduction in percent body fat associated with exercise.[112] The mechanism is almost certainly multifactorial. Nonetheless, for a host of health-related reasons, frequent moderate to vigorous physical activity can be recommended to most patients without hesitation.

Smoking

Consistent with a 35- to 40-year time lag between exposure and induction of cancer, early studies did not demonstrate an association between cigarette smoking and colorectal neoplasia. More recent studies are more consistently positive. In a review of the literature conducted in 2001,[113] 21 of 22 studies evaluating the relationship between cigarette smoking and colorectal adenoma were positive, smokers demonstrating a two- to threefold increase of adenoma risk as compared with nonsmokers. Twenty-seven epidemiologic studies have been conducted that demonstrate an association between tobacco and risk of CRC.[113] Of studies conducted in the United States, conducted after 1970 in men, and 1990 in women (studies with adequate induction time—35 to 40 years after smoking became prevalent), most demonstrated an association between heavy smoking and increased CRC risk. Most studies demonstrated an effect at relatively high levels of smoking (20 or more cigarettes per day). In the studies reviewed, the CRC risk was 1.4- to 2-fold higher in smokers than in nonsmokers.

Smoking may modify the effect of micronutrients on CRC risk. In a randomized, controlled trial of antioxidants including β-carotene, or vitamin C and E supplementation in the prevention of recurrence of colorectal adenomas, among subjects who neither smoked nor drank alcohol, β-carotene was associated with a substantial reduction in the risk of recurrent adenoma (RR = 0.56). This effect was significantly attenuated in participants who were either smokers or drinkers. For participants who were both smokers and drank alcohol, β-carotene supplementation actually resulted in a doubling of the risk of recurrent adenoma formation.[114] A large study[115] found that patients with MSI-positive tumors were more likely to smoke more than 20 cigarettes a day, and had smoked for longer period of times than controls or patients with MSI-negative tumors. In this study, other factors such as physical activity, NSAID use, and body mass index were less consistently associated with MSI-positive tumors. The authors postulate that cigarette smoke may generate replication errors, overwhelming the DNA mismatch repair (MMR) mechanism, or may affect MMR directly.

Cholecystectomy

Abnormal bile acid metabolism may predispose both to CRC and cholelithiasis. After cholecystectomy, increased quantities of secondary bile acids have been detected in the feces and may have a role in colonic carcinogenesis. Studies in this area are difficult, because dietary and lifestyle factors related to cholelithiasis may confound the relationship between gallbladder disease and CRC risk. A metaanalysis of studies evaluating the effect of cholecystectomy on CRC risk published in 1993[116] demonstrated conflicting results. Analysis of the 33 case-control studies generated a pooled RR for CRC after cholecystectomy of 1.34 (95% CI, 1.14–1.57), limited to the proximal colon. However, no significant effect was found when the results of six cohort studies were evaluated.

Two recent large prospective cohort studies have been conducted to evaluate this relationship. In a long-term follow-up study of 278,460 patients after cholecystectomy followed for up to 33 years,[117] a significantly increased risk of small bowel malignancies and proximal colonic malignancies was found as compared with the general population. No association was found with more distal bowel cancer. In a study using data from the Nurses' Health Study,[118] a significant positive association between cholecystectomy and the risk of CRC was found (RR 1.21, 95% CI 1.01–1.46, after adjusting for important CRC risk factors including diet, family history, calcium intake, body mass index, and use of hormone replacement therapy). In this study, the risk of CRC after cholecystectomy was increased both for proximal bowel and rectal cancers. A history of gallstones was associated with similar risks. No increase in the risk of colorectal adenoma was identified in those patients having had a cholecystectomy.

