American Journal of Medicine and Medical Sciences 2026, 16(5): 2743-2750
DOI: 10.5923/j.ajmms.20261605.99

Epidemiology of Colorectal Cancer: Incidence, Mortality, Survival, Risk Factors

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Abstract Colorectal cancer (CRC) is one of the most common and deadly malignancies worldwide, representing a major public health challenge due to its increasing incidence and mortality rates. This article provides a comprehensive overview of the epidemiology, etiology, risk factors, survival outcomes, and prevention strategies associated with CRC. Global epidemiological data demonstrate substantial geographic, sex-related, and age-related variations in CRC incidence and mortality, with developed countries showing higher rates compared with developing regions. However, rapid lifestyle transitions and population aging are contributing to a growing burden of CRC worldwide. The pathogenesis of CRC is closely linked to genetic and epigenetic alterations, chronic inflammation, dietary habits, obesity, physical inactivity, smoking, alcohol consumption, and intestinal microbiota imbalance. Both modifiable and non-modifiable risk factors are discussed in detail, including hereditary syndromes, inflammatory bowel diseases, diabetes mellitus, and lifestyle-associated factors. Advances in screening methods such as colonoscopy, CT colonography, and fecal immunochemical testing have significantly improved early detection and survival outcomes. Preventive strategies based on healthy lifestyle modification, dietary regulation, and appropriate medical interventions may substantially reduce CRC risk and mortality. Understanding the epidemiological trends and multifactorial mechanisms underlying CRC development is essential for improving prevention, diagnosis, and treatment approaches and for reducing the global impact of colorectal cancer.

Keywords Colorectal cancer, Epidemiology, Incidence, Mortality, Survival, Risk factors, Modifiable risk factors, Non-modifiable risk factors, Prevention, Screening, Genetic syndromes, Lifestyle, Diet, Obesity, Inflammatory bowel disease

1. Introduction

Colorectal cancer (CRC) remains one of the most significant challenges in global oncology, ranking as the third most frequently diagnosed malignancy and the second leading cause of cancer-related death worldwide. In 2018 alone, over 1.8 million new cases and 881,000 deaths were attributed to CRC, and these numbers are projected to rise substantially in the coming decades [28,30]. While the disease burden is highest in high-income regions, developing countries are experiencing a rapid increase in incidence, driven by economic transitions, aging populations, and the adoption of westernized lifestyles. CRC arises from the glandular epithelium of the colon and rectum through a well-characterized sequence of genetic and epigenetic alterations, most commonly progressing from benign adenomatous polyps to invasive adenocarcinoma over a period of 10–20 years. However, the molecular landscape of CRC is markedly heterogeneous, encompassing a spectrum of mutational profiles, microsatellite instability statuses, and epigenetic patterns that influence both clinical behavior and therapeutic response. This complexity has direct implications for patient management, as early-stage disease is highly curable with surgical resection, whereas metastatic CRC continues to carry a dismal prognosis, with five-year survival rates around 12%. At the population level, CRC incidence and mortality exhibit striking variations by geography, sex, age, and ethnicity. These disparities are only partially explained by genetic predisposition; a substantial proportion of the global CRC burden is attributable to modifiable risk factors, including obesity, physical inactivity, diets rich in red and processed meats, tobacco smoking, and alcohol consumption. In parallel, non-modifiable factors such as age, sex, hereditary cancer syndromes (e.g., Lynch syndrome, familial adenomatous polyposis), inflammatory bowel disease, and prior radiation therapy contribute significantly to individual risk. Notably, recent trends reveal a worrying rise in early-onset CRC (diagnosed before age 50) in several high-income settings, alongside a decline in incidence among older adults, underscoring the dynamic nature of CRC epidemiology and the need for updated preventive strategies.

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Received: Apr. 28, 2026; Accepted: May 19, 2026; Published: May 30, 2026
Published online at http://journal.sapub.org/ajmms

2. Epidemiology

According to GLOBOCAN 2018 data, colon cancer is the fourth most common cancer worldwide, while rectal cancer ranks eighth among malignant tumors. Together, colorectal cancer (CRC) is the third most frequent malignancy, accounting for 11% of all cancers [28,29].

