Review Article

Let food be thy medicine: the role of diet in colorectal cancer: a narrative review

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Background and Objective: Colorectal cancer (CRC) is the third most common cancer worldwide, and the incidence and mortality rates continue to increase annually. Many factors, including genetic, immune, and environmental factors, influence the occurrence and development of CRC. Along with the economic development, changes in lifestyle, especially dietary factors, have been shown to greatly affect the progression of CRC. Increasing evidence showed that dietary patterns influence the risk of CRC and affect CRC treatment. The present review describes the role of diet in the prevention and treatment of CRC with the hope that doctors attach importance to dietary patterns in educating patients with CRC or at risk of CRC and that diet may be regarded as an auxiliary treatment strategy to improve patients' outcomes.

Methods: English language articles published from 2000 to December 2021 in PubMed and Embase were identified by searching titles for keywords including "diet", "colorectal cancer", "dietary pattern", and "dietary factor"; 101 articles were selected for review.

Key Content and Findings: The present review describes the role of different dietary patterns and factors in the prevention and treatment of CRC. We found that dietary intervention is closely related to the occurrence, development, and prognosis of CRC. Adherence to the Mediterranean diet (MD), the Dietary Approaches to Stop Hypertension (DASH) diet, fasting, vegetarian diets and the ketogenic diet (KD) were found to reduce the risk of CRC, prolong patient survival, and delay disease progression. Moderate intake of dietary fiber (DF), omega-3 fatty acids, micronutrients (e.g., calcium, iron, and selenium), and vitamins have been shown to be beneficial in the prevention and treatment of CRC. Conversely, diets high in fat or sugar and those rich in red meat or processed meat promote CRC.

Conclusions: People at high risk of CRC and those with CRC are recommended to eat a plant-based diet rich in fruits, vegetables, and whole grains with appropriate DF intake and to avoid high levels of processed meat, red meat, and highly refined grains.

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Introduction

According to the latest global burden of cancer data for 2020 released by the International Agency for Research on Cancer (IARC) within the World Health Organization (WHO), more than 1.93 million people worldwide were newly diagnosed with colorectal cancer (CRC), accounting for 10% of all newly diagnosed cancers worldwide and ranking third in incidence and second in mortality at 9.4% (1). In 2020, a total of 555,477 new cases of CRC and 286,162 CRC-related deaths occurred in China, and CRC ranked second (12.2%) and fifth (9.5%) for these statistics, respectively, among all cancers (1). The 5-year relative survival rate of CRC in China from 2012 to 2015 was only 52.7% (2). Current cancer treatments, such as surgery, chemoradiotherapy, immune checkpoint inhibitors, and molecular targeted drugs, have evolved and improved the prognosis of cancer patients, but limitations remain (3).

A variety of healthy dietary patterns have evolved with the development of human civilization, including the Mediterranean diet (MD), the Dietary Approaches to Stop Hypertension (DASH) diet, and fasting. For example, the MD emphasizes the consumption of plenty of fruits and vegetables, whole grains, and a small amount of red meat, with olive oil as the main dietary fat (4). Recent studies found that various dietary patterns are closely related to the occurrence, development, and prognosis of cancer. The present review focuses on different dietary patterns and factors. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-32/rc).

Methods

Table 1 shows the search strategy summary. In this review, we searched the PubMed and Embase databases for original articles reporting the results of preclinical and clinical trials published from 2000 to 2021 with the keywords "diet", "colorectal cancer", "dietary pattern" and "dietary factor". The articles were limited to full-text publications in English. Studies on the use of the dietary pattern or factor in patients at high risk of CRC and in those with CRC were included.

Effects of different dietary patterns on CRC

Table 2 summarizes the role of different dietary patterns in the prevention and treatment of CRC.

MD

The MD was originally consumed by people along the Mediterranean coast. Observational studies in the 1950s found that these people had lower rates of cancer than people in other parts of Europe. Since the MD was recognized and regarded as a healthy dietary pattern (30). The current MD is characterized by a high intake of vegetables, legumes, fresh fruits, whole grains and nuts, with olive oil (generally virgin olive oil with less than 0.8% acidity obtained via mechanical extraction) as the main dietary fat, and moderate consumption of fish, dairy products (primarily cheese and skim milk), red meat and red wine (5). With the development of modern medicine, an increasing number of studies have found that food emphasized in this diet protects against many diseases, such as cardiovascular disease, breast cancer, and asthma (31).

