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ORIGINAL ARTICLE

Associations between diet and nutritional supplements and colorectal cancer: A systematic review

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Abstract

Background and Aim: Colorectal cancer (CRC) is one of the most prevalent cancers around the world. The link between nutrients and the likelihood of developing CRC remains uncertain. The primary objective of the present study was to investigate the potential connection between dietary intake/dietary supplements and the occurrence of CRC through a literature review.

Methods: A comprehensive online search was conducted in PubMed, Scopus, Web of Science, and the Cochrane Library from January 1990 to March 2023 using appropriate keywords. A systematic search was conducted for clinical trials and cohort studies in order to determine the relationship between dietary components/supplements and CRC.

Results: The intake of long-chain n-3 polyunsaturated fatty acids (n-3 LCPUFAs), consisting of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has the potential to decrease the likelihood of developing CRC (eight studies found positive effects and four studies found no association). Some other dietary components such as probiotics, prebiotics, and synbiotics may contribute to suppressing CRC development (three studies found positive effects, whereas three studies did not find any association). There is inconclusive evidence that supplementation with certain micronutrients including vitamin D (one trial found positive effects and another trial reported no association), folate, zinc, and selenium may reduce the risk of CRC.

Conclusion: Some dietary supplements such as n-3 LCPUFAs and probiotics have the potential to reduce the risk of developing CRC. Further studies are necessary to validate these results and understand the underlying mechanisms.

Introduction

Colorectal cancer (CRC) is a prevalent type of malignancy and is responsible for a great majority of cancer mortality.[1] Over the past few years, the prevalence of CRC in Iran has increased to 7–8 occurrences per 100 000 people.[2] A variety of factors, including genetics, age, and lifestyle, have been shown to be associated with an elevated risk of developing and recurrence of CRC.[3] Moreover, there are other variables that might potentially increase the risk of CRC[4] such as hereditary disorders,[5] alcohol intake, smoking, lack of physical exercise, a diet rich in fats, and the consumption of processed red meat.[6] Some studies have reported that cancer risk may be affected by dietary components and dietary supplements. However, conflicting findings have been reported in other studies.[7] Poor nutrition is well recognized as a significant contributing factor to mortality resulting from CRC.[8] Therefore, dietary modification may reduce cancer severity. Several studies have been conducted to investigate the association between dietary patterns and the risk of developing CRC.[6,7,9] Several epidemiological studies have demonstrated the preventative properties of n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in relation to CRC. However, the

impact of n-3 LCPUFAs on CRC has been inconclusive.[10] One meta-analysis found that fish oil reduced CRC risk by 12%.[11] Conversely, Daniel *et al.* found that women who consumed sources rich in α-linolenic acid (ALA) had a greater risk of CRC.[12]

Moreover, some studies have indicated that other dietary components such as folate, trace elements, and probiotics may prevent CRC.[13] For instance, Shang *et al.* found in an animal study that probiotics inhibited the proliferation of colon tumor cells.[14] Another study reported that supplementation with probiotics may decrease serum zonulin levels, thereby increase the permeability of tight junctions between cells of the wall of the digestive tract and induce inflammation and cancer in patients with colorectal metastases.[15] Since conclusive evidence regarding the impact of dietary components on CRC is limited, this study aimed to investigate the potential effects of nutritional supplements on both the risk of developing CRC and its progression.

Methods

This systematic review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[16] The study investigated the possible effects of dietary supplements as a preventative factor for CRC. We included intervention and cohort studies evaluating the effects of dietary components and dietary supplements on CRC in adult participants. In Figure 1, we show the search, screening, inclusion, and exclusion processes according to our predefined criteria.