In 2018, an estimated 1,096,000 new cases of colon cancer and 704,000 new cases of rectal cancer were diagnosed worldwide. CRC was the most commonly diagnosed cancer in men in 10 out of 191 countries. Notably, there are no countries reporting a predominance of female CRC patients [28].

CRC incidence is 3–4 times higher in men than in women and is more frequent in developed than in developing countries. Age-standardized incidence rates were 19.7 per 100,000 population for both sexes combined, 23.6 for men, and 16.3 for women [67]; rates reached 30.1 for men in developed countries versus 8.4 for men in developing countries, and 20.9 versus 5.9 for women, respectively [19].

In 2018, there were 576,000 newly diagnosed cases of CRC among men and 521,000 among women, corresponding to a cumulative risk of 1.51% for men and 1.12% for women aged 0–74 years. For rectal cancer, there were 430,000 cases in men and 274,000 in women (cumulative risk 1.2% and 0.65%, respectively) [28].

The highest incidence rates of colon cancer were observed in Southern Europe, Australia/New Zealand, Northern Europe, and North America, while rectal cancer was most common in Eastern Europe, Australia/New Zealand, East Asia, and North America. The highest CRC incidence was recorded in Hungary (70.6 per 100,000 men) and Norway (29.3 per 100,000 women). Africa and South Asia were the regions with the lowest incidence rates for both sexes [28]. Thus, CRC incidence varies up to eightfold between countries. Even within a single country, such as the United States, regional differences reach 3–4 fold (e.g., between Alaska, with the highest rate, and the southern states, with the lowest), which may be attributable to lifestyle factors as well as screening accessibility [19].

The interplay between environmental exposures, host genetics, and the gut microbiome is increasingly recognized as a pivotal axis in CRC pathogenesis, offering promising avenues for risk stratification, chemoprevention, and targeted interventions. Moreover, evidence suggests that long-term use of medications such as aspirin, statins, bisphosphonates, and ACE inhibitors may confer protective effects, although their routine use for CRC prevention is not yet recommended at the population level due to insufficient evidence or potential adverse effects [4,13,17,20].

This article provides a comprehensive overview of the current epidemiology of CRC, synthesizing data on global incidence, mortality, survival, and the complex network of risk factors that drive the disease. By clarifying these epidemiological patterns and their underlying determinants, we aim to inform evidence-based strategies for risk reduction, early detection, and ultimately, a reduction in the global impact of colorectal cancer. The following sections examine in detail the descriptive epidemiology, long-term trends, survival outcomes, and the full spectrum of modifiable and non-modifiable risk factors shaping the CRC landscape.

Colorectal cancer (CRC) is the third leading cause of cancer mortality worldwide. The incidence of CRC is increasing, particularly in developing countries. The tumor colorectal adenocarcinoma arises from glandular epithelial cells of the large intestine. Its pathogenesis involves a genetic or epigenetic mutation in a particular cell [5]. Aberrant activation of replication and suppression of apoptosis lead to the formation of a benign adenoma, which subsequently evolves into carcinoma and metastasizes [21].

The primary function of the large intestine is the reabsorption of water, minerals, and nutrients from chyme. The intestinal lumen harbors a microbiota that breaks down remaining large molecules. To enhance reabsorption, the epithelium is organized along a crypt–villus axis. Intestinal stem cells reside at the base of the crypts. The function of stem cells is self-renewal and regeneration of the intestinal epithelium [15,23]. As cells differentiate, they migrate from the crypt bottom toward the villus tip. Differentiated epithelial cells comprise several populations, including Paneth cells, enteroendocrine cells, and enterocytes. Upon reaching the villus tip after approximately 14 days, the cells undergo apoptosis and are eliminated with fecal matter [11,18]. This process is regulated by signaling proteins and growth and transformation factors [13,15,17].

CRC represents a heterogeneous group of diseases pathogenetically driven by diverse mutational patterns, which explains the difficulty in developing molecular therapies. Surgical resection remains the primary treatment option when the disease is diagnosed early, but its effectiveness declines in cases of longstanding, complicated, or metastatic tumors, which account for up to 25% of all newly diagnosed cases [18]. For such patients, neoadjuvant cytotoxic therapy is a treatment option; however, tumor recurrence and progressive drug resistance continue to pose a challenge [9].