Researchers recently reported that the MD decreases the risk of CRC. For example, Zhong *et al.* (6) in 2020 performed a meta-analysis of 13 prospective cohort studies and found a 10% reduction in CRC incidence associated with MD compliance. The meta-analysis by Schwingshackl *et al.* (7) included 21 cohort studies and 12 case-control studies, comprising 1,368,736 and 62,725 subjects, respectively, and the results showed that high compliance with the MD reduced the risk of CRC by 15%. Rosato *et al.* (8) retrospectively analyzed 3,745 cases of CRC and 6,804 cases of non-CRC in Italy and found that the MD reduced the incidence of CRC.

More recent reports have consistently shown that adherence to the MD before or after CRC diagnosis reduced CRC mortality. For example, Van Blarigan *et al.* (9) observed the diet of 1,284 patients with metastatic CRC within

Table 1 The search strategy summary

Items	Specification
Date of search	30-Dec-21
Databases and other sources searched	PubMed and Embase
Search term used	"diet", "colorectal cancer", "dietary pattern" and "dietary factor"
Timeframe	2000 to 2021
Inclusion and exclusion criteria	Inclusion criteria: preclinical and clinical studies on the relationship of diet and CRC; the articles were limited to full-text publications in English Exclusion criteria: clinical studies with a small sample size; published in a language other than English
Selection process	Eligible articles were screened by two authors (YZ and LM)
Any additional considerations, if applicable	None

CRC, colorectal cancer.

Table 2 The role of different dietary patterns in the prevention and treatment of CRC

Dietary patterns	Characteristic	Shortcoming	Influence on the incidence of CRC	Impact on survival of patients with CRC
MD	High intake of vegetables, legumes, fresh fruits, whole grains and nuts, with olive oil (generally virgin olive oil with an acidity of less than 0.8% obtained through mechanical extraction) as the main dietary fat, moderate consumption of fish and dairy products (primarily cheese and skim milk), moderate consumption of red meat and moderate consumption of red wine (5)		MD lowers risk of CRC (6-8)	Reduces cancer mortality (9-11)
DASH diet	Higher intake of fruits, vegetables, legumes, and nuts, moderate intake of low-fat dairy products, lower intake of animal protein, and controlled salt intake (12)	The DASH diet showed no significant benefit in reducing CRC mortality (9,10,13)	DASH diet may reduce the risk of CRC (14,15)	
Fasting	Fasting is considered a "green" natural therapy that entails consuming a moderate amount of drinking water and a small amount of vegetable juice and fruit juice while fasting from all other food for a limited period of time and relying on the energy stored in the body to support life activities (16)	For most people, especially cancer patients, it is difficult to adhere to fasting for a long time. Therefore, clinical studies primarily used the FMD instead of fasting, and related studies remain in the exploratory stage	The most effective nutritional intervention in the prevention and treatment of CRC, extending survival and disease progression (17)	
Vegetarian diet	Vegetarian diet is characterized by the consumption of fruits, vegetables, legumes, pulses, grains, nuts, seeds, fungi, algae, yeast and/or other nonanimal-based foods, with or without dairy products, honey and/or eggs (18)	A long-term plant-based diet increases the risk of malnutrition, and the effect of the application in the prevention and treatment of CRC is controversial	Helps reduce the risk of CRC (19-21)	
KD	A high fat, medium protein, and low carbohydrate diet (22)	The impact of KD on CRC requires more preclinical and clinical trials	Preclinical studies showed that KD intervention effectively slowed the growth of CRC (23,24)	KD has shown benefits in CRC treatment (25-29)

CRC, colorectal cancer; MD, Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; FMD, fasting-mimicking diet; KD, ketogenic diet.

4 weeks after treatment, and introduced the concept of an alternative Mediterranean diet (AMED) score based on the work of Fung *et al.* (32). The results showed that a higher AMED score negatively correlated with the mortality of patients with CRC. Jacobs *et al.* (10) also reported that adherence to a diet with a high AMED score before diagnosis reduced CRC mortality. Bloomfield *et al.* (11) performed a cohort study and showed that consumption of the MD without limiting fat intake reduced mortality among CRC patients.

