PART 1

Diagnosis
CHAPTER 1
Epidemiology

Mala Pande & Marsha L. Frazier
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

KEY POINTS

Descriptive epidemiology: assessment of the distribution of colorectal cancer
- Ecological studies of populations are used to determine variation in rates. Incidence, mortality rate, time trends, and prevalence are some key measures.
- The burden of colorectal cancer varies globally: the incidence rate is 10 times higher and the mortality rate 5 times higher in countries with the highest rates than in countries with the lowest rates.
- Worldwide, colorectal cancer is the third most common cancer in men, the second most common cancer in women, and the fourth leading cause of cancer deaths.
- In the United States, colorectal cancer is the third most common cancer in both men and women (9% of the estimated incident cancer cases in both men and women in 2012) and the third leading cause of cancer deaths (9% of estimated cancer deaths in both men and women in 2012).
- There are geographic variations in incidence and mortality, with higher incidence but lower mortality rates in developed countries than in developing countries.
- Colorectal cancer incidence rates have been declining in the United States, and have been stable or declining in most developed countries but are rising in developing countries.
- The increasing risk of colorectal cancer in developing countries may be attributable to increased longevity, and adverse lifestyle changes including smoking, lack of physical activity, and adoption of a westernized diet.
- Colorectal cancer incidence and mortality rate vary by geographic location, age, sex, race/ethnicity, and over time.
- The prevalence of colorectal cancer is high because it has a relatively good prognosis. As a result, there are over 1 million colorectal cancer survivors in the United States.

Analytic epidemiology: assessment of determinants of colorectal cancer:
- Cross-sectional, case-control, and cohort study designs can be used to determine the association of suspected environmental, lifestyle, and other exposures with colorectal cancer risk. Randomized controlled trials are the gold standard for determining cause and effect.
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- Factors that increase the risk of colorectal cancer include older age, African-American race/ethnicity, inherited predisposition syndromes, family history of colorectal cancer or colorectal polyps, inflammatory bowel disease, personal history of colorectal cancer or polyps, diabetes, obesity, physical inactivity, smoking, and alcohol.
- Many other probable risk factors are under investigation.

Introduction

In the last decade, cancer has become the leading cause of death in economically developed countries and the second leading cause of death in developing countries. Globally, colorectal cancer (CRC) is the third most common cancer in men, the second most common cancer in women, and the fourth leading cause of cancer deaths. In 2008, an estimated 665,000 men and 570,000 women were diagnosed with CRC, and 668,000 deaths were attributable to CRC, accounting for 8% of all cancer deaths [1].

Colorectal cancer incidence worldwide

There is almost a 10-fold variation in CRC incidence rates (proportion of newly diagnosed cases per year) worldwide for both sexes. CRC incidence rates are highest in Australia/New Zealand and Western Europe and lowest in Middle Africa and South-Central Asia [1] (Figure 1.1).

Although developed countries account for almost two-thirds of CRC cases (with the exception of a few countries in Eastern Europe, Eastern Asia, and Spain), the rates in developed countries have mostly remained stable or declined over time, whereas rates in developing countries are rising [1;2]. These differences may be attributable to changes in lifestyle and environmental factors as well as underlying genetic susceptibility. The rapid increase in the cancer burden in developing countries is possibly due to population growth and aging, and adverse lifestyle changes such as increased smoking, physical inactivity, and westernized diets [3]. Worldwide, the age-standardized rate (ASR) for CRC incidence is 17.3 per 100,000 population and the cumulative risk for CRC from birth to age 74 years is 0.9% [1]. The incidence of CRC is higher in men than in women (overall male:female ratio of age-standardized rates is 1.4:1). Country-specific rates for CRC incidence and mortality are available from the GLOBCAN database from the World Health Organization’s International Agency for Research on Cancer (http://globocan.iarc.fr/).
Colorectal cancer incidence, time trends, and lifetime risk in the United States (US)

It is estimated that 143,460 men and women (73,420 men and 70,040 women) will be diagnosed with CRC in the US in 2012 [4]. Of all CRCs diagnosed, about 72% affect the colon and the remaining 28% affect the rectum. Incidence rates for CRC in the US have declined roughly by 2–3% every year over the last 15–20 years [5], largely attributable to the advent of CRC screening, which allows for early detection and removal of precancerous polyps [6]. The lifetime incidence of CRC in the US is 5%, or 1 in 20 people are predicted to get CRC over their lifetime. The incidence of CRC is 25% higher in men than in women, and most (>90%) cases occur in men and women older than 50 years. Rates vary significantly by race/ethnicity; the incidence of CRC in African-American men is 20% higher than in white men [3].