Mortality

CRC is the second most lethal cancer worldwide. In 2018, approximately 881,000 deaths were attributable to CRC. Colon cancer ranked fifth among causes of cancer-related death (551,000 deaths, 5.8% of all cancer deaths), while rectal cancer ranked tenth (310,000 deaths, 3.2%). The cumulative risk of death from colon cancer is 0.66% for men and 0.44% for women; for rectal cancer, it is 0.46% and 0.26%, respectively. The age-standardized mortality rate for CRC for both sexes combined is 8.9 per 100,000 [28].

CRC is the leading cause of cancer death among men in three countries worldwide (Saudi Arabia, Oman, United Arab Emirates) and among women in five countries (Algeria, Belarus, Japan, Spain, Portugal) [28]. The highest CRC mortality was observed in Hungary (31.2 deaths per 100,000 men and 14.8 per 100,000 women).

CRC mortality rates differ 2–3 fold between developed

and developing countries (among men, 12.8 versus 5.7 per 100,000; among women, 8.5 versus 3.8, respectively) [28].

Trends

Three distinct trends in CRC incidence and mortality dynamics have emerged globally. In countries such as Brazil, Russia, Latin American nations, the Philippines, and the Baltic states, both CRC incidence and mortality have increased over the past decade, likely reflecting changing economic circumstances. In Canada, the United Kingdom, Germany, and Singapore, CRC incidence has risen while mortality has declined, probably due to advances in medical technologies. In the United States, Iceland, Japan, and France, both incidence and mortality have decreased, reflecting improvements in both treatment strategies and preventive measures [12].

Over the past 50 years, CRC incidence has risen among young adults (aged 20–49) in the United States, from 9.3 per 100,000 in 1975 to 13.7 per 100,000 in 2015 (+47.31%), whereas among individuals aged 50 and older, incidence has significantly declined [19].

In the future, the global burden of CRC is projected to increase to 2.2 million new cases and 1.1 million deaths per year by 2030. This anticipated rise is associated with economic development, environmental changes, shifts in lifestyle, increasing prevalence of obesity, higher consumption of processed foods, alcohol, and meat, as well as increasing life expectancy [12].

Survival

Advances in CRC treatment have led to a reduction in CRC mortality. The main reason for this decline has been the removal of colonic polyps, along with early diagnosis of neoplasms using various improved modalities colonoscopy, CT colonography, fecal immunochemical testing, and other high-tech methods of laboratory and instrumental diagnostics [6]. The introduction of new diagnostic methods initially leads to an increase in incidence rates as previously undiagnosed tumors are detected; however, it is subsequently associated with a decrease in mortality owing to the possibility of curing the disease at early stages [12].

In the United States, the five-year survival rate for stage I CRC is 92%; for stages IIA and IIB, it is 87% and 65%, respectively. Notably, five-year survival for stages IIIA and IIIB is considerably higher, at 90% and 72%, respectively. For stage IIIC, survival is 53%, whereas for stage IV (metastatic CRC) it is only 12% [19].

For rectal cancer, five-year survival is 88% for stage I, 81% for stage IIA, 50% for stage IIB, 83% for stage IIIA, 72% for stage IIIB, 58% for stage IIIC, and 13% for stage IV [19]. The use of novel diagnostic methods helps explain the improvement in survival among patients with stage II and III CRC [23].

In countries with limited access to health care, as well as in low-income populations within developed countries, survival rates are substantially lower than the figures cited above [17,19].

Etiology

CRC typically begins as a noncancerous proliferation of mucosal epithelial cells. These lesions are called polyps. Colonic polyps grow over a period of 10–20 years before malignant transformation occurs. The most common form is the adenoma, or polyp, arising from glandular cells whose function is to produce the mucus that lines the large intestine [19]. Only 10% of adenomas progress to invasive cancer. The risk increases with the duration of polyp presence and with polyp size. CRC originating from such polyps is classified as adenocarcinoma and accounts for 96% of all CRC cases [19].

