PREFACE

The rapid growth in the number of options available for the management of colorectal cancer presents the clinician with new opportunities and new complexities. An explosion of understanding in the basic science that underlies both the disease and its potential therapies has translated into remarkable technological advances that can now be applied. So many specialties and subspecialties have now been brought to bear that it is appropriate to attempt to bring the expertise from these areas together in one volume, so that practitioners in one aspect of colorectal cancer management can maintain knowledge and expertise regarding the capabilities of other colleagues working in this disease.

Colorectal Cancer: Multimodality Management provides a concise, focused, and current review of the methodological and technological advances that have recently occurred in the management of colorectal cancer. The book has been divided into six basic parts. The first part, dealing with epidemiology and prevention, focuses on the molecular genetic events that occur in the development of colorectal cancer, as well as on our understanding of dietary and environmental factors, and possible strategies for prevention. Part II focuses on both diagnostic and therapeutic radiology in the management of colorectal cancer, dealing with innumerable advances in imaging, and with the progress in the science and art of radiation therapy. The third section deals with the surgical aspects of management of colorectal cancer, starting with surgical pathology. Specifics of surgery for the colon and rectum, the role of minimal access surgery, management of early stage disease, and issues of resection of metastatic disease are discussed. Also, ablative techniques such as cryosurgery and radiofrequency ablation are reviewed. The fourth main area is medical oncology. This part starts with a review of fluorouracil and biomodulation, and moves forward into a thorough discussion of the currently available drugs for first and second line management of metastatic colorectal cancer. Issues of chemotherapy for adjuvant management are discussed, and local regional therapies, such as intrahepatic and intraperitoneal chemotherapy, are reviewed. Part V, entitled Supportive Management, deals with aspects of pain syndromes and pain control, issues of sexuality and fertility, and complementary and alternative medicine approaches. Finally in a forward-looking conclusion, Part VI discusses some of the new agents in development in colorectal cancer, including targeted therapies, vaccine strategies, and gene therapy.

The aim of *Colorectal Cancer: Multimodality Management* is to provide a well-balanced, authoritative, evidence-based review of the current approaches to the prevention, diagnosis, and treatment of colorectal cancer. We have seen decreases in both incidence and mortality from this disease over the past several decades. It is hoped that this book will further facilitate the dissemination of information to practitioners, and will thereby help contribute to further progress in the prevention and treatment of colorectal cancer.

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2 Epidemiological Trends in Colorectal Cancer

Susan M. Talbot and Alfred I. Neugut

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1. INTRODUCTION

Colorectal cancer is the fourth most common cancer worldwide, accounting for approximately 10% of the world total with 782,800 new cases in 1990 (Table 1) *(1)*. In 1990, it accounted for 437,000 deaths *(2)*. It is particularly common in North America, Australia, New Zealand, and parts of Europe, is rare in Asia, and is uncommon in Africa. In developed countries, the lifetime probability of developing colorectal cancer is 4.6% in men and 3.2% in females *(2)*. It affects men and women almost equally, with a similar incidence and number of deaths in the two sexes *(3,4)*. As we enter the new millennium, the incidence and mortality rates for colorectal cancer overall are now declining *(5)*. Rectal cancer incidence, however, as a separate entity, has remained relatively stable over this same time period.

Ethnic and racial differences in colon cancer, as well as studies on migrants, suggest that environmental factors play a major role in the etiology of the disease. In the last decade, multiple genetic mutations have been discovered that play a critical role in colorectal tumorigenesis, in what has become termed the adenoma–carcinoma sequence.

The association between the risk of colorectal cancer and specific conditions such as inflammatory bowel disease, environmental factors such as diet, occupation, smoking, alcohol intake, body mass, and physical activity, and reproductive factors will also be addressed in this chapter.

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Table 1
Estimate of New Cancer Cases Occurring in 1990 Worldwide

Tumor site	*Number of cases*	*Percentage of total*
Lung	1,036,900	12.8
Stomach	798,300	9.9
Breast	795,600	9.8
Colon/rectum	782,800	9.7
Liver	437,400	5.4
Prostate	396,100	4.9
Cervix uteri	371,200	4.6
Esophagus	315,800	3.9
Bladder	260,700	3.2
Leukemia	231,200	2.9
Total	8,083,300	100

Adapted from ref. *1*.

2. DESCRIPTIVE EPIDEMIOLOGY

2.1. Incidence and Mortality in the United States

There were an estimated 93,800 new colon cancer cases in the United States in 2000: 43,400 in men and 50,400 in women *(6)*. It was the fourth most common cancer overall, and the third leading form of cancer specifically among both men and women. Estimated new rectal cancer cases for the same time period were 36,400, with 20,200 occurring in males and 16,200 in females. Rectal cancer was the eighth most common cancer overall, seventh most common among men, and eighth most common among women.

There were an estimated 47,700 colon cancer deaths in the United States in 2000, with 23,100 in men and 24,600 in women. It was the second most common cause of death resulting from cancer (after lung cancer), ranking third among both men and women. Rectal cancer accounted for an additional 8600 deaths, with 4700 men and 3900 women. It was ranked 15th among the leading causes of cancer deaths, 12th among men, and 13th among women.

Between 1986 and 1997, there was a decline in the overall cancer incidence and mortality rates within the United States *(5)*, as depicted in Fig. 1 *(7)*.

There is variability in colorectal cancer incidence rates in different states within the United States. This state-to-state variation ranged from 32.4 new cases per 100,000 in Utah to 51.9 cases per 100,000 in Rhode Island *(5)*. During the same time period, the same state-to-state variation in death rates from colorectal cancer ranged from 12.3 per 100,000 in Utah to 20.0 per 100,000 in New Jersey *(5)*. These state-to state variations may reflect different subject demographics, such as race and ethnicity, differences in cancer registration, as well as differences in environmental factors, such as diet and occupation.

2.2. International Variations

International variations in the incidence and mortality rates from colon and rectal cancer differ. Colon cancer varies approx 20-fold internationally *(8)*. Although there is evidence for genetic predisposition to colon cancer, most of this variation is attributed to differences in dietary habits and other environmental factors.

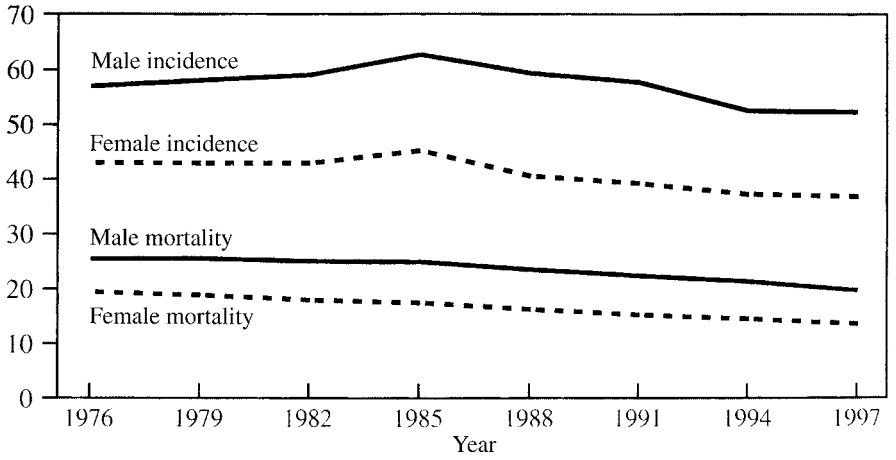

Fig. 1. Age-adjusted mortality rates (per 100,000) for colon and rectal cancer. *SEER Cancer Statistics Review*, 1973–1997 *(7)*.