Colorectal cancer mortality worldwide

CRC is the fourth most common cause of death from cancer, accounting for 8% of all cancer deaths worldwide. Globally, mortality rates continue to increase for deaths due to CRC (the ASR is 8.2/100,000). Cancer survival
Colorectal cancer tends to be poorer in developing countries, possibly because cancer is diagnosed at later stages and patients have limited access to timely and standard care [3]. There is less variability in mortality rates worldwide (6 times higher in men and 5 times higher in women, in countries with the highest rates than in countries with the lowest rates), with the highest estimated mortality rates in both sexes in Central and Eastern Europe (20.1/100,000 for men and 12.2/100,000 for women), and the lowest in Middle Africa (3.5/100,000 for men and 2.7/100,000 for women) [1].

The mortality rate for CRC is roughly half the incidence rate, so its prognosis is relatively good. Thus, CRC has a high 5-year prevalence (number of cases in the population at a given time), with an estimated 3.26 million people alive with CRC diagnosed within the past 5 years [1;7]. The decrease in mortality may be due to changes in incidence, progress in therapy, improved early detection due to widespread screening, diagnosis at earlier stages (when the cancer is more amenable to treatment), and many other factors [8].

Colorectal cancer mortality in the US

An estimated 51,690 people will die of CRC in 2012 [4]. CRC-related deaths in the US have been declining steadily from 1975 to 2009, with an annual percentage change of 0.5–4% [4]. The US mortality rate for CRC from 2005 to 2009 was 16.7 per 100,000 patients per year. However, mortality rates varied significantly by both sex and race/ethnicity. Mortality rates are highest for African-American men (29.8/100,000) and lowest for Asian-Pacific Islander women (9.6/100,000). The largest proportion (29%) of CRC deaths occurred in patients aged 75–84 years, and the median age at death was 74 years [4]. The mortality rate for CRC is roughly one-third the incidence rate, resulting in a high prevalence of patients diagnosed with CRC. On January 1, 2009, over 1.14 million people with a history of CRC were alive in the US [4]. The 5-year survival rate for CRC is related to the stage at diagnosis; CRC diagnosed at the local stage has a 5-year survival rate of 90%, but the rate drops to only 12% if CRC is diagnosed after it has metastasized [9]. Overall, the US has one of the highest 5-year survival rates for CRC in the world: 61% for patients diagnosed at any stage.

Colorectal cancer risk factors

Epidemiologic studies have identified many factors that may increase or decrease risk of CRC. Some of these factors, such as a personal or family
history of CRC or a history of inflammatory bowel disease, are non-modifiable, but many lifestyle risk factors, such as smoking, alcohol use, and lack of physical activity, are modifiable. It was recently reported that following a healthy lifestyle that includes being physically active for at least 30 minutes per day, following a healthy diet, controlling abdominal adiposity, not smoking, and not drinking alcohol in excess could have prevented 23% of the CRC cases in a cohort of more than 50,000 people aged 50–64 years, who were cancer-free at baseline and followed up for an average of 10 years [10]. Genetic susceptibility due to inherited germline mutations is the cause of CRC in about 5% of patients; however, most cases are sporadic, not familial.

**Age**

Age is a major risk factor influencing CRC incidence and death rate, because both rates increase with age. Over 90% of new CRC cases and deaths occur in people older than 50 years. However, CRC incidence rates in that age group have been steadily declining since the mid-1980s, whereas incidence rates in people younger than 50 years have consistently increased since the early 1990s [11]. Researchers are not sure what is causing the increase in younger adults, but a recent study found that young-onset CRC was more prevalent than later-onset CRC among patients of non-white race/ethnicity, patients who had no insurance or Medicaid insurance, and patients living in the Southern and Western US [11]. Younger patients also had a more advanced stage at diagnosis, location distal to the splenic flexure or in the rectum, a mucinous or signet ring histologic subtype, and poor or no cell differentiation [11].

