Review Article

# Epidemiology and risk factors of colorectal cancer in China

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## Abstract

In China, colorectal cancer (CRC) ranked fourth and fifth in the highest incidence and mortality rates of all malignancies in 2018, respectively. Although these rates are below the world average, China placed first worldwide in the number of new CRC cases and CRC-related deaths because of its comparatively large population. This disease represents a threat to the health of population and incurs a heavy economic burden on the society and individuals. CRC has various risk factors, including age, sex, lifestyle, genetic factors, obesity, diabetes, gut microbiota status, and precancerous lesions. Furthermore, incidence and mortality rates of CRC are closely related to socioeconomic development levels, varying according to regional and population characteristics. Prevention is the main strategy to reduce incidence and mortality rates of CRC. This can be achieved through strategies stimulating lifestyle changes, healthy diet habits, and early screening for high-risk individuals. To reduce the burden of CRC, public health officials should promote prevention and management of modifiable risk factors through national policies. The rising incidence and mortality rates of CRC in China may be timely curbed by clarifying specific epidemiological characteristics, optimizing early screening strategies, and strictly implementing diagnosis and treatment guidelines. Thus, this study aimed to collect and report the current research status on epidemiology and risk factors of CRC in China.

**Keywords:** Colorectal cancer; epidemiology; review; risk factors

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## Introduction

According to the GLOBOCAN 2018 assessment on cancer incidence and mortality published by the International Agency for Research on Cancer, more than 1.8 million new colorectal cancer (CRC) cases and 881,000 CRC-related deaths occurred in 2018, classifying it with the third (10.2%) and second (9.2%) highest incidence and mortality rates, respectively, among all cancer types (1,2). Specifically, countries in Europe (Hungary, Slovenia, Slovakia, the Netherlands, and Norway), North America, and East Asia (Japan, South Korea, and Singapore), as well as Australia and New Zealand, have the highest incidence rates.

According to the Chinese Cancer Registration Report of 2018, which comprises population-based cancer registration data collected by the National Cancer Center, 387,600 CRC new cases and 187,100 CRC-related deaths occurred in China during 2015, ranking it the fourth (9.87%) and fifth (8.01%) highest incidence and mortality

rates, respectively, among all cancers (3). Despite lower rates compared with the world average (incidence, 17.81/100,000 persons; mortality, 8.12/100,000 persons) (3,4), China has the highest number of CRC new cases and CRC-related deaths in the world because of its relatively large population (5). Moreover, the country faces a tough challenge of increasing CRC cases related to a westernized lifestyle, which threatens the health of individuals and incurs a heavy social and economic burden (6,7).

## Epidemiological characteristics

The incidence and mortality rates of CRC vary among different countries because of differences in socioeconomic development and lifestyle. Arnold *et al.* reported that in the last decade, CRC incidence and mortality rates increased in Russia, China, and Brazil, whereas these rates decreased in the USA, Japan, and France (8). Furthermore, the regional distribution of CRC cases varies in China: the eastern region has the highest incidence and mortality rates, followed by the western region, while the central region has the lowest rates. Regarding urban and rural distribution, the former has considerably higher rates than the latter (3). Overall, the incidence of CRC increases with age; in China, this incidence increases rapidly in individuals older than 50 years old, reaching its peak after the age of 80 years (2,3).

According to the American Cancer Society, the incidence and mortality rates of CRC in the United States are declining since 2000, with a decrease of 2.5% per year and 2.1% per year in incidence (2007–2016) and mortality (2008–2017) rates, respectively (9). In contrast, the National Cancer Center of China reported that the incidence of CRC increased by 2.5% per year in males and 1.5% per year in females; moreover, mortality rates increased by 1.3% per year and 0.4% per year in male and female patients, respectively, between 2000 and 2013 (4).

Cancer stage at diagnosis is the most important survival predictor. In the USA, the 5-year overall survival (OS) for CRC ranges from 90% for those diagnosed with a localized disease to 14% for those diagnosed with distant metastases (9). Comparatively, the 5-year OS of CRC patients in China is lower than that in the USA (56.9% 2012–2015 *vs.* 64% 2009–2015) (10). Moreover, the current rate of local CRC at diagnosis is less than 10% in China, a rate lower than that in Japan (20% in 1991) and South Korea (>20% in 2009) (11).