CRC grows within the wall of the colon or rectum and can penetrate blood vessels and lymphatic channels, leading to metastasis to distant organs (hematogenous spread) or regional lymph nodes (lymphogenous spread). CRC *in situ* refers to polyps that have not yet reached the stage of invasion into the bowel wall and are not classified as cancer. Localized cancer is cancer that grows into the thickness of the bowel wall but does not extend beyond it. Regional cancer is cancer with invasion into regional lymph nodes and adjacent organs and tissues. Distant cancer is cancer with distant hematogenous metastases.

Certain dietary and lifestyle factors can induce and promote inflammation of the intestinal wall and alter the composition of the gut microbiota in a manner that provokes an immune response. These changes are associated with polyp formation and its transformation into CRC. Hereditary or spontaneous mutations in oncogenes and tumor suppressor genes give rise to cells with hyperproliferative capacity and a propensity for carcinogenesis. These considerations suggest that measures aimed at lifestyle modification, early colorectal screening, and genetic testing could have a positive impact on CRC detection and prevention.

Non-Modifiable Risk Factors

Differences in survival within countries may be attributable to ethnicity. In the United States, African American and American Indian populations exhibit a higher incidence of CRC and lower survival rates across all tumor stages. In contrast, the Hispanic population in the U.S. demonstrates rates similar to those of the non-Hispanic white population. Until the 1980s, CRC incidence was similar among Black and White residents of the U.S.; however, epidemiological trends subsequently diverged. According to SEER data, the CRC incidence rate before 1975 was 56.9 per 100,000 among African Americans and 60.2 among Whites, whereas in 2015 the rates were 44.7 and 36.2 per 100,000, respectively [17]. However, these differences are likely attributable not only to the genetic characteristics of the population but also, to a large extent, to unhealthy lifestyle habits, diet, educational level, socioeconomic status, and access to health care [21].

In all countries and populations, male sex is associated with a 1.5-fold increased risk of CRC [28]. This disparity is greatest among younger individuals and diminishes with advancing patient age [2]. At the same time, right-sided

tumors, which are characterized by more aggressive growth compared with left-sided tumors, are more common in women [1,13]. The five-year survival rate for women over 70 years of age is lower than that for men of the same age [1,5,20].

CRC incidence increases with age; it is 3 times more common in individuals over 65 years of age than in those aged 50–64 years and 30 times more common than in the 25–49 age group. In recent decades, CRC incidence has declined among individuals over 50 years of age and has increased among those under 50 [1,7,26]. This trend is presumed to be a consequence of a sedentary lifestyle. Current guidelines recommend lowering the age for initial CRC screening to 45 years in order to detect the disease in the younger population [6,22].

A hereditary predisposition is traceable in 7–10% of cases of non-polyposis CRC, as well as in adenomatous and hamartomatous polyposis syndromes [5]. Eleven hereditary syndromes associated with an increased risk of developing CRC have been identified. All are characterized by an autosomal dominant mode of inheritance: familial adenomatous polyposis (FAP) (classic and attenuated FAP), Gardner's syndrome (a variant of FAP), Turcot syndrome (a variant of FAP), hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome), MUTYH-associated polyposis (MAP), juvenile polyposis syndrome (JPS), Peutz–Jeghers syndrome (PJS), polymerase proofreading-associated polyposis (PPAP), PTEN hamartoma tumor syndrome (PHTS), Cowden syndrome, and familial colorectal cancer type X.

Up to 30% of CRC patients have a family history of malignancy, even in the absence of an identifiable genetic marker. First-degree relatives have a 2- to 4-fold higher risk of developing CRC than the general population. The risk persists, albeit to a lesser degree, with more distant relatives [5,7].

Lynch syndrome is diagnosed in 2–4% of CRC patients. In individuals with Lynch syndrome, the risk of developing CRC is 20% by the age of 50 and 50% by the age of 70. This syndrome is associated not only with CRC but also with cancers of other sites—esophagus, endometrium, small intestine, ovaries, and stomach [23]. Because of the high cost of genetic testing, Lynch syndrome is diagnosed in 99% of cases based on clinical and family history features rather than on genetic analysis [8,32].

Familial adenomatous polyposis is the second most common genetic syndrome associated with CRC, accounting for 1% of all cases. In this syndrome, numerous (thousands of) precancerous colonic polyps are already diagnosed by the age of 10–12 years [1,6,30]. By the age of 40, the risk of malignant transformation reaches 100% [7,30].