Inflammatory Bowel Disease

Patients with long-standing inflammatory bowel disease (IBD) are known to be at an increased risk of CRC, although it is difficult to precisely estimate the risk. The magnitude of the risk has been studied extensively in ulcerative colitis (UC); however, rates vary among studies, particularly those performed in referral centers versus population-based studies. In addition, treatment and surveillance may influence the risk and thus more recent studies may have a lower risk than in studies before surveillance was common. A metaanalysis[119] of 116 studies evaluating the risk of CRC in UC patients

found the overall prevalence of CRC in UC patients was 3.7% (95% CI, 3.2%–4.2%). In 19 of the studies reviewed, the duration of colitis was reported by decade. In the first 10 years after onset of colitis, the incidence rate of CRC was 2/1000 per year of disease, for the second decade the incidence rate of CRC was estimated to be 7/1000 per year of disease, and in the third decade the incidence rate of CRC was 12/1000 per year of disease. This corresponds to a cumulative probability of CRC of 2% after 10 years of disease, 8% after 20 years, and 18% after 30 years. The risk of CRC geographically varied and was higher in studies conducted in the United States. The metaanalysis did not evaluate extent of disease (pancolitis versus left-sided disease versus proctitis).

Extent of disease does seem to have a significant influence on CRC risk in UC. In a Swedish population-based cohort of 3117 patients with UC,[120] less extensive disease was associated with a lesser risk of CRC. As a ratio of the observed incidence and expected incidence, the increased risk of CRC in this cohort was 1.7 for those with ulcerative proctitis (95% CI, 0.8–3.2); 2.8 for those with left-sided colitis (95% CI, 1.6–4.4); and 14.8 for those with pancolitis (95% CI, 11.4–18.9). Other studies have supported these findings.[121]

Other factors that may modify the risk of CRC in patients with UC but are currently not proven include age at onset of UC, family history of CRC, and the related diagnosis of primary sclerosing cholangitis.[121] For patients with long-standing extensive UC, colectomy is an effective (albeit aggressive) strategy for prevention of CRC. Other strategies include endoscopic surveillance for dysplasia and/or the use of chemopreventive agents. Overall, the evidence for the effectiveness of surveillance colonoscopy is weak[122]; there are no randomized, controlled trials or cohort studies that have been conducted to evaluate surveillance colonoscopy in the prevention of CRC in UC.[123] In addition, neither of the two published case-control studies[124,125] has demonstrated a clear statistically significant benefit for endoscopic surveillance (although there was a trend toward benefit). Nevertheless, endoscopic surveillance is usually performed in patients with pancolitis for more than 10 years' duration who wish to avoid colectomy. There is also some evidence that chemoprevention of CRC in patients with UC may be possible. There is some evidence that 5-ASA products may decrease the rate of dysplasia in patients with UC.[126] Other promising agents include folate, calcium, and in patients with primary sclerosing cholangitis, ursodiol.[126]

The relationship between Crohn's disease and the development of CRC has been less consistently demonstrated. In studies using data from referral-based practices, the risk of development of CRC seems to be significantly increased in patients with extensive Crohn's colitis.[121] The magnitude of increased risk seems similar to that of UC[127]; however, in population-based studies, particularly those more recently published, a less dramatic effect is seen. The two largest studies have conflicting results. In a Canadian population-based cohort study, the risk of CRC in 2857 patients with Crohn's disease was compared with a randomly selected group of controls matched 10:1 for age, gender, and geographic location. Patients with Crohn's disease were found to have an increased risk of colon cancer [incidence rate ratio (IRR) = 2.6; 95% CI, 1.69–4.12] but not rectal cancer (IRR = 1.08; 95% CI, 0.43–2.70). Patients with Crohn's disease also had an increased risk of cancer of the small intestine (IRR = 17.4; 95% CI, 4.16–72.9), and lymphoma (IRR = 2.40; 95% CI, 1.17–4.97). Some of these results are similar to those data from a population-based study in Denmark of 2645 patients hospitalized for Crohn's disease[128] and followed for up to 17 years. The rate of CRC in this group was not substantially increased as compared with the expected rate of CRC in the Danish population, the standardized incidence ratio for CRC was 1.1 (95% CI, 0.6–1.9). However, similar to the Canadian study, the risk of small intestinal cancer was increased 18-fold in the Crohn's disease group. Of note, in both studies, relatively few cases of CRC developed in Crohn's patients. Still, it is difficult to explain the dramatically different findings of the studies. It is possible that the pattern of disease or treatment differs between these two populations in a way that influenced CRC risk. Regardless, the effect of Crohn's disease on development of CRC requires further investigation.