The estimated age-standardized incidence rates of colon and rectal cancer (per 100,000) by region, and gender are shown in Table 2 *(9)*. The highest rates are seen in Western countries, such as Australia/New Zealand (45.8 male, 34.8 female), North America (44.3 male, 32.8 female), and western Europe (39.8 male, 29.0 female), with lower rates in all parts of Africa (except South Africa) and South Central Asia (5.0 male, 3.8 female).

Incidence rates have risen in most regions since 1985, except for North America, where they have decreased. The estimated number of cases has increased by 15.5% between 1985 and 1990 (21% in men, 10% in females) *(9)*.

Age-adjusted mortality rates per 100,000 population for 45 countries for 1994 to 1997 indicate the highest rates in Western countries, such as New Zealand (26.4 male, 19.1 female), Australia (20.2 male, 13.3 female), United Kingdom (18.0 male, 11.6 female), United States (15.2 male, 10.4 female), and eastern European countries such as the Czech Republic (34.3 male, 17.3 female) and Hungary (34.3 male, 18.7 female), with low rates in Asian countries, such as China (7.9 male, 6.4 female) and South America (Table 3) *(6)*.

Cancers of the colon and rectum are similar with respect to their geographical distribution. In high-risk populations, the ratio of colon cancer to rectal cancer is greater than or equal to 2 : 1, whereas in low-risk countries, the rates are similar *(2)*.

Within countries, there is also a variation in incidence between urban and rural centers, with an increased incidence in urban regions *(10)*.

2.3. Age

The probability of developing invasive colorectal cancer in the United States in 2000 increased with increasing age, irrespective of gender *(6)*. Colorectal cancer is uncommon among those less than 40 yr of age, with a rapid increase in incidence after age 50 yr *(11)*. This has implications for screening, which is most cost-effective for those at higher risk.

During the period 1994–1996, the risk of developing colorectal cancer for men was 1 in 1579 from birth to age 39, 1 in 124 for ages 40–59, and 1 in 29 for ages 60–79. For women, the risk was 1 in 1947 from birth to age 39, 1 in 149 for ages 40–59, and 1 in 33 for ages 60–79 *(6)*.

Table 2
Estimated Age Standardized Rates of Colon/Rectum Cancer Incidence by Sex and Area, 1990 (per 100,000)

Site	*Male*	*Female*
Eastern Africa	8.1	4.2
Middle Africa	2.3	3.4
Northern Africa	6.0	4.2
Southern Africa	11.2	8.4
Western Africa	4.7	3.9
Caribbean	16.0	15.5
Central America	8.8	7.9
South America (temperate)	27.2	24.4
South America (tropical)	15.0	13.6
North America	44.3	32.8
Eastern Asia: China	13.3	10.2
Eastern Asia: Japan	39.5	24.6
Eastern Asia: Other	21.3	14.1
South Eastern Asia	11.9	8.9
South Central Asia	5.0	3.8
Western Asia	8.8	7.6
Eastern Europe	25.3	18.5
Northern Europe	34.4	26.1
Southern Europe	28.8	20.2
Western Europe	39.8	29.0
Ausatrlia/New Zealand	45.8	34.8
Melanesia	11.1	5.3
Micronesia/Polynesia	17.6	11.3
Developed Countries	35.9	25.4
Developing Countries	10.2	8.1
All areas	19.4	15.3

Adapted from ref. *9*.

For patients ≥ 50 yr, colorectal cancer incidence rates were higher for men than women *(5)*. For patients < 50 yr of age, the incidence rates were similar for men and women.

2.4. Gender

In the Annual Report to the Nation on the Status of Cancer 1973–1997, colorectal cancer rates were higher in men than women, regardless of race *(5)*. The colorectal cancer incidence rate was greater than 40% higher in men than women.

The overall sex ratio for colon cancer worldwide is nearly equal. This is in contrast to rectal cancer, for which there is a male predominance, especially with increasing age *(2)*.

In terms of incidence, colorectal cancer is the third most frequent cancer among males and ranks second for women *(2)*. It is the fourth leading cause of cancer mortality for both sexes, with a more favorable outcome than some cancers at other sites *(2)*. In males, age-standardized rates range from 25.3 per 100,000 (Eastern Europe) to 45.8 (Australia/New Zealand). For females, the rates range from 18.5 (Eastern Europe) to 34.8 (Australia/New Zealand) (Table 2) *(9)*.

Table 3
Cancer Around the World: Age-Adjusted Death Rates per 100,000 Population for Colon and Rectal Cancer for Different Countries, 1994–1997*

Country	*Male*	*Female*
United States[a]	15.2 *(27)*	10.4 *(23)*
Australia[b]	20.2 *(10)*	13.3 *(10)*
Austria[a]	21.7 *(8)*	12.2 *(14)*
Bulgaria[c]	17.2 *(20)*	11.4 *(19)*
Canada[b]	16.1 *(26)*	10.3 *(25)*
Chile[c]	7.0 *(38)*	6.7 *(36)*
China[c]	7.9 *(36)*	6.4 *(37)*
Colombia[c]	4.8 *(44)*	5.1 *(40)*
Croatia[d]	22.5 *(6)*	11.5 *(18)*
Cuba[b]	9.4 *(34)*	11.3 *(20)*
Czech Republic[e]	34.3 *(1)*	17.3 *(3)*
Denmark[e]	22.7 *(5)*	15.6 *(4)*
France[b]	16.6 *(22)*	9.6 *(29)*
Germany[a]	20.8 *(9)*	14.0 *(7)*
Greece[e]	8.0 *(35)*	6.2 *(38)*
Hungary[f]	34.3 *(2)*	18.7 *(2)*
Ireland[b]	22.5 *(7)*	13.3 *(9)*
Israel[e]	17.9 *(18)*	13.8 *(8)*
Japan[g]	17.1 *(21)*	9.9 *(28)*
Mexico[b]	3.6 *(45)*	3.3 *(45)*
New Zealand[c]	26.4 *(3)*	19.1 *(1)*
Russian Fed[b]	18.2 *(14)*	12.6 *(12)*
United Kingdom[a]	18.0 *(17)*	11.6 *(17)*

Adapted from ref. *6*.
*Rates are age-adjusted to the World Health Organization world standard population:
[a]1994–1997; [b]1994–1995; [c]1994 only; [d]1995–1996; [e]1994–1996; [f]1996–1997; [g]1995–1997.