Recently, despite an overall decline, the CRC incidence rate increased in individuals under 50 years of age in the USA, with the largest increase in rectal and distal colon cancers (9). In Asia, most CRC cases are rectal cancers (>50%), while it represents less than 40% of cases in Europe and North America (12,13). In China, the CRC tumor location has shifted to the proximal colon since 1980 (12,13). Accordingly, the proportion of rectal cancer declined from 71.2% in the 1980s to 66.7% in the 1990s, whereas that of ascending and transverse colon cancers increased from 10.9% to 15.2% during the same period (14). According to the newly released statistics on CRC in Haining City, Zhejiang Province, colon cancer represented 37.1% of new CRC cases during 1977–1990, but increased to 58.1% during 2005–2018. Similarly, the proportion of colon cancer-related deaths rose from 37.6% during 1977–1990 to 59.6% during 2005–2018 (15). Although this change may be related to improved diagnostic techniques and different CRC etiologies, its reason remains unknown.

## Risk factors

### *Age and sex*

CRC incidence rate increases rapidly with age: it doubles with each 5-year age increase until the age of 50 years old, then increases by 30% in subsequent groups aged 55 years and older (9). However, CRC incidence is increasing among young adults. Accordingly, the median age at diagnosis decreased from 72 years during 2001–2002 to 66 years during 2015–2016 (9).

Regarding sex, the American Cancer Society report showed that after the age of 50 years, the CRC incidence in male is higher than that in female, with incidence (23.6 *vs.* 16.3 per 100,000 persons per year) and mortality (10.8 *vs.* 7.2 per 100,000 persons per year) rates 1.4- and 1.5-fold (16). Data from China's National Cancer Center in 2018 demonstrated that CRC incidence increased gradually with an increase in age, and the incidence rate in male was higher than that in female in all age groups. In China, the incidence rate for individuals under 25 years old was <1/100,000 persons, increasing rapidly to reach a peak in the 80–84-year-old group of 212.69/100,000 persons for males and 153.83/100,000 persons for females (3).

### *Lifestyle*

#### Smoking

Smoking is a detriment to human health and represents a risk factor for many malignant tumors. In 2020, a meta-

analysis, including 188 original studies by Botteri *et al.* (17), showed that relative risk (RR) of CRC was 1.14, 1.17, and 1.18 for current smokers, past smokers, and former smokers at any time, respectively, compared with that for never smokers. They also demonstrated that quitting smoking reduces the risk of CRC: after 10 years, the risk began to decrease; after 26 years, the risk of former smokers was significantly lower than that of current smokers. Despite various tobacco control policies, the number of smokers is still quite large in China. According to statistics published by the Chinese Center for Disease Control and Prevention (18), the smoking rate of individuals aged ≥15 years old was 26.6% in 2018. Of these, the proportion of male smokers was higher than that of female smokers (50.5% *vs.* 2.1%), and those living in rural regions smoked more than those living in urban regions (28.9% *vs.* 25.1%).

More than 1 million people die each year from smoking-related diseases, and over 100,000 die from exposure to second-hand smoke, i.e., passive smoking. Chen *et al.* found that passive smoking and CRC were significantly correlated (RR=1.14) with passive smoking being associated with an increased risk of CRC (19). According to the Health China Action guidelines (2019–2030) (20) released by the Committee for the Promotion of Health in China in 2019, tobacco-related health risks are one of the most serious worldwide public health concerns of today. The World Health Organization (WHO) developed the first international public health treaty: the Framework Convention on Tobacco Control, which was formally implemented in China in January of 2006. With over 300 million smokers, an urgent need to prevent tobacco-related health risks exists in China.

**Drinking**

Excessive drinking leads to the accumulation of harmful substances in the body, and long-term drinking poses a threat to human health. Studies demonstrated that excessive alcohol consumption can increase the risk of CRC (21). Moreover, a meta-analysis showed a causal relationship between alcohol consumption and CRC, with a positive correlation between heavy alcohol consumption (>50 g/day) and CRC mortality rate. In the Asian population, this positive correlation was stronger than that in the US population. This difference may be influenced by genetic factors (22,23).