Family History

Individuals with a family history of CRC are at an increased risk of themselves developing CRC. In a metaanalysis[129] of 27 observational studies that have evaluated the risk of family history on development of CRC, individuals with a first-degree relative with CRC had a 2.25 RR (95% CI, 2.00–2.53) of developing CRC as compared with those without a family history. The risk was slightly higher with a first-degree relative with colon cancer (RR = 2.42) than with rectal cancer (RR = 1.89). The risk increased if more than one first-degree relative had CRC (RR = 4.25) or if a relative was diagnosed before the age of 45 (RR = 3.87). The RR of CRC was also increased if a first-degree relative had a history of a colorectal adenoma (RR = 1.99). The clustering of risk in families may be attributed to an inherited susceptibility, common environmental exposures, or a combination of both factors. The influence of a more distant family history of CRC on individual risk has not been determined with certainty.

Some of the increased risk attributed to family history is due to inheritance of known susceptibility genes, such as mutations in the adenomatous polyposis coli gene, *p53* gene, or in MMR genes, particularly *MSH2*, *MLH1*, and *MSH6*[130] and these are discussed in detail elsewhere in this text. Importantly, the majority of cases of CRC cannot be attributed to known genetic defects even when associated with a family history of CRC. Recognized genetic syndromes account for only a small proportion of all cases of CRC. Additional autosomal dominant genetic defects conferring a high risk of CRC will almost certainly be found; however, at

least some of the increased risk of CRC associated with a family history is likely attributable to other genetic factors, such as recessive susceptibility genes, autosomal dominant genes with low penetrance, or complex interactions between an individual's genetic makeup and environmental factors.

Despite the importance of family history on risk of CRC, up to 25% of individuals with a first-degree relative with confirmed CRC do not report having such a family history,[131] and even those that do report a history may not be aware of the increased risk associated with this.[132] This fact has important implications for assessment of family history as well as patient and family counseling.

Other Risk Factors

Radiation

Cases of rectal carcinoma have been reported in individuals who have undergone radiation for pelvic malignancies, primarily cervical cancer[133] and prostate cancer.[134] Because rectal cancer is relatively common, these cases may represent sporadic rectal cancers developing after long-term survival from other pelvic malignancies. However, the cancers occur in the radiated field, tend to be associated with radiation changes to the adjacent rectal mucosa, and are more likely to be of mucinous histology[135,136] than typical sporadic cancers, thereby strengthening the likelihood of a causal association. Nevertheless, the vast majority of individuals undergoing radiation for pelvic malignancies will not develop rectal cancer.

Ureterosigmoidostomy

Formation of a ureterosigmoidostomy has been associated with an increased risk of carcinoma in the area of the ureterosigmoid anastomoses. It is difficult to estimate the increase in risk of colon cancer attributable to ureterosigmoidostomy—many were fashioned for malignant diseases that may themselves be associated with an increased risk of colon cancer, nevertheless the risk seems to be high. The estimated increase ranges from 100 to 7000 times the risk in the normal population[137] and up to 24% of patients with a ureterosigmoidostomy will develop neoplasia at the anastomosis. The average latency period from formation of the ureterosigmoidostomy to development of malignancy is 26 years.[138] Patients who have undergone conversion to another form of urinary diversion remain at risk of neoplasia if the ureterosigmoid anastomoses were not resected in their entirety. Although the cause of this dramatic increased risk is not known, it seems to require the exposure of colonic mucosa to the mixture of urine and feces.[137]