**Sex**

Worldwide, and in the US, men are at greater risk for CRC than women, but the reasons for the difference in CRC incidence and mortality rates by sex are not well understood. The sex-specific differences may be related to hormonal risk factors, differences in screening and access to medical care, and sex-specific genetic and molecular interactions with environmental risk factors [12]. Sex also affects the CRC site, men having a higher incidence of rectal cancers (31% of CRCs) than women (24%) [9].

**Race/ethnicity**

The burden of CRC varies significantly by race/ethnicity (Figure 1.2). African-Americans have the highest incidence and mortality rates in the US, followed by non-Hispanic whites. CRC incidence rates are lowest in Hispanics. CRC-related mortality rates have declined over time for all races/ethnicities, but the
Figure 1.2 Trends in CRC incidence and mortality rate by race-ethnicity and sex, 1975–2007 [4].


Sources: Incidence – Surveillance, Epidemiology, and End Results (SEER) Program; Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the SEER Program, National Cancer Institute.
decline has been significantly larger among US whites than among African-Americans.

**Geographic differences**
CRC incidence rates vary globally and between US states. Developed nations have higher CRC incidence rates than developing nations; the highest rates are seen in Australia and Canada, and the lowest rates are seen in Middle Africa (Figure 1.1). Incidence rates have rapidly increased in countries that have recently transitioned from relatively low-income to high-income economies, such as Japan, Singapore, and some Eastern European countries (Figure 1.3) [13;14]. Geographic variation in rates is also observed between US states/regions; socioeconomic factors contribute to this variation by influencing access to screening and treatment.

Geographic distribution of CRC in the US also varies by race/ethnicity and sex. CRC incidence rates (per 100,000) among white men range from 44.4 in Utah to 68.7 in North Dakota, and incidence rates among African-American men range from 46.4 in Arizona to 82.4 in Kentucky. Similar variations across states are seen among white women (ranging from 31.8 in Utah to 48.6 in West Virginia) and African-American women (ranging from 34.8 in New Mexico to 61.5 in West Virginia) [9].

**Genetic predisposition**
Roughly 5% of CRC cases are attributable to a genetic predisposition. That is, inherited mutations in certain key genes result in a greatly increased lifetime risk of CRC. Several genetic susceptibility syndromes predispose people to CRC, the most common of which is Lynch syndrome. People with Lynch syndrome inherit germline mutations in one of the DNA mismatch repair genes, \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, or \textit{PMS2}, and this predisposes them to cancers of the colorectum, endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin. These mutations have an autosomal dominant pattern of inheritance, so offspring have a 50% probability of being affected. Other characteristics of CRC associated with genetic susceptibility include an earlier age at onset (the median age at CRC diagnosis is 45 years in patients with Lynch syndrome), multiple family members may be affected, and patients are susceptible to develop other primary cancers besides CRC. Cancers are largely right-sided in patients with Lynch syndrome as compared to left-sided in sporadic CRC, and tumors in patients with Lynch syndrome display characteristic microsatellite instability. Histologically, tumors in these patients exhibit poor differentiation, tumor-infiltrating lymphocytes, and mucinous, signet ring, or cribriform histology.
Figure 1.3 Trends in colorectal cancer incidence and mortality rate in selected countries (aged-standardized (world) per 100,000 men) [1].
Immunohistochemical staining of the tumors for loss of DNA mismatch repair protein, microsatellite instability testing, and family history are the hallmarks of screening for suspected Lynch syndrome mutation carriers prior to definitive mismatch repair gene mutation testing.

Other, less common genetic susceptibility syndromes include familial adenomatous polyposis, Peutz-Jeghers syndrome, and mutY homolog (MUTYH)-associated polyposis [15].

Familial adenomatous polyposis accounts for less than 1% of CRCs and is caused by mutations in the APC gene; its characteristic phenotype is early-onset of multiple (up to thousands) adenomas, which lead to CRC if untreated. An attenuated form of familial adenomatous polyposis with a less severe polyposis phenotype is due to mutations in APC at different sites. Peutz-Jeghers syndrome is another rare syndrome, caused by mutations in the STK11 (also called LKB1) gene. Patients with Peutz-Jeghers syndrome develop characteristic hyperpigmentation of the lips, fingers, and toes and are at increased risk of developing hamartomatous polyps in the digestive tract and of breast, colorectal, and other cancers. Patients with MUTYH-associated polyposis present with multiple colorectal adenomas or CRC as a result of autosomal recessively inherited biallelic mutations in the base excision repair gene MUTYH [15].