DASH diet

The DASH diet is a treatment for high blood pressure that originated with the large hypertension prevention and treatment program created by the National Heart, Lung, and Blood Institute (NHLBI) in 1997. It emphasizes higher intakes of fruits, vegetables, legumes, and nuts; moderate intake of low-fat dairy products; lower intake of animal protein; and a controlled salt intake (12). The DASH diet has beneficial effects on high blood pressure, diabetes, and breast cancer (33).

Notably, the DASH diet was recently associated with a lower incidence of CRC. For example, a meta-analysis by Tangestani *et al.* (14) also found a significant negative association between adherence to the DASH diet and CRC risk. Vargas *et al.* (15) evaluated 938 women in a cross-sectional study and found that the patients who strictly followed the DASH diet recommendations had a lower risk of CRC.

Although the DASH diet was associated with a reduced risk of CRC, it was unclear whether this dietary pattern has a positive effect on CRC treatment. Jacobs *et al.* (10) reported no significant association between the DASH diet and CRC mortality; this result is consistent with Fung *et al.* (13). A prospective cohort study of patients with metastatic CRC also concluded that the DASH diet did not extend survival (9).

Fasting

Fasting, which originated from European religions, is considered a green, or nature, therapy that entails the consumption of a moderate amount of drinking water and a small amount of vegetable juice and fruit juice while fasting from all other food for a limited period of time; adherents to this diet rely on energy stored in the body to support life activities (16). This particular approach alters energy metabolism and affects the course of a variety of diseases, such as inflammatory bowel disease (IBD) (34) and breast cancer (35).

Fasting-based diets in the field of oncology include simple fasting and the fasting-mimicking diet (FMD) (36). The FMD is a plant-based, low-calorie, low-protein, and low-carbohydrate diet designed to mimic fasting while providing adequate micronutrients (vitamins, minerals, etc.) and minimizing the burden of fasting. Originally proposed by Brandhorst *et al.* (17), the FMD is a cyclical diet (600 kcal on day 1; 300 kcal on days 2 to 5) interspersed with periods of a normal feeding regimen. With the further development of FMD research, many diets with similar characteristics and cycles have emerged (17,35).

Fasting is the most effective nutritional intervention for the prevention and treatment of CRC because it changes the energy metabolism in CRC cells, inhibits CRC cell growth, prolongs patients' survival, and delays disease progression (37). Preclinical studies have confirmed these effects. For example, Yamamoto *et al.* (38) showed a significant reduction in the incidence and number of colorectal tumors in the calorie-restricted diet group compared to the free diet group. Weng *et al.* (39) studied the effects of fasting on glucose metabolism and CRC malignant behavior and found that fasting inhibited CRC cells in proliferation in combination with mammalian target of rapamycin (mTOR) inhibitors.

However, it is difficult for most people, especially cancer patients, to adhere to fasting for a long time. Therefore, the FMD is primarily used instead of fasting in clinical studies, and related studies remain in the exploratory stage. For example, Brandhorst *et al.* (17) performed an initial randomized controlled clinical trial with 38 subjects and found that the FMD group had a lower risk of CRC than the control group.

Vegetarian diet

Vegetarian diets originated in 3200 BC when ancient Egyptian civilizations started adopting vegetarianism (40). Approximately 100 years ago, researchers began identifying potential health benefits of vegetarian diets. According to the Vegetarian Society (18), a vegetarian diet is characterized by the consumption of fruits, vegetables, legumes, pulses, grains, nuts, seeds, fungi, algae, yeast and/or other nonanimal-based foods, with or without dairy products, honey and/or eggs.

Previous prospective cohort studies and randomized clinical trials showed that a vegetarian diet reduced the risk of CRC. For example, Orlich *et al.* (19) studied 77,659 participants and found that those adhering to a vegetarian diet had a 22% lower risk of CRC than nonvegetarians. The cohort study by Gilsing *et al.* (20) followed 10,210 subjects

for 20.3 years and observed a significant reduction in CRC risk in vegetarians compared to meat consumers. A cohort study of 10,998 subjects recorded 95 cases of CRC after an average follow-up of 17 years; in this study, vegetarians had a 15% lower risk of CRC compared to nonvegetarians (21).

Although some studies have reported positive results for a vegetarian diet in preventing and treating CRC, others have reported conflicting results. For example, Godos *et al.* (41) performed a meta-analysis of a vegetarian diet and the risk of CRC and found no significant association between a vegetarian diet and a lower risk of CRC. Erben *et al.* (42) also showed that a vegetarian diet did not significantly reduce the risk of CRC. Dinu *et al.* (43) reported that a vegetarian diet did not reduce the risk of death from CRC. A meta-analysis of several prospective studies by Ginter *et al.* (44) showed no significant difference in CRC-related mortality between vegetarians and "health-conscious" nonvegetarians.