Fortunately, with several options for urinary diversion, this procedure is now rarely performed. Those individuals living with a functional ureterosigmoidostomy should be counseled regarding their heightened risk and undergo regular sigmoidoscopic surveillance.[137]

Acromegaly

Acromegaly, a rare endocrine syndrome resulting from secretion of excess growth hormone from a pituitary neoplasm has been found to be associated with an increased risk of CRC in several studies.[139–141] The magnitude of the risk is unclear, with reports ranging from nonsignificant increases in risk to an RR of 18.3.[141] In a population-based cohort study performed in Sweden and Denmark, the standardized incidence ratio of colon cancer in patients with acromegaly as compared with the general population was 2.6 (95% CI, 1.6–2.7).[139] Patients with acromegaly have increased levels of circulating IGF-1, and this may be responsible for the increased risk of colorectal neoplasia identified in these patients.[142]

Molecular Basis

All cancer, at its root, has a genetic basis. Carcinogenesis is a multistep process, requiring an accumulation of acquired and inherited genetic alterations. With this succession of genetic alterations, cells acquire a growth advantage over surrounding cells, and in a Darwinian-type process normal cells evolve into cancer cells.[143] In normal cells, growth and replication is a highly regulated process, and disruption of this regulation at multiple levels is required for clinically relevant cancer to develop. Defects in genes that code for important proteins in the regulation of the cell cycle seem to be critical for carcinogenesis. Hanahan and Weinberg[143] have described six alterations in regulatory mechanisms that seem constant in most cancers from the several hundred genetic mutations that have been identified in cancer cells (Figure 23-4):

1. Self-sufficiency in growth signals. Ordinarily, cells must receive growth signals to actively proliferate, assuring that cellular proliferation occurs only when necessary to maintain homeostasis. To proliferate autonomously, cancer cells must lose this need for exogenous growth signal.
2. Insensitivity to antigrowth signals. Normally, there are numerous growth-inhibitory signals that function within a cell to maintain the cell in a quiescent and/or differentiated state. Cells with neoplastic potential must develop mechanisms to evade these antigrowth signals, enabling proliferation and dedifferentiation.
3. Evading apoptosis. Development of cancer requires not only a loss of control over cellular proliferation, but also a loss of control over programmed cell death (apoptosis). Apoptosis normally occurs in response to the cellular environment and is likely a major mechanism whereby cells that have acquired significant genetic mutations are destroyed. Tumor cells must circumvent apoptosis (either at a regulatory level or at an effector level) to continue to develop and proliferate.
4. Limitless replicative potential. Many cells are able to replicate only a finite number of times preventing clonal expansion of any given cell. Even after acquiring independence

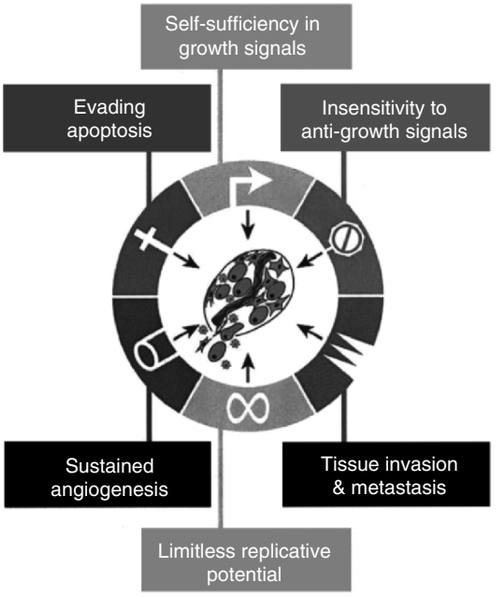

FIGURE 23-4. Alterations in regulatory mechanisms important for carcinogenesis. (Reprinted from Hanahan and Weinberg,[143] copyright © 2000, with permission from Elsevier.)

from normal signals for cellular growth and death to develop into clinically significant cancer, cancer cells must gain unlimited capacity for replication. Intrinsic limits to proliferation must be evaded.