Family history

Family history is an important risk factor for CRC, even without the increased familial risk due to genetic predisposition syndromes. Familial risk is likely to be an interaction of genetic and environmental causes [16]. Having a first-degree relative (parent, sibling, or child) with CRC increases CRC risk to almost double that of the general population, and CRC risk is increased further if two first-degree relatives are affected or if a family member is diagnosed with CRC at younger than 60 years [17;18]. A family history of large (>1 cm) adenoma or histologically advanced adenoma is associated with roughly the same risk of CRC as a family history of CRC [18]. Those with a history of one or two small (<1 cm) adenomas are not considered at substantially increased risk [19]. However, a recent review has reported that the risk associated with a family history of adenomas or CRC may be overestimated because of the likelihood of looking for cancer in families who already have a history of CRC (as people with a family history of CRC are more likely to be screened than others) and because the family history for colon polyps may be inaccurate [20].

A possible genetic basis for familial CRC has been investigated by recent genome-wide association studies (GWAS) examining genetic variation across the genome for markers of CRC risk. However, the genetic polymorphisms
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Identified by these studies are largely low-penetrance markers and account for only a small proportion of familial aggregation of CRC [21]. A study estimated that the contribution of 10 GWAS loci to variance in familial CRC risk was only 9% [22]. Larger, more powerful studies, including meta-analyses, are finding additional susceptibility loci [23] that may account for a larger proportion of familial CRC, supporting the idea that familial CRC results from the effects of many low-penetrance genes [24].

Personal medical history

A history of adenomas, prior CRC, and inflammatory bowel disease significantly increases the risk of CRC. Patients with a prior history of large (>1 cm) adenomatous polyps or villous or tubulovillous polyps, particularly a history of multiple polyps, are considered to be at increased risk of CRC [25–27]. Among CRC patients with a history of resection of a single CRC, 1.5–3% are likely to develop metachronous primary CRC during the first 5 years postoperatively [28].

Patients with a history of inflammatory bowel disease are at an increased lifetime risk of CRC, particularly patients with ulcerative colitis. The overall incidence of CRC in patients with inflammatory bowel disease was 95 cases per 100,000 in a population-based study in Sweden [29]. CRC risk may differ by sex; in a large Swedish cohort, the CRC risk for men was 60% higher than for women, and the cumulative incidence of CRC 40 years after the diagnosis of inflammatory bowel disease was 8.3% for men and 3.5% for women [30].

The CRC risk associated with ulcerative colitis depends on the activity and duration of the colitis, extent of colon involvement, and involved site in the colon [31;32] Age and extent of disease at diagnosis are also independent predictors of increased CRC risk [33]. In a population-based Swedish cohort of patients with ulcerative colitis, pancolitis was associated with a 15 times higher incidence of CRC as compared to the general population, and left-sided colitis was associated with a 3 times higher incidence, but the CRC incidence associated with proctitis or proctosigmoiditis was not significantly increased compared with the expected CRC incidence in the general population [33]. The likelihood of developing cancer begins 8–10 years after diagnosis of pancolitis and 15–20 years after diagnosis of more localized colitis [33]. The cumulative incidence of CRC is approximately 5–10% after 20 years and 12–20% after 30 years with colitis [33–36], although some studies have reported lower cumulative incidence rates, possibly due to improved surveillance [37;38].

The risk of CRC is not as well documented in patients with Crohn’s disease as in patients with ulcerative colitis. Some studies have reported an increased CRC risk for Crohn’s disease of long duration similar to that for ulcerative
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Colitis [39–42], whereas other studies have found no clear increase in CRC risk associated with Crohn’s disease [31;43;44].

In a study comparing CRC outcomes in Crohn’s disease and ulcerative colitis, the times until CRC development were similar for the two diseases (median 15 and 18 years, respectively), although the median age at CRC diagnosis was higher in Crohn’s disease patients than in those with ulcerative colitis (55 and 43 years, respectively) [45]. It is well documented that CRC in inflammatory bowel disease is preceded by dysplasia, necessitating a regimen of increased surveillance for these patients for early detection and possible prophylactic colectomy to prevent CRC.