2.5. Time Trends

Colorectal cancer mortality rates have been decreasing among women since 1950 *(5)*. The death rates for men did not begin to decrease until the 1980s. Time trends with respect to subsite distribution generally show an increase in right-sided and sigmoid tumors, with stability in the incidence rate of rectal tumors *(12)*.

Time trends in the United States from 1973 to 1997 demonstrate that after a 13-yr increase in the incidence of colorectal cancer, incidence rates began to fall in 1986 for the first time and have continued their downward trend since that time *(5)*, as depicted in Fig. 1 *(7)*. Colorectal cancer incidence rates have decreased an average of 1.6% per year *(5)*. This decline was predominantly in the distal colon and rectum and was almost equal in males and females. From 1973 to 1994, the age-adjusted incidence rate of cancer had decreased in the distal colon and rectum by 24% in white males and by 26% in white females. A decrease in incidence rates was also seen in the proximal colon, with 12% in white males and 14% in white females. Rates among African-Americans were variable, showing no clear pattern of decline, and an increase in the incidence of cancers in the proximal colon in both sexes has occurred since 1986.

In contrast, the incidence rate of colorectal cancer in England and Wales has been gradually rising and is most marked for colon cancer in males, irrespective of age *(13)*. Similar trends were found in the rest of Europe, in particular eastern Europe, where an average increase of greater than 14% in age-specific incidence rates per 5-yr period was seen between 1973 and 1987.

A rise in the age-specific incidence of colorectal cancer per 5-yr period of more than 35% in males and 27% in females was also seen in Japan between 1973 and 1987.

From 1990 to 1996, colon and rectal cancer death rates in the United States decreased significantly, an average of 1.7% per year. Colon and rectum cancer deaths among men were at their highest level in 1990, at 28,635, and had declined to 28,075 in 1997. Although the recorded number of cancer deaths for women have continued to increase, colorectal cancer deaths as a subset have declined, falling from a peak of 29,237 in 1995 to 28,621 in 1997.

Early detection through appropriate screening may be partly responsible for these changes in incidence and mortality. Improvements in mortality may also reflect improvements in definitive therapy, such as surgical techniques and adjuvant therapy *(14)*. Other possible factors contributing to the decline in incidence rates may be changes in diet *(14)* and physical activity *(15)*. Although not in widespread use, chemoprevention with aspirin *(16)* and other nonsteroidal anti-inflammatory drugs (NSAIDs) *(17,18)* is also continuing to show promise

2.6. Race/Ethnicity

Among US women, colorectal cancer was more common for Hispanic, American Indians/Alaska Natives, and Asian/Pacific Islanders, ranking second only to breast cancer, whereas it ranked third after both breast and lung cancer for white and black women *(5)*. Black women are more likely than white women to develop cancers of the colon and rectum *(5,19)*.

Between 1990 and 1996, the age-adjusted incidence rate for cancers of both the colon and rectum was 44.9 per 100,000 for black women compared with 36.8 per 100,000 for white women *(6)*. The incidence rates were lower for Asian/Pacific Islanders, American Indians, and Hispanic Americans (Table 4) *(6)*.

The incidence rate for colorectal cancer increased until 1984 for white women, but has subsequently decreased *(5)*. The colorectal cancer incidence rate for black women also increased until 1980, but has been approximately level since then.

Black women are more likely to die of colon and rectal cancers than women of other ethnic and racial groups. During the same time period, the mortality rates were 20.0 per 100,000 for black women and 14.5 per 100,000 for white women *(6)*. Mortality rates were also lower for Asian/Pacific Islanders, American Indians, and Hispanic Americans *(5)* (Table 5) *(6)*.

There was a decline in death rates for colorectal cancer for white women between 1973 and 1997. The decline was more rapid after 1984 *(5)*. The mortality rates for black women first began to decline in 1985. This decline was less marked for black women than for white women.

Black men have the highest rates for cancers of the colon and rectum, as well as for lung and prostate cancers. Between 1990 and 1996, the male incidence rates for cancers of both the colon and rectum was 58.1 per 100,000 for black men compared with 53.2 per 100,000 for white men *(6)*. Similar to the incidence rates in women, rates among men were lower among Asian/Pacific Islanders, American Indians, and Hispanic Americans *(5)* (Table 4) *(6)*.

Table 4
Incidence Rates of Colon and Rectum Cancer by Race and Ethnicity, US, 1990–1996*

	White	*Black*	*Asian/Pacific Islander*	*American Indian*	*Hispanic*[a]
Total	43.9	50.4	38.6	16.4	29.0
Male	53.2	58.1	47.5	21.5	35.7
Female	36.8	44.9	31.4	12.4	24.0

Adapted from ref. *6*.
*Rates are per 100,000 population and are age-adjusted to the 1970 US standard population.
[a]Hispanic is not mutually exclusive of white, black, Asian/Pacific Islander, or American Indian.

Table 5
Mortality Rates for Colon and Rectum Cancer by Race and Ethnicity, US, 1990–1996*

	White	*Black*	*Asian/Pacific Islander*	*American Indian*	*Hispanic*[a]
Total	17.4	23.1	10.9	9.9	10.4
Male	21.5	27.8	13.4	11.0	13.2
Female	14.5	20.0	9.0	8.9	8.4

Adapted from ref. *6*.
*Rates are per 100,000 population and are age-adjusted to the 1970 US standard population.
[a]Hispanic are not mutually exclusive of white, black, Asian/Pacific Islander, or American Indian.

Colorectal cancer incidence rates among white men began decreasing after 1985, with the most rapid decline between 1991 and 1995. Rates in black men increased by an average of 4.4% per year between 1973 and 1980, but have remained level since that time *(5)*. Between 1973 and 1990, estimated incidence rates for colorectal cancer were lower for black men than white men. Since 1990, colorectal cancer incidence rates have been lower for white men than black men.

Colorectal cancer incidence rates among white men began decreasing after 1985, with the most rapid decline occurring between 1991 and 1995. Rates in black men increased by an average of 4.4% per year between 1973 and 1980 but have remained level since that time *(5)*.

Black men also have the highest mortality rates from these cancers. Between 1973 and 1990, the mortality rates were 27.8 per 100,000 for black men and 21.5 per 100,000 for white men *(6)*. The mortality rates among men were lower for Asian Pacific Islanders, American Indians, and Hispanic Americans (Table 5) *(6)*.

Colorectal mortality rates began to decline by 0.6% per year between 1978 and 1986 for white men. Since 1986, the decrease per year has been even more rapid. Colorectal cancer incidence rates among white men were level between 1973 and 1978 and began to decline between 1978 and 1986 by 0.6% per year *(5)*. Death rates among black men rose until 1989 and have leveled off since that time. Prior to 1980, mortality rates for colorectal cancer were lower for black men than white men.