5. Sustained angiogenesis. Virtually all cells must reside within 100 µm of a capillary to supply the cell with oxygen and nutrients required for functioning. Angiogenesis in normal tissue is closely regulated, and balancing of inducers and inhibitors of angiogenesis is an essential component of homeostasis. For neoplastic cells to develop into clinically significant cancer, they must develop the ability to induce and sustain angiogenesis, circumventing these homeostatic mechanisms to provide an adequate blood supply to support their ongoing growth.
6. Development of ability to invade and metastasize. For cancer cells to develop the ability to invade other tissue and metastasize, a number of changes must occur. Normally, cells in tissue adhere to each other. A loss of this normal cell to cell adhesion must occur in the cancer microenvironment to permit metastasis to occur. In addition, the cancer cells must develop methods of modifying new environments to support continued growth.

Although all six alterations in cell regulation are required for the development of clinically significant cancer, the sequence of events and mechanisms are variable. The sequence of genetic mutations (or alterations) is less important than the accumulation of mutations, although some mutations tend to occur early in the neoplastic process and are termed initiators, whereas others tend to occur later and are termed promoters. In addition, certain genetic mutations (somatic or inherited) may be particularly critical and affect cell regulation in several important ways. Many such critical genes belong to two broad categories of genes involved in carcinogenesis: oncogenes and tumor suppressor genes. Additionally, caretaker genes that function to prevent the accumulation of somatic mutations are also critical to colorectal carcinogenesis. Abnormalities in caretaker genes greatly increase the risk of cancer development, independent of environmental influence. Of note, although the role of genes in carcinogenesis is described, in reality it is the protein products of the genes that are directly involved in changes in cell regulation.

Mutations in oncogenes result in an abnormal gain or excess of a particular protein function. An oncogene product when expressed in a given cell (or when the product is expressed at the wrong time in the cell cycle, expressed with an enhanced function, or expressed in larger quantities than normally present) contributes to development of critical alterations in the mechanisms of cell regulation. Mutations causing such expression behave in a dominant manner, i.e., mutation of only one of the two alleles present is required to produce activation and phenotypic expression and promote carcinogenesis. The *ras* oncogene is the most frequently mutated oncogene identified in CRCs. The *K-ras* proto-oncogene, located on the short arm of chromosome 12 (12p) is mutated in approximately half of all CRCs.[144] The *K-ras* gene product seems to be involved in the transduction of exogenous growth signals. Point mutations in the *K-ras* gene lead to a function gain, conferring a growth advantage to the cells, although the role of *K-ras* in carcinogenesis is incompletely understood. Other oncogenes that are frequently identified in sporadic colon cancer include *c-myc* and *c-erbB2*.[145]

Tumor suppressor genes normally inhibit cellular proliferation or promote apoptosis. When gene expression is lost, there is a loss of this normal inhibitory control of the cell cycle. In general, gene expression is lost only when both alleles of the gene are inactivated [Knudson's two-hit theory of carcinogenesis[146] (Figure 23-5)], either through inherited mutation, somatic mutations, or both.

There are a number of tumor suppressor genes that have been found to have an important role in CRC carcinogenesis, including the *APC*, *DCC*, *p53*, and *MCC* genes.

The adenomatous polyposis coli (*APC*) gene located on the long arm of chromosome 5 (5q), is considered a gatekeeper gene of colorectal carcinogenesis as mutations in the *APC* gene seem to be initiators of this disease. Mutations in the *APC* gene have been found in 50% of sporadic adenomas and in 75% of sporadic cases of CRC.[144] FAP, discussed in detail elsewhere in this text, results from inheritance of a germline mutation in the *APC* gene. Mutations involve base-pair mutations, insertions or deletions that result in the formation of a stop codon, halting protein synthesis leading to formation of a truncated or shortened protein product that affects the function of the protein. The location of the germline mutation in the *APC* gene varies between families with FAP, and results