Hamartomatous polyps in Peutz–Jeghers syndrome, juvenile polyposis syndrome, and hamartomatous tumor syndrome are rare and poorly understood conditions. Their progression differs from that of adenomatous polyps. These polyps originate not in the epithelium but in the lamina propria and subsequently spread intraepithelially [33].

Chronic inflammatory bowel diseases also double the risk of developing CRC. Inflammation is associated with abnormal cytokine levels, increased blood flow, and the generation of free radicals all factors that induce carcinogenesis. In a Swedish study [13], patients with Crohn's disease and ulcerative colitis (UC), especially those with disease onset in childhood, were found to be at risk of cancer in any part of the gastrointestinal tract, both during childhood and later in life. The risk of CRC in patients with UC is 33.3 per 1,000 person-years, compared with 5.8 in patients with Crohn's disease [1,4,8].

Ulcerative colitis is characterized by inflammation and ulceration of the colon. The etiology of the disease is unknown, although diet, stress, and excessive physical exertion can trigger disease activity. The pathogenesis of UC involves an autoimmune reaction that develops as a complication of a viral or bacterial infection. A hereditary component also plays a role. A meta-analysis of eight studies demonstrated a 2.4-fold increase in CRC risk. Male sex, young age, and the extent of colonic involvement increase the risk of CRC [10].

Crohn's disease is an autoimmune, partly hereditary inflammatory condition of the large intestine characterized by penetrating inflammation without ulceration. Both inflammatory bowel diseases are more common in developed countries and their prevalence is increasing over time. The prevalence of inflammatory bowel disease in the United States is 3.1 million people; the risk of disease is associated with an unhealthy lifestyle, environmental pollution, and low socioeconomic status [3,8].

The risk of CRC is significantly elevated in children who have received radiation therapy for abdominal malignancies. The risk increases by 70% for every 10 Gy of total radiation dose. The use of alkylating agent-based chemotherapy increases the risk of CRC 8.8-fold [1,4,5]. Men with prostate cancer have an increased risk of developing CRC; additionally, the use of radiation therapy is associated with a further increase in the risk of rectal cancer compared with those who did not receive radiation therapy [5,8,16].

An increased risk of CRC is observed in patients with cystic fibrosis. A meta-analysis of six studies (99,925 patients) found that the risk of CRC in cystic fibrosis patients is increased 10-fold, amounting to 0.39 cases per 1,000 person-years.

Cholecystectomy is associated with an increased risk of cancer of the proximal and right colon. A negative effect of bile on the colonic epithelium is presumed to play a role. These data have been confirmed in a meta-analysis of ten cohort studies [2,33].

An increased risk of CRC is also observed in prostate cancer patients receiving gonadotropin-releasing hormone therapy (androgen deprivation) or after orchiectomy. The risk is increased when androgen deprivation lasts longer than 25 months [7,8].

Modifiable Risk Factors

Obesity and a sedentary lifestyle represent the most

significant CRC risk factors related to an unhealthy way of life and account for differences in CRC incidence across populations. Individuals who engage in regular physical activity have a 25% lower risk of developing CRC. In those who are physically inactive, the risk of CRC increases by 50%. A sedentary lifestyle is associated with obesity, alterations in the gut microbiota, colonic inflammation, cytokine release, and carcinogenesis. Obesity is associated with cancer not only of the bowel but also of other sites, as adipose tissue is the most active source of cytokines, including tumor-promoting cytokines. Increased body weight disrupts metabolic processes, leading to an even greater release of mutagenic cytokines and free radicals.

Obese men show a 50% increase in the risk of colon cancer and a 20% increase in the risk of rectal cancer (for women, 20% and 10%, respectively). The obesity-related increase in risk is independent of the risk associated with physical inactivity; rather, these risks are cumulative. A meta-analysis of 13 cohort studies demonstrated that a 5 kg increase in body weight is associated with a 3% increase in CRC risk. Abdominal obesity is the most hazardous component of obesity with respect to CRC (as it is for cardiovascular disease and cerebrovascular disorders). Obesity and physical inactivity not only increase the incidence of CRC but also reduce patient survival [16].