2.7. Migrants

Migrant data suggest a 20-fold international difference in the incidence ratio of colorectal cancer *(8)*. Studies looking at the incidence of colorectal cancer among migrants, Japanese living in the United States and Europeans living in either the United States or Australia,

indicate that migrants from low-risk areas to high-risk areas, exposed to the environment of the host population, develop the same cancer risk as that population *(12,20)*.

Among Japanese in Japan, colorectal cancer has a very low incidence rate, although it is rising *(21)*. In Japan, the fat intake is low in comparison to Western countries. Dietary fiber intake was high and is now decreasing *(22)*. Japanese migrating to Hawaii and California experience increases in colorectal cancer incidence, with first-generation immigrants having about double the frequency of cancers of the sigmoid colon and rectum as their white neighbors *(21,23)*. In another study, US-born Japanese men had incidence rates of colorectal cancer twice that of foreign-born Japanese men and about 60% higher than those of US-born white men *(24)*. United States-born Japanese women had a colorectal cancer incidence rate that was about 40% higher than among Japanese women born in Japan or US-born white women.

Similarly, colorectal cancer rates among were four to seven times higher than rates in China; this was most striking among men and with increasing age *(25)*.

3. PATHOLOGIC ISSUES

3.1. Adenoma–Carcinoma Sequence

The adenoma–carcinoma sequence was originally proposed by Hill and colleagues in 1978 *(26)*. It is generally believed that almost all colorectal adenocarcinomas arise from adenomas.

Vogelstein and colleagues have provided evidence for a series of specific chromosomal and somatic genetic changes that occur during the transition from normal colonic mucosa to invasive carcinoma *(27–29)*. The most common changes are point mutations of the K-ras protooncogene, and mutations in three growth suppressor genes, *p53* on chromosome 17p *(30)*, the adenomatous polyposis coli (APC) gene on chromosome 5q *(31)*, and DCC (deleted in colon cancer) gene on chromosome 18q *(29)*. Both alleles of the three tumor suppressor genes must be lost or defective for phenotypic expression to occur, whereas in the case of the protooncogene, K-ras, mutation need only occur in one allele for phenotypic expression to occur *(32)*. No gene has been implicated as occurring in all cases of colorectal cancer. Figure 2 depicts a proposed sequence of allelic losses during colorectal cancer development, although the exact number and sequence of genetic mutations necessary for carcinoma formation remain to be determined.

The APC gene has been mapped to the tumor supressor locus (5q21–q22) *(33)*, and it is thought to be involved in the initiation of adenoma formation *(34)*. Inactivation of the APC gene by two mutations is involved in the development of adenomas, and loss of heterozygosity of the APC gene is associated with further progression to carcinoma *(35)*. It is mutated in between 30% and 75% of sporadic adenomas and adenocarcinomas *(32,33,35)*. The mutation is apparent even in early adenomas, and it remains constant throughout the malignant transformation *(33)*. Mutation of the APC gene is the most frequent genetic mutation seen in colorectal cancer *(29)*. Germline mutations of the APC gene are also responsible for the formation of multiple adenomas in familial adenomatous polyposis (FAP) *(31,35)*.

The APC protein may be involved in a series of interactions between proteins involved in cell signaling *(36)*, apoptosis *(37)*, and cell adhesion *(38)*.

K-ras is thought to promote tumorigenesis by causing hyperproliferation of colorectal cells, both at the early adenoma stage and later at the time of malignant transformation. Expression of the protooncogene is less in small adenomas, becoming more pronounced at

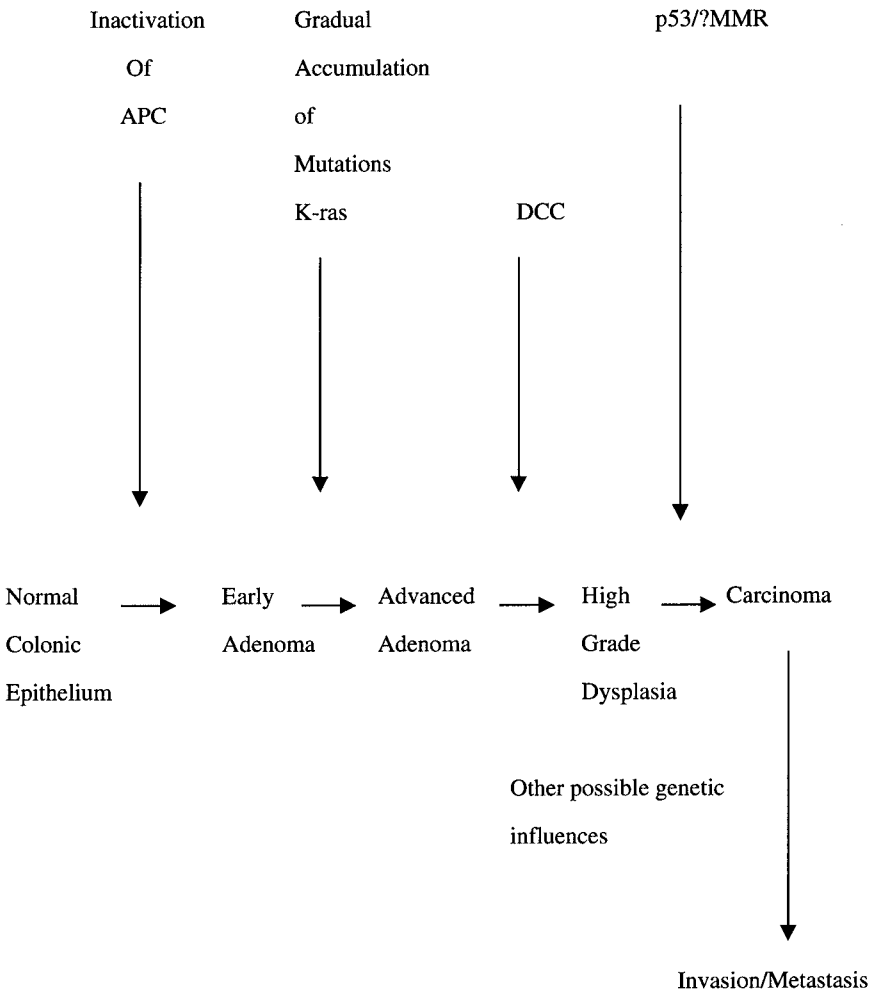

Fig. 2. A model of genetic events in colorectal carcinogenesis.

around 50% in larger adenomas (>1 cm in size) and adenocarcinomas *(27,39)*. The role of the K-ras mutation in tumorigenesis is not entirely clear, as mutations have also been found in normal colonic epithelium *(40)* and aberrant crypt foci *(41)*.