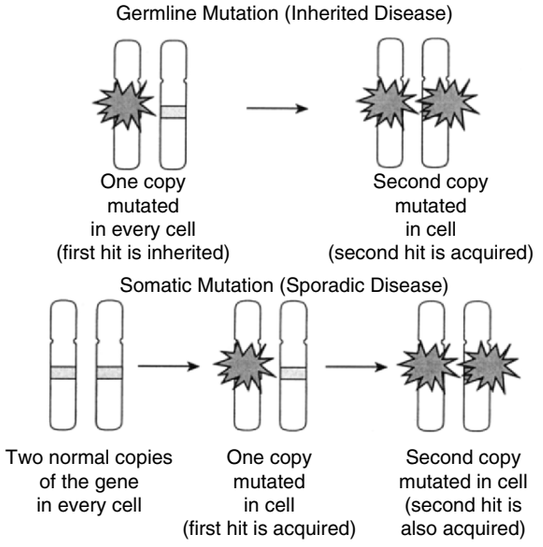

FIGURE 23-5. Loss of suppressor-gene function. (Reprinted from Calvert and Frucht[145] with permission from Annals of Internal Medicine.)

in the varying phenotypic expression of FAP found between families. Although only a single abnormal allele is inherited in FAP, sporadic mutations are always acquired resulting in the formation of hundreds to thousands of colonic adenomas and ultimately carcinoma. A specific germline mutation of the *APC* gene, the *I1307K* mutation, although not resulting in FAP, is found primarily in persons of Ashkenazi Jewish origin,[147] and results in an increased predisposition to CRC,[148] although the risk is much lower than for individuals with FAP. An additional mutation, *E1317Q*, may also result in an increased predisposition to CRC.[149]

The APC protein normally regulates the *Wnt* (wingless signaling pathway), an important pathway in cell regulation and development, through modulation of beta-catenin—a critical protein in the *Wnt* pathway. Normally, the protein product of the *APC* gene binds beta-catenin intracellularly forming a multiprotein complex that inhibits beta-catenin function. The increased functional levels of beta-catenin that result from alterations in APC protein product function leads to cell proliferation, and enhances cell to cell adhesion, limiting cell migration. Thus, hyperproliferating cells accumulate and aberrant crypt foci, the earliest phase of colorectal neoplasia.[150]

The *p53* gene, located on the short arm of chromosome 17 (17p) is an important gatekeeper gene for carcinogenesis—it is the most frequently mutated gene in human cancers.[151] Normally, by slowing the cell cycle, *p53* facilitates DNA repair during replication When repair is not feasible, *p53* induces apoptosis. Inactivation of *p53* is found in up to 75% of sporadic colorectal tumors[145]; however, the mutation seems to occur late in the tumorigenic sequence. Thus *p53* gene mutations do not seem to be initiators of carcinogenesis but act as key limiting factors for malignant transformation. This thought is supported by the finding that patients with Li Fraumeni syndrome (an inherited defect in *p53*) do not have an increased risk of CRC.[152] In addition, *p53* expression may be an independent prognostic marker in patients with CRC.[153,154] Most studies demonstrate a lower survival rate in patients with advanced cancers that are *p53* negative as compared with those whose tumors express *p53* gene product particularly in those who receive chemotherapy.[155]

The "deleted in colorectal cancer" (*DCC*) gene was identified on the long arm of chromosome 18 (18q) in 1989.[156] Mutations in this gene have been found in the majority of CRCs. The gene product of *DCC* is a transmembrane protein that is important in cell–cell adhesion, and therefore inactivation of *DCC* may enhance the metastatic potential of CRC through changes in adhesion. Similar to *p53*, patients who have *DCC*-positive tumors may have a better prognosis than those with *DCC*-negative (mutated) tumors.[157]

Located in close proximity to the *DCC* gene, mutations in a group of genes termed *SMAD*s (*SMAD2* and *SMAD4*) have been reported in CRCs. The protein products of these genes are components of the transforming growth factor (TGF)-β signaling pathway, which mediates growth inhibitory signals from cell surface to nucleus.