Many factors may influence the effectiveness of a vegetarian diet in the prevention and treatment of CRC, such as whether the diet contains eggs and dairy products, the ethnicity of the vegetarians, and the location of their residence. More studies are needed to assess whether a specific vegetarian diet reduces the risk of CRC in a particular population in a particular region and whether a vegetarian diet has potential as an adjunct to CRC treatment.

Ketogenic diet (KD)

Researchers in the 1920s developed a high-fat, medium-protein, and low-carbohydrate diet called the KD to treat intractable epilepsy (22). The KD has been used to treat epilepsy and Alzheimer's disease (45).

More preclinical studies have shown that the KD effectively slows CRC growth. For example, Zhang *et al.* (23) performed *in vitro* and *in vivo* studies with BALB/C mice and found that the KD prevented CRC progression by inducing oxidative stress, inhibiting matrix metallopeptidase-9 (MMP-9) expression, and enhancing the M2 to M1 polarization of tumor-associated macrophages (TAMs). Nakamura *et al.* (24) found that the KD suppressed CRC progression and significantly suppressed the systemic inflammatory response and muscle loss associated with cancer progression in an animal study.

Recent clinical trials also demonstrated that the KD has benefits in CRC treatment. For example, Klement *et al.* (25) studied a cohort 49 CRC patients undergoing radiotherapy, of which 24 adhered to a KD. The results showed that the KD significantly reduced body weight and fat mass, maintained skeletal muscle mass, and synergized with radiotherapy to evoke a trend of a pathological tumor response. Tulipan *et al.* (26) performed an online survey of 94 CRC patients and found that adherence to the KD during treatment was associated with improved self-reported quality of life. The strict KD improved CRC outcomes by promoting the switch to fat-free mass, one of the two human body components (fat and everything else) (27). Obesity is a well-established risk factor for CRC, and a strict KD reduced body fat percent and improved CRC patient survival (28). Klement *et al.* (29) initiated a phase I clinical trial to investigate whether an intermittent KD (such as eating a ketogenic breakfasts) after radiotherapy has a similar effect as a strict KD on the body composition of cancer patients. The results showed that the intermittent KD combined with concurrent radiotherapy had a significant beneficial effect on fat-free mass and protected normal tissue from ionizing radiation compared to the strict KD. These results demonstrate that the KD may have value in combination therapies to improve the efficacy of classical cancer therapy. However, more carefully designed and in-depth studies are needed.

Effects of different dietary factors on CRC

Based on the acknowledgment that dietary patterns rich in processed meat, red meat, and highly refined grains increase CRC risk and because of the prevalence of nutritional and micronutrient deficiencies in CRC patients, researchers investigated the influence of dietary elements on the development of CRC. The following paragraphs discusses the effects of factors, such as fats, dietary fiber (DF), and trace elements, on the incidence and progression of CRC.

DF

DF is a polysaccharide that is not digested in the gastrointestinal tract and produces no energy. The results of in-depth studies of intestinal bacteria have led to increased attention on DF, and DF supplements have been found to help prevent and treat depression, chronic obstructive pulmonary disease, and diabetes (46).

Researchers have shifted their attention to the relationship between the amount of DF consumed per day and the prevention of CRC in people at high risk of CRC. For example, Peto *et al.* (47) showed that diets high in fiber (≥23 g/day) reduced CRC risk by 12%. The Scientific Advisory Committee on Nutrition in the UK performed

a meta-analysis of the role of DF and found that the risk of CRC decreased by 8% for each 7 g/day increase in DF intake from food (48). O'Keefe *et al.* (49) recommended that DF intake be increased to more than 50 g/day to prevent CRC.

Song *et al.* (50) performed a prospective cohort study of 1,575 CRC patients and found that those who increased their fiber intake from prediagnosis levels had lower mortality, and each additional 5 g/day of fiber intake was associated with an 18% reduction in CRC-specific mortality. Unfortunately, the global per capita intake of DF is less than 20 g/day (51).

Therefore, increasing DF consumption should be encouraged. Future studies should determine the precise recommended number of grams of DF intake for people at high risk of CRC. The effects of DF from different sources should also be compared to ascertain the source that will achieve the best therapeutic effect.