The rising prevalence of obesity and physical inactivity in developed countries correlates with the increasing incidence of CRC. The prevalence of obesity in the United States rose from 15% in 1979 to 39.8% in 2016; 70% of the U.S. population is obese or overweight. However, a trend toward reduced physical inactivity is currently observed in many countries. In the United States, for instance, the proportion of residents engaging in physical exercise increased from 41% in 2006 to 50% in 2012 [17]. The effectiveness of this strategy is responsible for the decline in CRC incidence in countries such as Iceland, Japan, and the United States [12].

Diet plays an important role in the development and prevention of CRC, independent of obesity. Diet actively influences the colonic microbiome, where the number of bacteria is ten times greater than the number of host cells. The diversity of bacterial species in the colonic lumen exceeds that of human cell types, reflecting the complexity of the microbiome. Different dietary components exert different effects on the microbial population and intestinal inflammation [14].

Red meat and processed foods increase the risk of CRC, as well as cancers of the stomach and small intestine, as confirmed by a meta-analysis of 60 studies [35]. Prospective studies have shown that the relative risk of cancer is 1.22 among consumers of red meat and processed foods [4]; specifically, the figure for red meat was 1.12, and for processed food, 1.15 [23]. Red meat is rich in fats and pro-inflammatory substances, likely generated during high-temperature cooking and smoking, which enhance carcinogenesis. In 2015, the International Agency for Research on Cancer classified processed meat as carcinogenic and red meat as probably carcinogenic, primarily based on their effect on CRC risk [13].

Calcium, dietary fiber, vitamin D, fruits, and vegetables exhibit protective properties with respect to CRC risk. Folic acid inhibits carcinogenesis but promotes the growth of other tumor types. Complex molecular-biological interactions have led to the recommendation not to use folates except in pregnancy or in specific metabolic disorders predisposing to high homocysteine levels. Dietary fiber in fruits, vegetables, and whole grains is particularly active in CRC prevention, as it accelerates stool transit and minimizes the toxic effect of potential carcinogens.

In 2009, the International Agency for Research on Cancer concluded that tobacco smoking is a trigger for carcinogenesis, particularly for CRC. Smoking is the main modifiable cause of cancer mortality. The relative risk of CRC with regular smoking is 1.18 [26]. Smoking exerts the most pronounced effect on rectal cancer a tumor associated with complex molecular abnormalities, including microsatellite instability, mutations, and metabolite methylation. Mutagens in tobacco smoke promote these and other mutations. A recent meta-analysis of 14 prospective cohort studies showed that both former and current smoking are associated with a poorer prognosis compared with never-smokers (relative risks 1.12 and 1.29, respectively). Smoking cessation reduces the risk of overall and CRC-specific mortality.

Alcohol consumption exceeding one drink per day is associated with an increased risk of CRC [15,29]. One to two drinks per day increase the risk of CRC by 20%, and consumption of three or more drinks per day increases it by 40%. The association is stronger in men, possibly owing to hormone-dependent features of alcohol metabolism. Men also tend to report lower alcohol consumption than they actually consume [26]. A meta-analysis of 61 studies showed that the relative risk of CRC for moderate alcohol consumption is 1.21 and for heavy consumption (more than four drinks per day) is 1.52 [6].

Medication-Related Influences

Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, reduces the risk of CRC and, when CRC does develop, is associated with a less aggressive tumor phenotype and improved survival. NSAIDs attenuate intestinal inflammation, thereby protecting against the development of CRC as well as gastric and small bowel cancers. However, because the benefit of such preventive action is accompanied by the risk of adverse effects such as gastrointestinal bleeding and cardiovascular events, this drug class is not recommended as a preventive measure for the general population. The U.S. Preventive Services Task Force guidelines recommend low-dose aspirin for individuals over 50 years of age who have cardiovascular risk factors [17].

Another NSAID, sulindac, has been used in combination with difluoromethylornithine, an inhibitor of ornithine decarboxylase, in an effort to reduce the risk of gastrointestinal bleeding and cardiotoxicity. This agent demonstrated a 92% reduction in the risk of advanced adenoma, and in combination with atorvastatin, a chemopreventive effect with an 80-85% reduction in CRC risk was shown in rats. The combined use of aspirin and atorvastatin yielded a 62% reduction in

CRC, which was greater than the effect of either drug alone. This regimen was also associated with a reduced risk of progression from adenoma to CRC in animal models [4].