Because millions of base-pairs must be replicated during mitosis, errors in DNA replication occur and must be corrected by caretaker genes. The MMR system has a critical function in the detection and correction of errors in DNA replication, maintaining DNA integrity. MMR genes function as spell checkers—base-pair mismatches are identified, excised, and the correct sequence is synthesized and replaced.[72] Lack of MMR function results in an accumulation in errors in DNA replication, increasing the probability that a mutation in an important gene in cell regulation will occur, will be preserved, and carcinogenesis will thus be initiated or promoted. Defects in the MMR system are identified by the detection microsatellite instability. Microsatellites are small regions of DNA located throughout the genome that do not code for individual genes. They consist of small base sequences that are repeated in a highly polymorphic manner—the number of repeats may range from dozens to hundreds and the number of repeats varies from allele to allele, and from individual to individual. Microsatellites are particularly susceptible to MMR gene defects, thus in cases of CRC attributable to MMR gene mutations, microsatellite replication errors accumulate, leading to detectable differences in the pattern of microsatellites in the tumor and in normal tissue; this is termed microsatellite instability (MSI). When testing CRC for MSI, laboratories evaluate a number of microsatellite loci. The National Cancer Institute recommends the testing of five microsatellite sequences[158] to determine the MSI status of a tumor. If two or more of the five sequences demonstrate MSI, the tumor is designated MSI-high (MSI-H). If only one of the five sequences demonstrates changes in tumor microsatellite markers, the tumor is designated MSI-low (MSI-L). If no markers are changed, the tumor is microsatellite stable.

Approximately 15% of CRC is MSI.[158] MSI-H tumors are more likely to be high-grade, right-sided,[159] mucinous, and have tumor-infiltrating lymphocytes.[160,161] In addition, MSI tumors may have a better prognosis than microsatellite stable tumors,[162] but may be less responsive to chemotherapy.[163]

A number of MMR genes (*MLH1*, *MSH2*, *MSH3*, *MSH6*, and *PMS1*) have been identified. Germline mutations in the *MLH1* and *MSH2* genes are responsible for the majority (>90%)[164,165] of cases of the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (discussed fully elsewhere in the text), whereas approximately 5%–10% of HNPCC cases are attributable to mutations in the *MSH6* gene. Germline mutations in other MMR genes are rare.[166] Similar to tumor suppressor genes, both alleles of an MMR gene must be mutated or inactivated for MMR function to be lost. Sporadic tumors that demonstrate an MSI-H phenotype generally have a loss of *MLH1* function, attributable not to mutation but to aberrant methylation of the promoter region of the *MLH1* gene.[167] Methylation of cytosines in cytosine–guanosinedinucleotide repeats (termed CpG islands) results in the silencing of transcription, without an actual change in the nucleotide sequence of the gene.[168] The cause of the methylation is unknown, although it is associated with increasing age[169] and is not limited to MMR genes.

MYH is an additional DNA repair gene specifically active for adenine-guanine mismatches.[170] This gene has been found to be responsible for some cases of *APC* mutation-negative FAP. This defect is inherited in an autosomal recessive manner, i.e., defects must be inherited from both parents to result in phenotypic expression of the disease.[171]

In their landmark article, Vogelstein et al.[172] (Figure 23-6) described the pathogenesis of colon cancer as one that follows a predictable sequence of events, from adenoma to carcinoma, with histologic changes developing as genetic mutations are acquired over time. Initially, a mutation in a gatekeeper gene such as the *APC* gene occurs resulting in proliferation of the colorectal mucosa and leads to the first histologically detectable event, the aberrant crypt focus. In aberrant crypt foci, the crypts have larger diameters than normal and stain more darkly with methylene blue[150] and can be detected in rats as soon as 2 weeks after carcinogen exposure.[173] With additional genetic changes, cells within the aberrant crypt become dysplastic and an adenoma forms. Further genetic alterations are acquired, resulting in an increase in the size of the adenoma. However, the majority of adenomas do not develop into carcinoma. Therefore, additional genetic alterations are required before the severity of dysplasia increases, and eventually, particularly with mutations in tumor promoters such as *p53*, carcinoma develops. This pathway to carcinogenesis is termed the chromosomal instability pathway. Tumors forming through this pathway demonstrate extensive cytogenetic abnormalities, such as aneuploidy, and visible chromosomal losses and gains.[174]