Dietary fats

The development of the modern society has led to the increasing common excessive intake of dietary fat, which may lead to obesity and chronic disease.

Animal and *in vitro* studies have shown a direct role for dietary fat in increasing colonic cell proliferation and associated risks (52-54). However, the results of clinical studies are complex and inconsistent. Wan *et al.* (55) performed a randomized controlled feeding trial of 217 people aged 18–35 years that lasted 6 months to compare a low-fat diet (20% fat energy), medium-fat diet (30% fat energy) and high-fat diet (40% fat energy). Intestinal floras populations associated with CRC increased in the high-fat diet group. Total fat, saturated fat, monounsaturated fat and n-6 polyunsaturated fat intake was not associated with CRC risk, according to the results of a case-control study (56). A meta-analysis by Kim *et al.* (57) showed no effect of dietary fat or fatty acids on CRC risk. Nakamura *et al.* (58) performed a randomized controlled trial of 373 patients after CRC surgery who were asked to consume at least 18–22% of total energy from fat. The results showed that tumor recurrence increased as fat intake decreased.

In contrast, omega-3 polyunsaturated fatty acids (PUFAs), such as α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may be protective agents against CRC (59). For example, Haidari *et al.* (60) showed that the combination of vitamin D (50,000 IU weekly) and omega-3 fatty acids (660 mg/day) reduced the levels of inflammation biomarkers in patients with CRC, improved the efficacy of chemotherapy drugs, and reduced the side effects of chemotherapy. Golkhalkhali *et al.* (61) demonstrated that supplementation with microbial cell preparations (MCPs) and omega-3 fatty acids (2 g/day for 8 weeks) improved the quality of life of patients with CRC and mitigated some side effects of chemotherapy. A randomized controlled trial evaluated 148 patients who were referred for elective CRC surgery and received an omega-3 fatty acids-enriched oral nutritional supplement (ONS: 2.0 g/day EPA and 1.0 g/day DHA) or a standard ONS for 7 days before surgery. The results showed that oral intake of omega-3 fatty acids had anti-inflammatory effects in surgical patients (62). Kim *et al.* (63) performed a meta-analysis of 20 prospective studies involving 18,102 cases and 1,360,046 participants and found that EPA and DHA intake was inversely associated with 11% and 12% lower CRC risk, respectively. The risk of CRC decreased 4% for every 1% increase in blood n-3 PUFA levels.

However, the effect of dietary fat on the prevention and treatment of CRC remains controversial, and more related clinical studies are needed to develop a better dietary fat intake plan.

Red and processed meats

Many epidemiological studies have examined the effects of red meat (e.g., beef, pork, and lamb) and processed meats. Most of these studies reported an association between an increased CRC risk and greater intake of red and processed meats. For example, a prospective study by the Health Professionals Follow-up Study (HPFS) reported that men who ate beef, pork or lamb more than five times per week had a threefold increased risk of CRC compared to men who ate less than one meal per month that included these meats (64). Bradbury *et al.* (65) followed 475,581 participants aged 40–69 years for an average of 5.7 years and identified 2,609 cases of CRC. In this study, participants who consumed an average of 76 g of red and processed meats daily had a 20% higher risk of CRC compared to those who consumed 21 g daily. Another prospective study (66) found that a higher daily intake of processed meat and barbequed/red meat products was associated with an increased risk of CRC in women.

The effect of red and processed meats on CRC patients survival was also investigated. An epidemiological investigation by Mattiuzzi *et al.* (67) showed that red meat and processed meat were related to 1.77% and 1.18% of global CRC deaths, respectively. Prospective observational studies showed that reducing red and processed meat intake in patients with CRC after diagnosis decreased the risk

of cancer recurrence and improved the overall survival of patients with early-stage CRC after standard treatment (68).

Therefore, it is necessary to encourage people at high risk of CRC and patients with CRC to reduce their intake of red and processed meats. However, different dietary habits entail different levels of raw meat and meat product consumption and various cooking methods. Therefore, future epidemiological studies should consider the dietary culture of each population to reliably elucidate the effects of processed meat intake, particularly on cancer incidence.

Sugars

A high-sugar diet is associated with obesity and diabetes. Previous studies showed an association between CRC risk and a high prevalence of insulin resistance, obesity, and diabetes (69), but the relationship between a high-sugar diet and CRC risk is not clear.