Prior abdominal radiation may also affect CRC risk. Two recent studies have reported that abdominal radiation for childhood malignancies may increase CRC risk for adult survivors [46;47].

**Obesity**

Increasing rates of obesity worldwide and particularly in the US are of growing concern, because obesity has been linked to many types of cancer, including CRC [48]. In a large prospective cohort of male health professionals, increasing body mass index (BMI) was associated with an increasing trend in risk for CRC [49]. Furthermore, abdominal adiposity was also associated with risk of CRC, even after adjusting for BMI [49]. Similarly, in an analysis of obesity and CRC risk among women in the Nurses’ Health Study prospective cohort, compared with women of normal weight, obese women were 1.5 times more likely to develop CRC [50]. In a meta-analysis of 29 studies, each 5 kg/m² increase in BMI was associated with a 24% increase in risk of colon cancer and a 9% increase in risk of rectal cancer in men and with a 9% increase in risk of colon cancer in women [48]. Obesity also increases the risk of dying from CRC [51]. The epidemiologic evidence for the impact of dietary and lifestyle factors on risk of colon and rectal cancer is shown in Figure 1.4.

**Diabetes mellitus**

The association between diabetes mellitus and increased risk for CRC is becoming increasingly strong [52–55]. A recent meta-analysis concluded that there was a 38% increase in risk for colon cancer and a 20% increase in risk for rectal cancer in patients with diabetes compared with those without diabetes, and the association was evident even after controlling for other risk factors including smoking, obesity, and physical activity. It has been postulated that hyperinsulinemia links diabetes to CRC. Studies have shown that insulin is an important growth factor for colonic mucosal cells and stimulates colonic tumor cells [56;57]. This is further supported by evidence of
Figure 1.4 The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiologic evidence citation [84]. Reproduced with permission of John Wiley & Sons Ltd.

associations between CRC risk and insulin biomarkers such as serum levels of insulin-like growth factor (IGF1), IGF binding protein-3 (IGFBP-3), and C-peptide [58;59]. Type 2 diabetes mellitus has also been linked to an increased mortality rate in patients with CRC; patients with CRC and type 2 diabetes were found to be at a higher risk of dying than CRC patients without diabetes [60].

Physical activity
There is strong evidence linking physical activity with decreased risk of CRC. In a meta-analysis of 52 cohort and case-control studies, an inverse
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association between physical activity and colon cancer was found in both men (relative risk [RR] 0.76; 95% confidence interval [CI] 0.71–0.82) and women (RR 0.79; 95% CI 0.71–0.88) [61]. Regular leisure time and occupational physical activity are also associated with protection from CRC.

Diet

Fruits and vegetables
The relationship between consumption of fruits and vegetables and CRC risk has been inconclusive. Some studies have found an inverse association between fruit and vegetable intake and CRC risk, comparing highest with lowest intakes of fruits and vegetables (RR 0.92; 95% CI 0.86–0.99) [62], whereas other large cohort and pooled studies have shown a weak or no protective effect [63;64]. The weak protective effect appears to be limited to distal colon cancers. Measurement of dietary exposures that depends on dietary recall can be challenging, and the imprecision of this measure may explain the heterogeneity in results.

Red meat consumption
Consumption of red meat or processed meat has been found to be associated with increased risk of CRC in many studies. A meta-analysis of prospective studies found a 22% (RR 1.22; 95% CI 1.11–1.34) increase in risk of CRC in the highest compared with the lowest intake of red and processed meats [65]. In addition, there was a dose-response relationship: for every 100 g/day increase in consumption, the CRC risk increased by 14%, and the associations with CRC risk were similar for colon and rectal cancer [65]. It has been hypothesized that the association between red meat and CRC is related to the cooking process. High-temperature cooking of meats, including barbecuing, has been found to increase the risk of both adenomas and CRC, likely through the production of polycyclic aromatic hydrocarbons and other cooking-related mutagens generated when meat is charred [66]. Other potential factors implicated in mediating CRC risk associated with red meat consumption include high iron and fat content in meat, and genetic variation in carcinogen-metabolizing enzymes that may influence the mutagenicity of the carcinogenic compounds in red meat [66–68].