Hormone replacement therapy for menopausal syndrome initially showed a preventive effect against CRC in pilot studies; however, long-term, randomized, controlled trials did not confirm this finding. To date, there is no statistical support for this hypothesis [9].

Studies suggest that the use of bisphosphonates, prescribed for osteoporosis prevention, may lower the risk of developing CRC (relative risk 0.87) compared with the general population. Bisphosphonates promote an immune response against cancer cells and inhibit tumor angiogenesis, invasion, adhesion, and progression. By inhibiting cholesterol synthesis, they disrupt tumor cell growth and metastasis. Bisphosphonate use reduces the risk not only of CRC but also of all gastrointestinal tract cancers, breast cancer, and bone metastases [28].

Angiotensin-converting enzyme inhibitors (ACE inhibitors), used to treat arterial hypertension, are also associated with a reduced risk of CRC (0.84 in patients taking ACE inhibitors for more than one year, and 0.75 in those taking them for more than five years, compared with the general population). The effect is dose-dependent; however, after five years of ACE inhibitor use, the risk-lowering effect diminishes [33].

Diabetes and Insulin Resistance

Diabetes predisposes individuals to various types of cancer. The increased cancer risk in diabetic patients is largely attributable to shared risk factors such as obesity and physical inactivity. Furthermore, hyperglycemia induces a carcinogenic shift in glycolysis, enhancing glucose metabolism (the Warburg effect). Even after adjusting for the effects of obesity, physical inactivity, and other common risk factors, patients with type 2 diabetes mellitus retain an elevated risk of CRC. The prevalence of type 2 diabetes is rising in developed countries, which may partly explain the upward trend in CRC incidence. In the United States, the number of individuals with diabetes more than doubled from 1990 to 2012, and an additional one-third of cases remain undiagnosed [20]. Some studies have shown a preventive effect of metformin on CRC risk in patients with type 2 diabetes, while other studies have not confirmed this hypothesis.

A recent meta-analysis of 29 prospective cohort studies (62,924 cases) from China reported a 27% increase in CRC risk among patients with type 2 diabetes compared with the general population [10]. In a prospective study of 0.5 million participants with type 2 diabetes, the risk of CRC was 1.18 [15].

Prevention

Differences in CRC incidence and mortality rates suggest that the pathogenesis of the disease has a substantial behavioral component and that preventive measures should be effective. Advances in early CRC screening strategies have led to reduced mortality in developed countries, even as incidence has increased. Several screening methods are recommended: colonoscopy every 10 years, CT colonography, double-contrast barium enema, and flexible sigmoidoscopy every 5 years. An annual high-sensitivity fecal test of various types is also an effective screening method with lower invasiveness [11].

Lifestyle modification is expected to reduce disease incidence. Increasing physical activity and maintaining a normal body weight can lower the risk of developing CRC by 25%, or cumulatively by 50%.

Dietary modification that includes increased consumption of vitamin D, calcium, low-fat products, fiber-rich fruits, vegetables, whole grains, and antioxidants reduces CRC risk. A dietary strategy also encompasses the intake of garlic, magnesium, fish, and vitamin B6. Folic acid-containing supplements may be effective in preventing tumor development but can accelerate the growth of existing tumors; therefore, folates are not recommended as a population-wide CRC prevention measure. Reducing the consumption of alcohol, tobacco, red meat, and processed meat collectively lowers the risk by up to 50% [14,15,30].

Certain medications prescribed for other conditions, such as NSAIDs, statins, and bisphosphonates, are also associated with a reduced risk of CRC, especially when used in combination. These agents may be used alongside chemotherapeutic drugs [4,9,20,33]. However, owing to the risk of adverse effects and an insufficient evidence base, these medications are not recommended as population-level prevention.

It is anticipated that patients with genetic syndromes predisposing to CRC will benefit the most from the use of genetic testing methods and lifestyle modification [23,34].

3. Conclusions

Testicular cancer is a highly curable malignancy when managed with modern evidence-based approaches a true “oncologic success story” in young adult males. Continued efforts in research, guideline implementation, and survivor care will ensure that this success is sustained and even further improved in the future.

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