Animal studies showed that a high-sugar diet promoted the development of CRC (70-72), but the results from clinical trials are more complex. For example, women who consumed more sugary drinks had a slightly higher risk of early-onset CRC than women who consumed less than five ounces (142 g) of sugary drinks per week, and women aged 13 to 18 years who drank eight ounces (227 g) of sugary drinks daily had a 32% increased risk of CRC by age 50, according to the results of a clinical observational study (73). Wang *et al.* (74) showed that sugar intake in men, in combination with smoking and alcohol consumption, correlated with CRC risk. However, other clinical observational studies reached the opposite conclusion. For example, a cohort study of 243 CRC patients showed that a relatively high intake of sugary beverages had no effect on the development of CRC (75).

Although the results of clinical trials are not as consistent as the results of animal experiments, people are keenly aware of the negative effects of sugar on the human body or the negative effects of sugar on the human body have become ingrained. More clinical trials are needed to confirm the effect of sugar on the occurrence and development of CRC.

Dairy products

Studies have shown that dairy products have protective effects against CRC, which may be related to their high levels of calcium, vitamin D, butyric acid, conjugated linoleic acid (CLA) and lactoferrin (76-78).

Available evidence suggests that the consumption of dairy products may prevent the occurrence of CRC. For example, a prospective cohort study followed 7,216 volunteers who did not initially have CRC for an average of 6 years, during which these participants were questioned about the frequency of various food intake; the results showed that high consumption of dairy products was significantly associated with a reduced CRC risk (79). In a meta-analysis of 15 cohort studies and 14 case-control studies, Barrubés *et al.* (76) found a consistent, significant decrease in CRC risk associated with higher total consumption of dairy products compared with lower consumption. Subsequently, a prospective cohort study by El Kinany *et al.* (80) showed a negative association between dairy intake and CRC incidence.

Consumption of dairy products may also affect the survival of CRC patients. A meta-analysis by Jin *et al.* (81) showed that subjects with a high dairy product intake had a 29% lower risk of dying from CRC than those with a low such intake. A prospective cohort study by Yang *et al.* (82) evaluated the relationship between dairy products intake and mortality before and after diagnosis in 2,284 patients with CRC and found a negative correlation between dairy product intake and all-cause mortality.

Micronutrients

Calcium, iron, selenium, and other micronutrients are essential for energy production and cell metabolism, and researchers found that they are closely related to the occurrence and development of CRC. CRC patients and people at high risk of CRC should ensure they maintain appropriate micronutrient levels.

Calcium and vitamin D

Dietary calcium supplementation has a certain preventive effect on the occurrence of CRC. Zhang *et al.* (83) collected dietary intake data from 2,380 CRC patients and 2,389 sex- and age-matched controls. The mean dietary calcium intakes was 406.94 and 468.21 mg/day, respectively, and the intake of dietary calcium reduced the risk of CRC. A prospective cohort study by Lee *et al.* (84) explored the relationship between dietary calcium intake and CRC development in 119,501 participants aged 40–69 years who were recruited between 2004 and 2013. The results showed that Korean women who adhered to the recommended intake of calcium (700–800 mg/day) had a reduced risk of CRC. A case-control study by Galas *et al.* (85) showed that a 100 mg/day increase in dietary calcium intake was associated with a 5% decrease in CRC risk, and participants taking >1,000 mg/day calcium had a 37% lower risk of CRC.

Some studies have revealed a relationship between calcium levels and quality of life in CRC patients. A

prospective study by Yang *et al.* (86) evaluated the association of calcium intake with CRC-specific and overall mortality after diagnosis in 1,660 patients with nonmetastatic CRC. The results showed that participants who increased calcium intake by at least 300 mg/day had an HR of 0.64 for CRC-specific mortality compared to those who did not appreciably alter their supplemental calcium intake (change <150 mg/day). However, participants who decreased their intake at least 300 mg/day had an HR of 1.23. The prospective cohort study by Um *et al.* (87) revealed that Ca^{2+} may be associated with a reduced risk of CRC mortality.

Vitamin D deficiency affects calcium absorption (88). The recommended dietary allowance (RDA) for vitamin D of 15 μg/day for adults between 51 and 70 years and 20 μg/day for older adults (>70 years) is widely established (89). Studies have shown an association between vitamin D deficiency and the occurrence of almost all cancers, with CRC being the most relevant type (90).