According to the Global Burden of Disease 2017, alcohol consumption caused 673,300 deaths in China that year, a 1.82-fold increase from 1990. The population risk percent attributable to alcohol consumption is high, from 3.92% in 1990 to 5.65% in 2017 (24). Among adults older than 18 years old in 25 provinces, the drinking rate for males and females reached 84.1% and 29.3%, respectively. In China, the number of deaths from alcohol-related chronic diseases was 565,100; of these, 172,500 were tumor-related (25).

**Exercise**

Epidemiological data show that certain modifiable lifestyle factors, such as dietary habits and physical activity, are more strongly correlated with the risk of CRC than with the risk of other cancer types (26). Ngoc Minh Pham *et al.* (27) showed an inverse relationship between physical exercise duration and CRC incidence among Japanese individuals, with colon cancer being more negatively correlated than rectal cancer. Gu *et al.* (28) demonstrated that low vegetable intake was a major risk factor for CRC in China, with a population attributable risk percent of 17.9%, followed by physical inactivity, with an attributable risk percent of 8.9%.

A cohort study from Norway conducted in 2018 reported a 31% increase in CRC risk [95% confidence interval (95% CI), 1.00–1.70] in people who exercised ≤8.3 Met-h/week compared with that of those who exercised more vigorously (16.6 Met-h/week). Furthermore, prolonged sitting (≥8 h/day) is an independent risk factor for CRC in men (29). Notably, a recent meta-analysis indicated that sedentary behavior increases the risk of death in patients diagnosed with CRC (30). According to the National Fitness Activities survey conducted in 2014, 33.9% of urban and rural residents regularly engage in physical exercise. Of these, 14.7% are 20–69 years old; thus, the proportion of adults who regularly exercise is low (20).

***Dietary habits***

In the past few decades, many prospective cohort studies have demonstrated that dietary habits play an important role in the development of CRC (31). A meta-analysis, including 111 independent cohort studies showed that CRC risk increased 12% for each 100 g/day intake of red and processed meats, and 7% for each 10 g/day intake of alcohol intake. Contrastingly, CRC risk decreased 17% and 13% for each 90 g/day and 400 g/day intake of whole grains and dairy products, respectively (32).

Red meat contains large amounts of heme iron, which destroys DNA and catalyzes the formation of cytotoxic aldehydes. Meat is also typically cooked at high

 

temperatures, which can lead to the formation of carcinogens, such as heterocyclic amines and polycyclic aromatic hydrocarbons (33). China's socioeconomic development led to a nearly 3-fold increase in meat consumption, from 29.6 million tons in 1990 to 87.6 million tons in 2013, with an average annual growth rate of 4.8%. During the same period, the annual meat consumption per capita increased 1.5-fold from 24.8 kg to 61.8 kg, with an average annual growth rate of 4.0%. As the world's largest meat consumer, China's meat consumption accounts for nearly one-third of the world's total meat consumption (34).

### *Hereditary factors*

Hereditary factors account for 35% of CRC risk; accordingly, nearly 30% of the UK population has a family history of CRC (35). Moreover, up to 10% of American adults have a first-degree relative diagnosed with CRC, which represents a two-fold increase in CRC risk, while those with multiple first-degree relatives diagnosed with the disease have a further increased risk of CRC and a younger age at diagnosis (36). CRC-related genetic syndromes, such as Lynch syndrome, familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), and adolescent polyposis, are caused by specific gene germline mutations and are responsible for 5%−10% of all CRC cases (35).

#### Lynch syndrome

Lynch syndrome is an autosomal dominant hereditary disease, commonly occurring in young adults under 45 years of age. Until 2010, this syndrome was known as hereditary non-polyposis CRC. Most Lynch syndrome-related cancers occur in the proximal colon, representing 2%−4% of all CRC cases (37).

Lynch syndrome is mainly caused by mutations in DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Alternatively, this syndrome may be caused by *EPCAM* gene deletion, which leads to high methylation of the MSH2 promoter and consequently, *MSH2* gene silencing. Among these, *MLH1* and *MSH2* mutations are the most common causes of Lynch syndrome, representing approximately 90% of all identified mutations (34). A large retrospective study from China reported an 8.7% detectable rate of deficient mismatch repair in CRC patients. Lynch syndrome accounted for 2.7% of CRC cases and 0.3% of CRC cases in those older than 70 years old (38). In China, mutated *MLH1* and *MSH2* are the most common pathogenic genes in Lynch syndrome, with the former having a higher frequency of mutation and expression loss than the latter. In some areas of China, the *MLH1* and *MSH2* expression loss rates in patients with Lynch syndrome are 15%−48% and 34%−40%, respectively (39).