The DCC gene is located on chromosome 18q *(27,42)*, and is a neural cell adhesion molecule. It may play a role in tumor progression, invasion, and metastasis. Allelic loss of this chromosome is seen in 50% of advanced adenomas and more than 70% of carcinomas.

The *p53* gene is located on chromosome 17p. It appears to be involved late in malignant transformation, during the conversion from adenoma to focal carcinoma *(30,43)*. Loss of the *p53* gene is uncommon in adenomas but occurs in greater than 75% of carcinomas *(27,30)*. Mutation of *p53* may also have multiple effects, including a decreased ability to detect DNA damage, karyotypic instability, impaired G1 cell-cycle arrest, and decreased apoptosis *(44–46)*.

Germline mismatch repair (MMR) mutations occur in hereditary nonpolyposis colon cancer (HNPCC). The MMR mutations are thought to increase the overall mutation rate, but they may also play a role in the initiation of tumorigenesis *(46)*. MMR mutations are also

found to occur in about 15% of sporadic colorectal cancers *(47,48)*. MMR mutations seem to occur at the stage of late adenoma or transformation to carcinoma *(49)*.

Microsatellite genetic instability has been demonstrated at the benign adenoma stage of HNPCC tumors. Carcinoma is more likely to occur in adenomas with a greater rate of genetic instability *(50)*. This finding supports the hypothesis of adenoma–carcinoma progression in HNPCC.

Other possible tumor suppressor genes have also been identified. These genes may be involved in later stages of tumorigenesis. An example is mutation at the p16 (MTS1) locus, resulting in failure of cell-cycle arrest *(51)*.

There may also be genetic changes specific for invasion and metastasis *(46)*.

3.2. Subsite Distribution

Surveillance, Epidemiology, and End Results Program (SEER) data show that left-sided tumors outnumber right-sided tumors throughout the United States *(52)*. There is evidence to support a progressive left-to-right shift in cancer distribution within the colon during the latter part of the last century *(52,53)*. SEER data show that the ratio of right-sided cancer to total colorectal cancer has increased from 1970 to 1990 among all age-, sex-, and race-matched cohorts *(52)*.

In the Annual Report to the Nation on the Status of Cancer between 1973 and 1997, all anatomic subsites demonstrated a decline in incidence rates except the right side of the colon, incorporating the cecum, appendix, ascending colon, and hepatic flexure *(5)*.

For whites, increased age has been associated with a progressive decline in the proportion of distal colorectal cancer for both genders, as evidenced by SEER incidence data from 1977, 1986, and 1994 *(54)*. The greatest and most consistent decline was seen in 1994. Distal colorectal cancer became less prevalent at about age 72 for women and age 82 for men. Among the younger age cohorts, distal colorectal cancer was more prevalent than proximal disease for both genders. There was no similar trend in subsite distribution among African-Americans, regardless of gender or age, although proximal disease is generally more prevalent than among whites.

There appears to be a relative increase in the incidence of right-sided tumors after age 70 *(55)*. This trend is more striking in females in higher-risk areas *(53)*. The relative risk for right-sided tumors also increases among males after the age of 70 in high-risk nations, but the ratio is usually less than 1.0 *(52,53)*.

A retrospective review of 1694 consecutive cases of colorectal cancer diagnosed at the University of Chicago Medical Center during a 25-yr period (1960–1984) demonstrated a 10.2% increase in cancers originating in the cecum or ascending colon and a 15.8% decline in rectal and rectosigmoid carcinomas during this period *(56)*.

A review of the National Cancer Registry registration data for colorectal cancer in New Zealand from 1972 to 1975 (4678 cases) showed an excess of right-sided colonic tumors in females compared with males, with males having a higher incidence of rectal cancers *(57)*. Environmental factors that may contribute to colon carcinogenesis may produce specific segmental effects within the large bowel.

In a study from western New York, total energy intake and dietary fat disproportionately increased the risk for left-sided tumors *(58)*. In contrast, other studies have demonstrated an increase in right-sided tumors in the setting of high-fat diets both for men *(59)* and women *(60)*.

An association between cholecystectomy and an increased risk of colon cancer has been suggested. Two meta-analyses found a slightly increased risk for right-sided colon cancers

(61,62). Possible explanations for this observation include changes in bile acid composition and flow and concomitant risk factors for both diseases, such as obesity *(63)*.

This increase in proximal colon cancers and change in subsite distribution within the large bowel add to the evidence for the need for full colonoscopic visualization as the optimal technique for detection of colorectal neoplasms.

4. RISK FACTORS

4.1. Diet

The large international variation in the incidence of colorectal cancer may be the result in part of genetic predisposition to colon cancer, but it may largely be related to differences in dietary habit. However, it remains difficult to interpret the impact of any one dietary constituent in isolation on the risk of colon cancer.

A thorough depiction of diet as a risk factor for colorectal cancer is beyond the scope of this chapter. An in-depth analysis of the literature with respect to the global impact of food and nutrition was recently published *(64)*.

There is convincing evidence that diets high in vegetables decrease the risk of colorectal cancer. Consumption of diets high in red meat probably increases the risk of colorectal cancer *(64)*. It is not clear that there is an association between the intake of dietary fiber and the risk of colorectal cancer *(65)*.

Dietary influences on colon cancer development are covered in detail in Chapter 3.

4.2. Family History and Genetics

Family history is an important risk factor for colorectal cancer. Epidemiological case-control studies of family history suggest that there is about a twofold to threefold risk of the development of colorectal cancer for an individual with a single first-degree relative suffering with the disease *(66–68)*. The risk becomes greater if more relatives are affected *(68)*. Rozen and colleagues studied 471 asymptomatic adults with first-degree relatives who had adenomatous polyps and/or cancer *(68)*. Those screened had a significant linear trend of increasing risk of colorectal neoplasia with increasing number of affected relatives. When considering cancer cases only, the risk was threefold if only one relative was affected, whereas the risk increased to ninefold with more than one affected relative. An increased risk was also seen in a reconstructed cohort study specifically addressing the risk of colorectal cancer among patients of colorectal adenomas, the relative risk being 1.74 (95% confidence interval [CI], 1.24–2.45) among first-degree relatives of patients with newly diagnosed adenomas compared with the risk among first-degree relatives of controls *(69)*.

A prospective cohort study of subjects from both the Nurses' Health Study and the Health Professionals Follow-up Study was analyzed specifically for whether a family history of colorectal cancer (in first-degree relatives) was an independent risk factor for colorectal cancer *(66)*. The age-adjusted relative risk of colorectal cancer for men and women with affected first-degree relatives, compared to those without a family history of the disease, was 1.72 (95% CI: 1.34–2.19). The relative risk for subjects with two or more affected first-degree relatives was 2.75 (95% CI: 1.34–5.63). The risk was greatest for patients under 45 yr with one or more affected first-degree relatives, with a relative risk of 5.37 (95% CI: 1.98–14.6).