A recent case-control study found that higher dietary intake of vitamin D and calcium was associated with 47% and 50% reductions, respectively, in CRC risk (91). Consistent with this result, a meta-analysis of nine case-control studies found that the risk of CRC decreased with increased dietary vitamin D intake (92); this same conclusion was reached in another meta-analysis of 17 cohort studies (93).

Animal studies (94) have shown that vitamin D supplementation has potential as an adjuvant therapy for CRC. A randomized controlled trial by Haidari *et al.* (60) revealed that vitamin D may be a novel adjuvant treatment because it can reduce inflammatory biomarkers and treatment resistance in CRC patients.

Selenium

Patients with CRC have low levels of selenium. Haidari *et al.* (60) measured the selenium concentration in the blood of 40 patients before surgery, and further analysis showed that selenium levels in the blood and colorectal tissue were significantly lower in patients with metastatic disease. Some observational studies have reported the anticancer effects of selenium. A case-control study by Luo *et al.* (95) examined the independent and combined effects of dietary zinc and selenium intake in 493 patients with CRC and 498 controls. Notably, there was a negative correlation between selenium intake and CRC risk. Tsilidis *et al.* (96) investigated the association of genetically predicted selenium concentration with CRC risk using Mendelian randomization (MR). The results showed that selenium intake negatively correlated with the incidence of CRC. In a double-blind, placebo-controlled, randomized trial, 200 μg/day selenium was prescribed to 1,312 subjects with a history of nonmelanoma skin cancer in the southeastern United States, and these participants were followed for 4.5 years to study the protective effects of selenium against cancer. The results showed no effect of selenium on the primary outcome, but there was a significant 58% reduction in CRC-related mortality (97).

B Vitamins

B vitamins, including folic acid (vitamin B9), riboflavin (vitamin B2), pyridoxine (vitamin B6), and cobalamin (vitamin B12), are essential for DNA methylation, synthesis, stability, and repair (98).

Evidence from epidemiological, zoological, and clinical studies suggests that vitamin B intake influences the development of CRC. A meta-analysis of a prospective study revealed a significant linear decrease in CRC risk with higher intake of vitamin B6; for each additional 1, 3, and 5 mg increase in vitamin B6 intake, the risk of CRC decreased 4%, 11% and 17%, respectively (99). Another meta-analysis (100) of 14 studies that reported vitamin B2 intake and 2 studies that reported blood vitamin B2 concentrations examined the relationship between vitamin B2 and CRC risk. The dose-response model showed a nonlinear trend, with a 10% reduction in CRC risk when vitamin B2 intake increased to 5 mg/day.

Vitamin B is associated with CRC risk and quality of life in CRC patients. Koole *et al.* (101) reported that folic acid supplementation before and after diagnosis improved the quality of life of CRC patients.

Discussion

This evaluation relevant literature from the last two decades on the association of diet patterns and factors with CRC demonstrates a role for diet in the prevention and treatment of CRC. No specific nutritional regimen has been shown to be effective in CRC patients. Thus, we encourage individuals at high risk of CRC to increase their DF, dairy products, and omega-3 fatty acids and to avoid excessive intake of sugar, red meat, and processed meat. For CRC patients, the MD, vegetarian diet, and KD may be implemented as a component of combination therapy. It should be noted that these diets should be followed under the care of a dietitian, and the supplementation of trace elements and vitamins should be emphasized to avoid the

risk of micronutrient deficiencies or, worse, malnutrition.

Summary and outlook

Diet is an integral part of the daily lives of patients and may be used effectively to provide daily nutrition and prevent and treat disease. People at high risk of CRC should focus on maintaining a healthy lifestyle to reduce or delay the incidence of cancer. CRC patients can improve their quality of life by improving dietary habits, following specific dietary patterns, or taking dietary supplements to alleviate disease.

Dietary intervention is part of the clinical prevention and treatment strategy for CRC, and it has achieved significant results. It may be used independently or in combination with immunosuppressants and other drugs to achieve better therapeutic results. The mechanism by which dietary intervention affects the development of CRC are not clear. Studies involving the microbiome, metabolome and proteome are beginning to provide evidence that will help guide more targeted dietary treatments in the future. The mechanism of dietary therapy must be further studied in clinical and preclinical models. Diet therapy is not effective in all patients, and more effective and personalized diets represent the new direction of diet therapy.

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