#### FAP and MAP

FAP is the second most common CRC-related hereditary syndrome after Lynch syndrome, representing approximately 1% of all CRC cases. The average age at diagnosis is 16 years old, and the average age at colon cancer onset is 39 years old for these patients. This syndrome can lead to the growth of hundreds of colonic adenomas in the large intestine (40). Polyps usually occur in early adolescence and if left untreated, the risk of CRC by the age of 40 years is almost 100% (41). Typical FAP features 100−1,000 adenomatous colon polyps, whereas attenuated FAP is mainly characterized by the occurrence of fewer polyps (10−99 adenomas) (41). In China, the incidence of FAP varies between 1/8,000 and 1/10,000 persons, representing 0.94% of CRC cases, and the estimated prevalence is 1−1.5/100,000 persons (42).

Previous studies indicated that the pathogenesis of FAP is mainly caused by mutations in *APC* gene located in human chromosome 5q21 (43). Recently, MAP, a subtype of FAP and autosomal recessive disorder related to mutations in the *MYH* gene, has received increased attention (44). The *MYH* gene mutation is responsible for 25% of FAP patients with APC (−) (45). However, a large proportion of FAP patients with APC (−) and MYH (−) also exist. In China, MAP is the most uncommon FAP subtype, representing 1%−5% of cases. The low prevalence of MAP may be related to poor identification and detection of *MYH* (46).

#### PJS and juvenile polyposis syndrome (JPS)

PJS and JPS are hamartoma-related diseases. PJS is an autosomal dominant genetic disease caused by a germline mutation in the *LKB1* gene. Typically diagnosed during childhood, this syndrome features multiple gastrointestinal hamartomas and pigmentation in specific areas such as the lips, oral mucosa, and eyes (47). JPS is an autosomal dominant disorder characterized by multiple juvenile polyps in the gastrointestinal tract caused by mutations in the *BMPR1A* or *SMAD4* genes. These polyps occur mainly in the colon, but may also occur in the stomach, duodenum, and small intestine (48).

 

### *Related diseases*

#### Obesity

Overnutrition and changes in lifestyle caused by socioeconomic development make obesity gradually become an important human health issue. In 2012, 30.1% and 11.9% of Chinese adults (>18 years old) were overweight and obese, respectively, an increase of 32.0% and 67.6% from 2002. A study published in the Lancet in 2016 demonstrated that the number of obese people in the world has been increasing rapidly in the past 40 years, from 105 million in 1975 to 641 million in 2014. China has the highest number of obese adults worldwide, 43.2 million men and 46.4 million women (49). The International Agency for Research on Cancer reported that obesity may directly lead to an increased risk of multiple cancers, including CRC (50). A prospective cohort study, including 85,256 American women showed that the risk of CRC by the age of 50 years old for overweight and obese women was 1.37- and 1.93-fold higher, respectively, than that for women with normal weight (51). Furthermore, obesity also affects CRC prognosis. Researchers conducted visceral and subcutaneous fat computed tomography scans in 3,262 patients with stage I–III CRC. The results showed that obesity-related accumulation of subcutaneous fat in men and visceral fat in women significantly increased the risk of death in patients with CRC (52).

#### Type 2 diabetes mellitus (T2DM)

Epidemiological statistics and meta-analysis results showed that patients with T2DM had a higher risk of CRC (53). Accordingly, timely administration of drugs to control blood glucose in these patients was helpful in reducing the incidence of colorectal adenoma (54). A recent report from Sweden's large-scale epidemiological statistics, including 12,614,256 individuals (comprising 559,375 patients with diabetes and 162,226 patients with CRC), followed up between 1964–2015 showed that a personal diabetes history increases the risk of CRC (0.4%) comparably with a family history of CRC (0.5%) in patients diagnosed with diabetes at <50 years old (55).