Hereditary colon cancer syndromes will be mentioned only briefly. A more detailed discussion is provided in a later chapter.

Familial adenomatous polyposis is an autosomally dominant inherited disease, which predisposes to the development of colorectal cancer *(70)*. The colon is involved with innumerable adenomatous polyps that occur early in life. Virtually all individuals affected will develop colorectal cancer unless they undergo a prophylactic colectomy, with 75% of subjects developing colorectal cancer by the age of 35 yr. APC is the germline mutation in FAP, involving a large deletion on chromosome 5q *(31,35)*. Carcinoma associated with FAP accounts for about 1% of all colorectal cancer cases *(71)*. Colorectal cancer cases in subjects with FAP have a left-sided predominance *(72)*.

Hereditary nonpolyposis colorectal cancer (Lynch syndrome) is an autosomally dominant inherited syndrome with an increased incidence of colorectal cancer. The associated germline mutations in mismatch repair genes have been identified as *MSH2*, *MLH1*, *PMS1*, and *PMS2*. Recently, the newly identified *hMLH3* gene has also been considered as another possible mismatch repair gene *(73)*. HNPCC probably accounts for at least 5% of all colorectal cancers. It is characterized by an earlier age of cancer onset, proximal predominance of disease, the development of multiple synchronous and metachronous cancers, and an excess of certain extra-colonic tumors *(74)*.

4.3. Inflammatory Bowel Disease

Long-standing ulcerative colitis is associated with an increased risk of colorectal cancer; reported relative risks compared to the general population vary between 1 and 20 *(75–77)*. Carcinomas begin to appear 5–8 yr after the onset of ulcerative colitis, with an absolute risk of colorectal cancer of 30% after 35 yr *(78)*. Incidence rates for the development of colorectal cancer in the setting of ulcerative colitis are not the same universally, with reports of lower rates in Scandinavia and Europe *(79,80)*.

The cumulative risk of colorectal cancer appears to vary according to the extent of colitis, with a significantly higher risk seen with pancolitis rather than just left-sided disease *(22,77)*. There is a higher proportion of right-sided and transverse colon carcinomas in patients with ulcerative colitis compared to patients without colitis *(81)*. Younger age at diagnosis of ulcerative colitis may be an independent risk factor for the development of colorectal cancer *(77)*. Additional risk factors may include the presence of primary sclerosing cholangitis *(82,83)*, the severity of the colitis and frequency of attacks *(84)*, the effect of medications for the disease *(85)*, and folate deficiency and folate supplementation *(86)*. The incidence of colorectal cancer is equal for both sexes. Often, the lesions are aggressive and poorly differentiated at the time of diagnosis. APC gene mutations have also been reported to occur at a lower frequency in colorectal cancers associated with ulcerative colitis than in sporadic cancers *(87)* and may not be the initiating event for malignant transformation *(88)*.

Patients with pancolitis of more than 8 yr duration should consider periodic colonoscopic surveillance or prophylactic colectomy *(89)*. Surveillance programs to detect dysplastic lesions prior to the development of colorectal cancer may be a method of preventing prophylactic colectomy. However, colorectal cancers that develop in ulcerative colitis patients often are infiltrative and schirrous, and their flat nature may make them more difficult to be detected at the time of endoscopy *(81)*.

The evidence for an increased incidence of colorectal cancer among people afflicted with Crohn's disease is less clear *(90)*. Actuarial data suggest that the risk of developing colorectal cancer as a complication of long-standing Crohn's disease may be 4.3–20 times that in the general population *(91,92)*.

4.4. Medications

Aspirin and other NSAIDs have recently been implicated as potential protective agents against the development of colorectal cancer and adenomatous polyps. This evidence is not yet conclusive. There is evidence supporting the beneficial effect of these drugs in chemically induced colon cancer in rodent models *(93–97)* and in patients with FAP *(17,18)*. There are several possible mechanisms by which these drugs may inhibit tumor development. NSAIDs appear to induce apoptosis *(98,99)* as well as inhibit cyclooxygenase-2 *(18)*.

Two randomized clinical trials showed a decrease in the number and size of colorectal polyps in patients with FAP treated with sulindac *(17,100)*. Polyps did not fully resolve, and they recurred on cessation of therapy.

Recently celecoxib, a selective cyclooxygenase-2 inhibitor, was shown to significantly reduce the number of colorectal polyps in patients with FAP in a double-blind, placebo-controlled study *(18)*. Treatment with celecoxib consisted of 100 mg or 400 mg twice daily for 6 mo. After 6 mo, the patients receiving 400 mg twice daily celecoxib had a 28% reduction in the mean number of colorectal polyps and a 30.7% reduction in the polyp burden (the sum of polyp diameters). The reductions in the group receiving 100 mg celecoxib twice a day were not statistically significant.

The first evidence to suggest that aspirin might reduce the risk of colorectal cancer was from a retrospective exploratory analysis published in 1988 by a group from Melbourne, Australia *(101)*. A 40% lower risk of incident colon cancer was found among people who regularly used aspirin, although the frequency of use was not specified. Decreased risk was also seen for subjects using NSAIDs other than aspirin.

The Boston Collaborative Drug Study conducted an epidemiologic study specifically to test the aspirin–colon cancer hypothesis *(102)*. They identified an approximately 50% lower risk of incident colorectal cancer among people who regularly used aspirin. Regular use was defined as at least 4 d a week for at least 3 mo.

The relation of aspirin use to fatal colon cancer was assessed in Cancer Prevention Study II (CPS II), a prospective cohort study that enrolled 1,185,239 Americans between 1982 and 1988 *(16)*. Death rates from colon cancer decreased in both men and women with more frequent use of aspirin. The trend of decreasing relative risk was similar after controlling for other potential risk factors for colon cancer *(103)*. For rectal cancer, aspirin use was associated with a greater reduction in risk in men than in women. Several other epidemiologic studies and clinical trials provide additional data on the aspirin–colon cancer hypothesis *(104–108)*.

These findings are in contrast to those of the U.S. Physicians Health Study, a randomized clinical trial of aspirin (325 mg every other day) in preventing cardiovascular disease. It was also the first randomized, placebo-controlled study of whether aspirin can reduce colon cancer incidence *(109)*. Male physicians given aspirin for 5 yr had a slightly higher risk of invasive colorectal cancer (relative risk [RR] = 1.15; range; 0.80–1.65) and lower risk of *in situ* cancer or polyps (RR = 0.86; range; 0.68–1.10), although they had no systematic screening for colorectal cancer or polyps. It is not clear why this result conflicts with findings from other studies. The every-other-day dosage is somewhat unusual, and it is possible that the duration of therapy may have been insufficient to demonstrate a protective effect.

Another prospective exploratory study assessing the risk of incident colon cancer among approx 14,000 elderly American daily aspirin users reported a small increased risk *(110)*. Overall the relative risk of colon cancer was 1.5 (95% CI = 1.1–2.2).