Fiber
Results from studies of dietary fiber and CRC risk have been inconsistent. In many studies, fiber was found to be associated with a decreased risk of adenomas and CRC, but others found no association or only a modest association. The World Cancer Research Fund/American Institute for Cancer Research
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reported a meta-analysis showing strong evidence that consumption of foods containing dietary fiber, in particular fiber from cereals and whole grains, protects against CRC [13;69]. There is a biological rationale for fiber’s possible protective role against CRC, because fiber dilutes fecal content, decreases its transit time, and increases its bulk, but the exact mechanism is not well understood [13].

Calcium and dairy
Dietary or supplemental calcium has been associated with a protective effect in CRC risk in several large cohort studies and pooled analyses, showing a 24–35% reduction in risk in the highest compared with the lowest levels of calcium intake [70–72]. However, in a large randomized controlled trial of 36,282 post-menopausal women who were given either a combination of calcium and vitamin D or a placebo, no significant difference in CRC rates between groups was observed during a mean follow-up time of 7 years [73]. Results of a longer follow-up from this study are pending. Overall, the evidence indicates a probable protective role of calcium on CRC risk as well as a plausible mechanism for this effect: calcium reduces cellular proliferation and promotes differentiation and apoptosis in normal and tumor colorectal cells [74].

In a meta-analysis of 19 cohort studies, higher levels of intake of milk and other dairy products were associated with a modest reduction in risk for colon but not rectal cancer [75].

Fish
A meta-analysis found evidence that fish consumption has a modest protective effect on CRC risk; the highest fish intake was associated with a lower incidence of CRC than the lowest fish intake (summary odds ratio 0.88; 95% CI 0.80–0.95) [76]. However, although suggestive, the evidence is still considered too limited to draw a conclusion [13].

Garlic
Studies investigating garlic consumption have suggested an inverse association between higher garlic intake and risk of CRC.

Smoking
Cigarette smoking is a preventable risk factor that is linked to many types of cancer, including CRC [77]. A large meta-analysis of more than 100 studies found an 18% increase in risk of developing CRC among smokers compared with non-smokers (RR 1.18; 95% CI 1.11–1.25) [78]. Smoking was also
associated with an increased risk of dying from CRC (RR 1.25; 95% CI 1.14–1.37) [78]. The associations between smoking and both CRC incidence and mortality were stronger for rectal cancer than colon cancer. Colon polyps, which are precursors of CRC, have also been linked to smoking. The influence of smoking on the risk of more advanced adenomatous polyps is particularly strong; smoking has been linked to both the formation and aggressiveness of adenomas [79]. Smoking may also modify CRC risk in patients with Lynch syndrome [80].

**Alcohol**

Alcohol consumption has been associated with an increased risk of CRC. In a meta-analysis of alcohol drinking and CRC risk across 27 cohort and 34 case-control studies, risk was increased by 21% for moderate drinkers (2–3 drinks/day) and by 52% for heavy drinkers (≥4 drinks/day) compared with non-drinkers and occasional drinkers [81]. Furthermore, in a dose-response analysis, RR increased with the amount of alcohol consumed, ranging from 7% in light drinkers (10 g/day) to 82% in those consuming 100 g/day [81]. It has been proposed that the risk may be mediated through the folate-related DNA methylation pathway, since alcohol may interfere with folate absorption and act as a methyl group antagonist [82;83].

**Drugs and supplements**

Many compounds such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 selective inhibitors, resistant starch, sulindac, hormones, bisphosphonates, statins, and supplements such as calcium, vitamin D, selenium, and folates may have a chemopreventive effect on colorectal adenomas and CRC. Promising preliminary evidence from observational and animal studies followed by confirmation in well-designed randomized clinical trials is required to assess any cancer prevention benefits at the population level. To date, none of the above agents is recommended for chemoprevention of CRC in the general population.