In 2015, Wang *et al*. (56) reported epidemiological data on tumor risk in a cohort, including 327,268 Chinese patients with T2DM. The risk of CRC in men and women increased 1.47- (95% CI, 1.29–1.67) and 1.33-fold (95% CI, 1.15–1.54), respectively. A study published in 2018 evaluated the overall prevalence of diabetes and pre-diabetes in mainland China as 12.8% and 35.2%, respectively. Accordingly, 129.8 million people are estimated to have diabetes in mainland China. Moreover, the incidence of T2DM differed significantly according to the region, with the highest prevalence occurring in North China (57). The specific mechanism by which patients with T2DM are susceptible to develop CRC is poorly understood. Researchers have attempted to explain the correlation from different perspectives, including the identification of epidermal growth factor (58), insulin-like growth factor 1 (IFG-1) (59), and inflammatory factors (60).

### *Gut microbiota*

Gut microbiota is an important part of complex environment of human intestinal tract (61) and it is closely involved in the occurrence, development, and treatment of many diseases. Regarding CRC, the progress in gene sequencing technology allowed researchers to identify significant differences in the composition of bacteria (62), fungi (63), archaea (64), and viruses (65) in the gut microecology of patients with CRC and healthy individuals.

Recently, many studies have linked *Fusobacterium nucleatum*, a pathogenic factor of periodontal disease, to intestinal diseases (66,67). *Fusobacterium nucleatum* is associated with colorectal cancer and promotes colonic tumor formation in preclinical models (68). Additionally, researchers found a significant correlation between *Clostridium difficile* and CRC (69).

Enterotoxigenic *Bacteroides fragilis* can secrete an unstable 20-kDa zinc-dependent *B. fragilis,* causing human diarrhea. Sequencing results showed that the relative abundance of *B. fragilis* was significantly increased in the intestinal flora of patients with CRC (70). In addition, many other strains are believed to be closely related to the occurrence of CRC, including anaerobic digestible *Streptococcus*, *pks*$^{+}$ *Escherichia coli* (71), *Campylobacter jejuni* (72), and enteric *Salmonella* (73). Besides the cancer-promoting effect of a single strain, the occurrence of CRC may also be related to the formation of biofilms (74). Presently, the gut microbiota is considered an important risk factor for CRC and may become a new marker for non-invasive diagnosis of CRC and adenoma (75).

## Precancerous lesions

Precancerous lesions refer to pathological changes closely related to CRC, including colorectal adenoma and

 

inflammatory bowel disease (IBD)-associated dysplasia (76,77). Timely treatment of precancerous lesions can prevent them from developing into malignant tumors, representing an important factor for developing preventive strategies.

### *Colorectal polyps*

Colorectal polyps are the most common precancerous lesions of CRC. WHO guidelines classify polyps as adenomatous, hamartomatous, inflammatory, and hyperplastic (76). Despite most polyps remaining benign, some may become malignant after a decade or more through the classic "adenoma-carcinoma" or serrated polyp pathway (77). At least 25% of men and 15% of women who undergo colonoscopic screening will discover one or more adenomas; among older adults (>60 years old), the incidence of adenomatous polyps reaches 40% (78). Accordingly, undergoing colorectal endoscopy screening and accepting timely treatment are particularly important for individuals aged 50 years or older (79). Moreover, Chen *et al.* (80) studied 4,485 patients with colorectal polyps aged 18–49 years during 2010–2018. Of them, 77.0% had at least one polyp located in the distal colon, mainly advanced adenoma or ≥10-mm serrated polyps, indicating that young and middle-aged Chinese individuals must undergo colorectal endoscopy screening with special attention to the distal site.

### *IBD*

IBD is a chronic disease characterized by intestinal inflammation, including ulcerative colitis (UC) and Crohn's disease (81). Since the end of the 20th century, the incidence of IBD has increased in Asia, with the highest incidence concentrated in East Asia (China, Japan, and South Korea) and South Asia (India). This increase is positively correlated with the industrialization and urbanization processes in these countries. Compared with western countries, Asian patients with Crohn's disease (who are mainly male) are likely to have more perianal lesions, and older Asian patients with UC tend to have fewer extraintestinal manifestations but worse clinical outcomes (82).