4.5. Occupation

Among asbestos workers, colorectal cancer is the third most common malignancy after lung cancer and mesothelioma *(111)*. There is a reported increased relative risk for colon cancer in the range of 1.4–3.0 *(111–115)*. There was no evidence for synergy between asbestos exposure and smoking for colon cancer, in contrast to the definite relationship seen with lung cancer *(113)*. The increased risk of colon cancer among asbestos workers is probably secondary to exposure of the colonic mucosa to swallowed asbestos-contaminated sputum *(113)*. There is a temporal relationship, with exposure predating the development of malignancy by at least 20 yr, and evidence to support a dose-response relationship *(111)*. Identification of asbestos bodies among colon cancer cells in an asbestos worker add supportive experimental evidence to the concept that occupational asbestos exposure is a colorectal cancer risk factor *(116)*. A case-control study conducted in New York City found an elevated risk for both adenomatous polyps and colorectal cancer among subjects with a significant exposure to asbestos *(117)*.

Acrylonitrile is a gaseous monomer widely used for the synthesis of plastic and synthetic rubber and fiber polymers. Two historical cohort studies of acrylonitrile workers showed increases in both the proportional mortality ratio (PMR) *(118)* and the standardized mortality rate (SMR) *(119)*. All of the cases of colorectal cancer occurred in workers who had more than 6 mo of exposure and with a long latency period of up to 10–30 yr.

Ethylacrylate and methyl methacrylate are monomers capable of conversion into versatile transparent polymers that were widely used during World War II in the manufacture of airplanes. An historical cohort study of mortality among workers employed at a manufacturing plant between 1933 and 1946 found an increased colorectal cancer SMR, with at least a 10–yr latency period *(111)*.

Dibromochloropropane (DMCP) and related halogenated organic compounds have a causal association with rectal cancer, with an increase in PMR documented by the National Institute for Occupational Safety and Health (NIOSH) *(111)* and two other historical cohort studies *(120,121)*.

An increased SMR for colon cancer has been reported among printing workers *(122)* and an excess of rectal cancers in a study of commercial pressmen over 65 yr of age *(123)*. Statistically significant SMRs were also found for colorectal cancer among automotive workers making wooden models and patterns *(124,125)*.

Two historical cohort studies of synthetic rubber workers demonstrated an increase in mortality from colorectal cancer as well as other cancers *(126,127)*. A British study failed to confirm this association, despite demonstrating increases in lung cancer and gastric cancer *(128)*.

An historical cohort study also demonstrated statistically significant SMRs for colon and rectal cancer among paint and varnish workers employed for at least 1 yr *(129)*. Colon and rectal cancer had the highest risks of any neoplasm studied.

4.6. Smoking and Alcohol

Smoking has not been conclusively shown to be a risk factor for colorectal cancer, but it has been consistently associated with adenomatous polyps. Cigarettes have been associated with an approximately twofold increase in risk of colon adenomas or polyps *(130–137)*.

In a large case-control study based on colonoscopy results in New York, there was a statistically increased risk between heavy cigarette smoking (smokers with ≥ 40 pack-years of

smoking) and risk of adenoma, but no increased colorectal cancer risk *(138)*. An hypothesis to explain the paradox of this finding was that the association between cigarette smoking and risk for colorectal cancer might have been masked by inclusion in the control group of subjects with adenomas. The authors also concluded that the major effect of smoking on the adenoma–carcinoma sequence occurred in the earlier stages of adenoma formation. It is likely in the causal relationship between smoking and colorectal adenomas, in contrast to cancers, that the effect of smoking on progression from an adenoma to invasive carcinoma is less evident as a result of other factors impacting on the malignant transformation *(139)*. Similar results were found in a case-control study from France *(140)*. Smoking was associated with a risk of adenomas in men, but there was no association between tobacco and cancer risk, adding support to the concept of an independent effect of tobacco in men at early steps of the adenoma–carcinoma sequence. In women, no association was observed between smoking and the risk for adenoma or cancer.

In a cohort study of 248,046 American male veterans followed prospectively over a 26-yr period, the risk of death was significantly increased for both colon and rectal cancer among current and former cigarette smokers in comparison with veterans who had never used tobacco *(141)*. The patterns of risk were less marked among pipe and cigar smokers. Risk of rectal cancer was also significantly increased among tobacco chewers or users of snuff. Risk increased significantly for both sites with number of pack-years, earlier onset of tobacco use, and total number of cigarettes smoked per day. A limitation of the study was that data were not available for other potential risk factors for colorectal cancer, in particular diet and total physical activity. In addition, mortality rather than incidence of colorectal cancer was the measure of effect, with death certificates being used to determine the type of cancer.

Five prior case-control studies using population controls had reported increased risks of colon cancer with cigarette smoking *(142–146)*, in contrast to earlier case-control and cohort studies that have not consistently shown an association between tobacco use and the incidence of colorectal cancer *(147–152)*.

The results of a large cohort study (the Physicians' Health Study I) recently reported on the association between lifetime cigarette smoking and colorectal cancer incidence *(14)*. A cohort of 22,000 healthy men aged between 40 and 84 yr were followed for more than 12 yr. Cigarette smoking was found to be an independent risk factor for the development of colorectal cancer. The strongest risk was found among current smokers of greater than or equal to 20 cigarettes a day. Cumulative lifetime exposure was also found to increase the risk of colorectal cancer.

Among smokers compared with nonsmokers, colorectal cancers appear to be diagnosed at a later stage *(153–155)* and also at an earlier age *(155)*.

Alcohol is inconsistently associated with an increased risk of colon cancer *(4)*. Similar to the findings for colon cancer, results are varied with respect to an association between alcohol consumption and risk of rectal cancer.

Cohort studies investigating the association between alcohol and colon cancer among alcoholics *(156,157)* and brewery workers *(158)* failed to show any significant increased risk. For rectal cancer, only one of seven cohort studies addressing a possible association among alcoholics or brewery workers showed a significant association—in brewery workers in Dublin, Ireland *(158)*. In contrast, cohort studies of the general population, investigating the effect of alcohol consumption on colon cancer risk showed a significant association *(159–163)*. A dose-response relationship between alcohol and rectal cancer was observed in three of these studies *(161–163)*.

Case-control studies investigating the association between alcohol and colon cancer have had mixed results, both positive *(147,164–166)* and negative *(142,149,150,167–169)*. Similar results were seen for studies specifically looking at rectal cancer, with both positive associations *(169,170)* and no association seen *(149,168)*. Beer appeared to have a stronger relationship to cancer of the rectum in men than in women *(171)*.

4.7. Obesity and Physical Activity

Diet and lifestyle factors are thought to have important roles in the carcinogenic process. Obesity as well as lack of physical activity has been associated with an increased risk of colon cancer *(172,173)*.

The correlation between obesity and colon cancer incidence may reflect the association between obesity and increased intake of energy or fat. Increased body mass has been associated with an increased mortality rate from cancer, including colon cancer *(174,175)*.