CRC most frequently demonstrates chromosomal instability, indicating this is the most common genetic cause of colorectal carcinogenesis.[175] However, tumors that are MSI-H appear to develop through a separate pathway, termed the microsatellite mutator or microsatellite unstable pathway. These tumors are diploid and tend not to demonstrate gross chromosomal abnormalities. MMR defects in these tumors

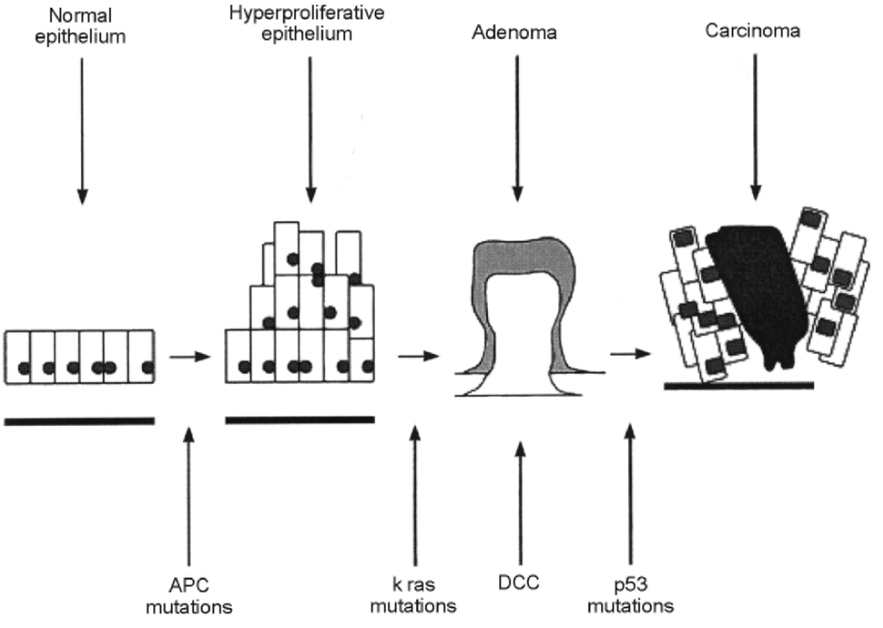

FIGURE 23-6. The adenoma to carcinoma sequence of colorectal carcinogenesis. (Reprinted from Hardy RG, Meltzer SJ, Jankowski JA. ABC of CRC. Molecular basis for risk factors. Br Med J 2000;321:886–889, with permission of the BMJ Publishing Group.)

lead to genetic mutations in key cell regulator genes, particularly the TGF-β pathway. Although MSI-H tumors may arise from adenomas, there is increasing evidence that sporadic MSI-H tumors also arise from hyperplastic polyps and serrated adenomas.[176] Serrated adenomas are polyps that in the past would have been classified as hyperplastic polyps but have architectural features both of hyperplastic polyps and cytologic features of classic adenomas. Because only 70% of all colorectal carcinomas are believed to arise from classic adenomas, serrated adenomas may be the precursor lesion for a substantial number of cancers.[177] However, the risk associated with serrated adenomas, in terms of progression to cancer, is unknown and currently under investigation.

Development of CRC in UC represents a third pathway to the carcinogenesis in the colon. Most cancers develop in UC without a precursor polyp and therefore a direct dysplasia to carcinoma sequence is postulated.[72] Genetically, cancers associated with UC seem to be heterogenous; aneuploidy and disruption of *p53* may occur as early events, however MMR genes may also be affected.

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