In China, the incidence of IBD is positively correlated with regional population density. Moreover, this incidence is significantly higher in western and southern China than that in other regions, owing to differences in living conditions and eating habits (83). Eaden *et al.* (84) conducted a meta-analysis, including 116 studies, involving 54,478 patients with UC and found that the incidence of UC-related CRC was 1.6% at 10 years, 8.3% at 20 years, and 18.4% at 30 years. In Hong Kong, the incidence of UC-related CRC is lower than that in western countries (0.81% *vs.* 3.7%) (85). In China, India, and other Asian countries, the risk of patients with UC developing CRC, accompanied by a worse prognosis and higher mortality rate, is twice as high as that of the general population (86). Recently, 20%–30% of new patients with IBD are under the age of 20 years old. Moreover, the increase in IBD prevalence in children indicates that these patients are considerably younger (87). In China, the incidence of IBD will likely continue to rise in the next decade with the acceleration of urbanization processes, rapid economic development, and improvement of medical diagnosis technology (88). Therefore, effective IBD prevention and treatment will be particularly important in the future.

## Prevention

### *Early screening*

CRC is one of the malignant tumors most suitable for population screening (89), and early screening represents an important strategy to reduce the incidence and mortality rates of CRC. The first CRC screening test was developed in Minnesota, USA, in 1975 (90). By 2016, 68% of American adults aged 50–75 years were screened for CRC (9). Levin *et al.* (91) reported that an organized CRC screening program based on large-scale community populations in the US resulted in higher screening rates among adults aged 51–75 years (38.9% in 2000 *vs.* 82.7% in 2015). Moreover, this increase was associated with a 25.5% and 52.4% reduction in the annual CRC incidence (95.8 *vs.* 71.4/100,000 persons) and mortality (30.9 *vs.* 14.7/100,000 persons) rates, respectively, during the same period. In 2017, a CRC screening model study in Australia demonstrated that 92,200 CRC cases and 59,000 deaths can be prevented when CRC screening population participation rate reaches 40% (the current level in Australia) (92). Comparatively, colonoscopy can prevent 1 death/52–59 persons, indicating that early screening is more cost-effective.

The first CRC screening test in China was performed in Haining, Zhejiang Province, during 1977–1980. After a 20-year follow-up, the risk factors for recurrence after adenoma resection were determined (93). Another CRC

 

screening study was conducted in a rural community in Jiashan, Zhejiang Province, during 1989–1999. After a 8-year follow-up, the cumulative mortality of rectal and colon cancer in the screening area decreased by 31.7% and 7.7%, respectively, compared with those in the control area (94). Despite early CRC screening being available in many Chinese cities, initial screening rates remain low and screening compliance needs to be improved urgently (95). According to data published by the National Cancer Center of China in 2019, between 2012–2015, the Chinese Urban Cancer Screening Program recruited 1,381,561 qualified participants from 16 provinces for colonoscopy screening combined with risk scores, but only 25,593 individuals completed the program, a participation rate of 14.0% (96).

CRC screening in China is conducted using a two-step method similar to most countries. First, high-risk groups are identified through CRC screening scores, questionnaires, or common initial screening tests. Those with high scores or positive results in fecal immunochemical tests and stool DNA tests are considered high-risk and undergo colonoscopy (97). In 2017, Gu *et al.* (98) conducted a meta-analysis on the Chinese population compliance with CRC screening during 2006–2015 and showed that 827,904 individuals underwent initial screening, with questionnaire survey, fecal occult blood test, and colonoscopy compliance rates of 56%, 50%, and 44%, respectively. Importantly, the American Cancer Society lowered the age to begin CRC screening to 45 and 40 years for those at average and high (family history of adenomas or first-degree relative with CRC) risk, respectively (98).

### *Lifestyle improvement*

Evidence indicates that diets high in fiber and low in red and processed meats, as well as regular physical activity, have a protective effect on CRC development (99). Many studies confirmed that high dietary fiber intake is negatively correlated with CRC (RR=0.84) (100), especially fiber derived from grains and fruits (101). For patients with CRC, physical exercise before or after diagnosis can reduce the risk of death (102). A meta-analysis estimated that after CRC diagnosis, every additional 15 Met-h/week (equivalent to the current recommendation of at least 225 min of moderate-intensity activity per week) of exercise reduces the mortality rate by 38% (103). The Healthy China Action (2019–2030) (20) recommends the consumption of at least 500 g of vegetables and fruits and 12 types of food per day, and 25 types per week. Concurrently, it recommends that adults maintain their body mass index at 18.524 kg/m$^2$, perform moderate-intensity exercise for >30 min more than 3 times a week, or accumulate 150 or 75 min of moderate- or high-intensity physical activity, respectively.