There have been conflicting results with respect to the association between obesity and colon adenomas. One case-control study found that an increased body mass index (BMI) in women was a risk factor for colonic adenomas, but the same did not apply for men *(176)*. In contrast, a German study showed no relationship between being overweight and the incidence of colorectal adenomas for either sex, but there was an increased risk of high-risk adenomas among obese men *(177)*.

In an American Cancer Society study, a cohort of 419,080 men and 336,442 women was followed to ascertain the relationship between body weight and a variety of illnesses *(178)*. Increased body weight was associated with an increased PMR from colon cancer among men. No association was found for women in this study.

In the Framingham study of 5200 men and women who were followed for 18 yr, there was no association between being overweight by 20% and an increased incidence of colorectal cancer *(179)*.

Body weight in adolescence has also been evaluated as a predictor of colon cancer development in later life. Data from the Harvard Growth Study, which recorded heights and weights of 3000 children aged between 13 and 18 yr, examined the effects of being overweight during adolescence on health 55 yr later *(180)*. There was a significant association between a high BMI during adolescence and an increased risk of colorectal cancer among men (although this was based on only six deaths), but not among women.

A similar study of Harvard University alumni relied on questionnaires completed in 1962 and 1966 that gathered information on height, weight, sociodemographic characteristics, and medical history *(181)*. Of the 17,595 subjects who were followed for more than 20 yr, the 20% who were heaviest on entering college and during the period of the questionnaires had nearly 2.5 times the risk for colon cancer when compared to the leanest 20% among the group. After adjustment for degree of physical activity, the increased risk of colon cancer in the overweight group was evident only in the setting of less physical activity.

A third study followed a cohort of 52,539 men born between 1913 and 1927 in Hawaii and linked them to the Hawaii Tumor Registry, investigating the role of obesity in early adulthood *(182)*. Between 1972 and 1986, 737 cases of colon cancer were identified, and each case was matched with an average of 3.8 control subjects. Increased body weight during early and middle age was associated with an increased risk of developing cancer of the sigmoid colon, but no increased risk of cancer for other segments of the colon.

There is evidence to support an association between physical activity and risk of colon cancer *(4,64)*. Physical activity is inversely associated with risk of colon cancer. The majority of studies evaluating this association have concentrated on occupational activity

(25,164,183,184), although there have been some studies examining leisure time and total activity *(25,173,185,186)*. These studies have demonstrated a reduced risk of colon cancer with increased physical activity.

Lee and colleagues showed that individuals who reported high levels of physical activity throughout their lives were at a lower risk of developing colorectal cancer than individuals who had only a short duration of physical activity *(173)*.

4.8. Reproductive Factors

Studies on the potential protective effect of postmenopausal estrogen replacement therapy on the incidence of colon cancer have been contradictory. A meta-analysis of observational studies published between 1974 and 1993 reported that the overall risk of colorectal cancer, in the setting of estrogen hormone replacement therapy, was 0.92 (95% CI: 0.74–1.5) *(187)*.

A multicenter population-based case-control study in the United States found that the use of hormone replacement therapy had a significant inverse relationship to the risk of colorectal carcinoma, with the effect limited to women who were recent users of therapy *(188)*.

A cohort study of over 40,000 postmenopausal women originally participating in the Breast Cancer Detection Demonstration Project (BCDDP) in the United States had a small reduction in risk of colorectal cancer for recent hormone therapy, especially if therapy had been for 5 or more years in duration *(189)*.

A clinical review assessed 35 studies, including 3 meta-analyses *(190)*. Twenty-three suggested some degree of protective effect of hormone replacement therapy, 11 reported null results, and 1 suggested a negative impact. Confounding factors were as follows: There was only one prospective randomized controlled trial with small numbers; studies did not uniformly specify hormone type, dose, duration of therapy, or provide a subset analysis of impact on right- versus left-sided tumors; estrogen and progesterone effects were usually not considered separately; and many studies did not adequately control for confounding variables, such as family history or indication for colonoscopy.

In a case-control study from New York, reproductive variables such as parity, history of spontaneous or induced abortion, infertility, type of menopause, age at menopause, use of oral contraceptives, and use of menopausal hormone replacement therapy had no statistically significant association with risk of colorectal adenomas *(191)*. A lower risk of colorectal adenomas was found for women who had menarche before age 13 yr.

Prospective studies are still needed to determine whether a protective effect from hormone replacement therapy exists, the extent of this effect, and the mechanism of the effect.

5. CONCLUSION

Colorectal cancer remains the fourth most common cancer worldwide. Colon cancer occurs almost equally for both men and women. The probability of developing invasive colorectal cancer increases with increasing age, irrespective of gender.

The highest incidence rates are found in Australasia, Western Europe, and the United States, with the lowest rates in south-central Asia and all areas of Africa except South Africa.

Time trends indicate a fall in both incidence and mortality rates for colorectal cancer in the United States at the very end of the last century. This decline was most evident among white men and women.

Migrant data suggest a 20-fold international difference in the incidence rates of colorectal cancer. Migrants from low-risk areas to high-risk areas develop the same cancer risk as that

population. This observation may reflect genetic differences, but is also probably largely a result of environmental and dietary differences.

The concept of an adenoma–carcinoma sequence is widely accepted and appears to occur for both familial and sporadic forms of colorectal cancer. The idea of screening for colorectal cancer becomes important in this context. The subsite distribution of colorectal cancers tends to suggest a trend toward increased right-sided colon lesions, suggesting that full visualization of the colon with colonoscopy, rather than flexible sigmoidoscopy, is desirable *(192,193)*. Inflammatory bowel disease has also been shown to result in an increased rate of colorectal cancer, necessitating surveillance and therapeutic interventions.

Much has been written about the relationship between diet and colorectal cancer incidence rates. There appears to be an increased risk of colorectal cancer with increasing consumption of fat, protein, and meat. The inverse result can also be seen with increased consumption of fruit and vegetables. The impact of fiber intake on the incidence rate of colorectal cancer is less certain. The most recently published large cohort study suggested no positive impact on colorectal cancer incidence *(65)*. Two recent randomized trials with adenoma recurrence as the outcome have also shed doubt on the role of fiber *(194,195)*. Mixed results have been reported regarding the role of other dietary factors such as calcium and caffeine on the incidence rate of colorectal cancer. The association between smoking and alcohol consumption, and the relative risk of colorectal cancer have shown mixed results.

There is increasing evidence to suggest that chemopreventive strategies with either aspirin or NSAIDs may have a major role to play in the prevention of colorectal cancer, both in sporadic and familial cases.

The recently published reports of a decline in both the incidence and mortality rates for colorectal cancer, in conjunction with an ever-increasing genetic understanding of the disease and ongoing advances in the area of chemoprevention of the disease, render colorectal cancer an area of great ongoing epidemiological interest.

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