There is strong evidence that aspirin [85] and COX-2 selective inhibitors such as celecoxib and rofecoxib [86–88] reduce the risk of CRC. However, the harms, such as risk of bleeding and cardiovascular toxicity, outweigh the benefits. Therefore, the consensus statement from the US Preventive Services Task Force advises that these agents should not be used for the prevention of CRC in asymptomatic adults at average risk for CRC [89]. A randomized controlled trial of difluoromethylornithine and sulindac (an NSAID) in patients with a previously resected adenoma found a significant reduction in adenoma recurrence, but the therapy was associated with drug-related ototoxicity [90].
A recent retrospective study found that regular use of aspirin after diagnosis of locally advanced CRC was associated with longer survival in patients with mutated-PIK3CA (phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit alpha polypeptide gene) but not among patients with wild-type PIK3CA cancer. Experimental evidence suggests that aspirin downregulates PI3K signaling through inhibition of cyclooxygenase-2 [91]. Yet the presence of the PIK3CA mutation is infrequent and is present only in 10–20% of all CRC patients. Therefore, adjuvant aspirin therapy may be indicated for specific subgroups of patients such as those with PIK3CA-mutated CRC. A prospective clinical trial to validate the beneficial role of aspirin in this specific patient population may be worth pursuing.

A meta-analysis has shown that post-menopausal hormone therapy has a protective effect against CRC [92]. However, use of hormone therapy for CRC chemoprevention is not recommended because of the associated risks of side effects with long-term use.

Certain drugs that are commonly used to treat other diseases, such as statins for cardiovascular disease and bisphosphonates for osteoporosis, also may protect against CRC [93–95].

Low vitamin D levels have been linked to increased CRC risk [95]. Vitamin D and calcium are interlinked, but as noted earlier, no significant difference in CRC rates was observed in a randomized controlled trial of vitamin D and calcium versus placebo [73].

The exact role of folic acid and folates in CRC chemoprevention is still unclear. A protective effect of folic acid supplementation was found for adenomas and CRC, particularly with prior longer-term use [97]. In contrast, two randomized controlled trials found that folic acid resulted in no reduction in risk for recurrent adenomas [98;99], and one randomized controlled trial suggested that folic acid increased adenoma risk [98]. However, an increased risk of CRC due to folic acid supplementation was not supported in another large cancer prevention cohort [100].

**Conclusion**

CRC is one of the common cancers with a significant global public health burden. Epidemiologic studies have identified demographic, lifestyle, clinical and genetic factors that influence CRC risk. Knowledge of these risk factors can be applied to promote CRC prevention with the ultimate objective to reduce the morbidity and mortality from CRC.
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TIPS AND TRICKS / KEY PITFALLS

- Variations in global, national, and regional rates provide clues for epidemiologic investigation into key genetic, environmental, and lifestyle risk factors.
- Population-based studies provide evidence for colorectal cancer prevention strategies, for example, lifestyle modifications such as avoiding smoking and excessive alcohol intake, engaging in regular physical activity, and maintaining optimal weight.
- Other probable risk and protective factors that may influence the development of colorectal cancer, such as dietary factors including consumption of fruits, vegetables, and fish, have inconsistent or insufficient evidence and therefore cannot yet be translated to the clinic.

CASE STUDY AND MULTIPLE-CHOICE QUESTIONS

Case 1
Colorectal cancer incidence rates in developed countries have remained stable or decreased over the last 10 years, whereas rates in developing countries have been rising.

1 Which of the following could contribute to a decrease in rates (there may be more than one correct answer)?
   A. Availability of colorectal cancer screening.
   B. Consumption of red meat.
   C. Aging population.
   D. Sedentary lifestyle.

2 Which of the following could contribute to an increase in colorectal cancer incidence rates (there may be more than one correct answer)?
   A. Availability of colorectal cancer screening.
   B. Consumption of red meat.
   C. Aging population.
   D. Sedentary lifestyle.

Case 2
An obese, diabetic patient who smokes and has a history of rectal polyps has a brother who was recently diagnosed with colon cancer. The patient is concerned about his risk for developing colorectal cancer.

1 What is his risk profile?
   A. Low risk
   B. Average risk
   C. More than average risk
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What can he do to reduce his risk (more than 1 answer may be correct)?

A. Quit smoking
B. Exercise regularly
C. Get regular screening
D. Take folic acid supplements

References


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**ANSWERS TO MULTIPLE-CHOICE QUESTIONS**

**Case 1**
1. A
2. B, C, D

**Case 2**
1. C
2. A, B, C