### *Chemoprevention*

Currently, non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most effective drugs for CRC chemoprevention. They prevent CRC mainly through cyclooxygenase-2 (COX-2) expression inhibition (104). Aspirin is the most widely used NSAID. Since Kune *et al.* (105) reported that aspirin can prevent CRC in 1988, many studies demonstrated that low-dose aspirin can reduce CRC incidence and mortality (106). Guidelines published by the United States Preventive Services Task Force in 2016 (16) recommended initiating low-dose aspirin (81 mg/d) use for cardiovascular disease and CRC primary prevention in adults aged 50–59 years with a ≥10% 10-year cardiovascular disease risk, not at increased risk for bleeding, ≥10-year life expectancy, and willing to take low-dose aspirin daily for ≥10 years.

Furthermore, Monica *et al.* (107) found that patients receiving placebo had an estimated three-year cumulative incidence of one or more colorectal adenomas of 60.7%, whereas those receiving 200 or 400 mg of celecoxib, a selective COX-2 inhibitor, twice daily had a cumulative incidence of 43.2% and 37.5%, respectively, indicating that celecoxib may effectively prevent the occurrence of colorectal adenoma in a dose-dependent manner. However, compared with placebo, celecoxib was associated with an increased risk of cardiovascular events, which limits its use in CRC prevention. In China, considering NSAIDs and COX-2 inhibitor-related peptic ulcer and cardiovascular adverse reactions; unclear preventive dose, age, and starting age; and benefit-risk and cost-benefit ratios of long-term use, these drugs are not currently recommended for initial colorectal adenoma prevention in the general population (108).

Metformin, a first-line drug to control blood sugar in patients with T2DM, has received interest as a potential CRC chemopreventive drug. A meta-analysis including 58 studies showed that the incidence of colorectal adenoma (RR=0.77) and CRC (RR=0.76) in patients with diabetes using metformin were significantly lower than in those not

 

using metformin (109). Although the impact of metformin use on CRC incidence in the general population is controversial, its role in reducing CRC incidence in patients with T2DM is positive. Moreover, consuming folic acid, magnesium, and dairy products reduces the risk of CRC, whereas the intake of tea, vitamin D, coffee, and omega-3 unsaturated fatty acids has controversial effects on CRC prevention (99).

### *Surgical prevention*

Endoscopic screening reduces CRC incidence and mortality through the preventive removal of precancerous lesions (110). For early-stage CRC and precancerous lesions, current treatment methods include hot biopsy forceps, snare resection, endoscopic mucosal resection, and endoscopic submucosal dissection (111). Besides strictly grasping indications for surgical resection, individualized follow-up is another important way to reduce CRC incidence (112). He *et al.* (113) reported that compared with patients who did not find polyps at initial endoscopy, the multivariable hazard ratio for developing CRC in patients with advanced adenoma or serrated polyps was 4.07 (95% CI, 2.89–5.72) and 3.35 (95% CI, 1.37–8.15), respectively. Contrastingly, the risk of developing CRC in patients with non-advanced adenomas was not significantly increased. Therefore, lower gastrointestinal endoscopy should be repeated within 3 years after advanced adenoma or large serrated polyps (≥10 mm) diagnosis, while patients with non-advanced adenoma or small serrated polyps (<10 mm) may need a similar level of surveillance to patients without polyps.

## Conclusions

China has the world's largest number of new CRC cases, representing a threat to the health of individuals and heavy socioeconomic burden. CRC has various risk factors, and prevention is the main strategy to reduce its incidence and mortality rates. Presently, prevention can be achieved through lifestyle changes, healthy diet, and early screening for high-risk individuals. Moreover, CRC incidence and mortality rates are closely related to socioeconomic development levels, varying according to regional and population characteristics. To reduce the burden of CRC, public health officials should promote prevention and management of modifiable risk factors through national policies. The increasing CRC incidence and mortality rates in China can be controlled and reduced through clarifying epidemiological characteristics, optimizing early screening strategies, and implementing strict guidelines for diagnosis and treatment.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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