Search strategy. Articles were collected from databases such as the Cochrane Library, PubMed, Scopus, and Web of Science. This list includes MeSH and non-MeSH terms that were merged as follows: "Diet" OR "Dietary" OR "Nutrient" OR "Fish oil" OR "eicosapentaenoic acid" OR "EPA" OR "docosahexaenoic acid" OR "DHA" OR "n-3 LCPUFA" OR "n-6 PUFAs" OR "probiotics" OR "prebiotics" OR "synbiotics" OR "dietary Supplements" OR "supplement" OR "vitamin D" OR "ergocalciferols" OR "cholecalciferol" OR "vitamin D2" OR "vitamin D3" OR "calciferol" OR "folate" OR "zinc" OR "calcium" OR "iron" OR "selenium" AND "colon cancer" OR "colorectal cancer" OR "rectal cancer" OR "malignancy" OR "neoplasia" (Table 1). In order to ensure comprehensive coverage of all relevant literature, we conducted a manual search of the reference lists of all qualifying studies and associated reviews.

Eligibility criteria. This study included interventional and cohort studies published in English language on dietary supplements and colorectal neoplasia and/or CRC.

Exclusion criteria. Studies with follow-up durations of less than 1 week, studies conducted prior to 1990, and studies lacking adequate outcomes of interest were excluded.

Data extraction. Two researchers (M.G.H. and M.B.) independently conducted the study selection, with the presence of a chief investigator (S.D.) to resolve any conflicts. The data gathered from each study included the first author's name, publication year, health status of participants, type and dosage of dietary supplements, and the main outcomes. The full texts of potentially eligible articles were carefully evaluated for final inclusion.

Results

Initially, 219 articles were collected. We excluded non-English ($n = 7$), non-clinical-trial or cohort studies ($n = 146$), and unrelated studies ($n = 45$). Finally, 21 studies were included in this systematic review.

n-3 LCPUFAs. In total, 12 studies were carried out on the effects of n-3 LCPUFAs on CRC, of which 8 studies showed a benefit and 4 studies did not show any benefit (Table 1). The n-3 LCPUFAs including EPA and DHA as dietary supplements derived from fish oil are known for their anti-inflammatory effects.[17,18] The results on the effects of n-3 PUFAs on CRC have been inconsistent. Several researches have indicated that there is a reverse correlation between the consumption of n-3 PUFAs and CRC.[10] Fish oil was found, in one meta-analysis, to lower the risk of CRC by 12%.[11] After 21.3 years of follow-up, a Swedish cohort study found that there was no overall connection between n-3 LCPUFAs and the risk of CRC. However, it was observed that a high intake of DHA was linked to a reduced risk of rectal cancer.[19] A study indicated that an elevated n-6 PUFA/n-3 LCPUFA ratio is associated with a higher risk of CRC.[20] Skeie *et al.* found that supplementation with cod liver oil decreased the risk of cancer.[21] In a cohort study investigating the relationship between fish oil supplementation and cancer risk, Liu *et al.* found that fish oil supplementation less than two times per week was associated with a decreased risk of CRC.[22] Contrarily, Daniel *et al.* found that while ALA increased the risk of CRC in women, it had no effect in men.[12] Another study found that sufficient intake of n-3 PUFAs could potentially increase the likelihood of developing cancer. On the other hand, a meta-analysis did not find any significant statistical association between supplementation of n-3 fatty acids and the risk of CRC.[23] Besides, various clinical trials have shown that the addition of n-3 PUFAs did not lead to a different likelihood of developing cancer.[24,25]

Subsequent research found a negative correlation between the quantity of ALA ingested through one's diet and the incidence of distal colon cancer among 42 536 individuals who were monitored for a duration of 13.8 years. No link was found between the consumption of marine n-3 PUFAs and the chances of developing CRC.[26]

A diet rich in n-3 LCPUFAs provides numerous health benefits against inflammatory diseases. There have been countless research studies indicating that consuming omega-3 fatty acids is linked to a lower risk of developing various types of cancer, including breast, prostate, and colon cancer. The anticancer effects of EPA and DHA include decreased apoptosis, inflammation, metastasis, and proliferation of cancer cells.[27] n-3 PUFAs may reduce the risk of CRC from several mechanisms, such as suppressing the production of PGE2 in the metabolism of eicosanoids which leads to anti-inflammatory effects,[28] lowering the formation of secondary bile acids in the luminal space,[29] and also lowering the activity of tyrosine-specific protein kinases, which are considered as carcinogens in the colon and liver.[30] Moreover, it has been observed that n-3 fatty acids have the ability to

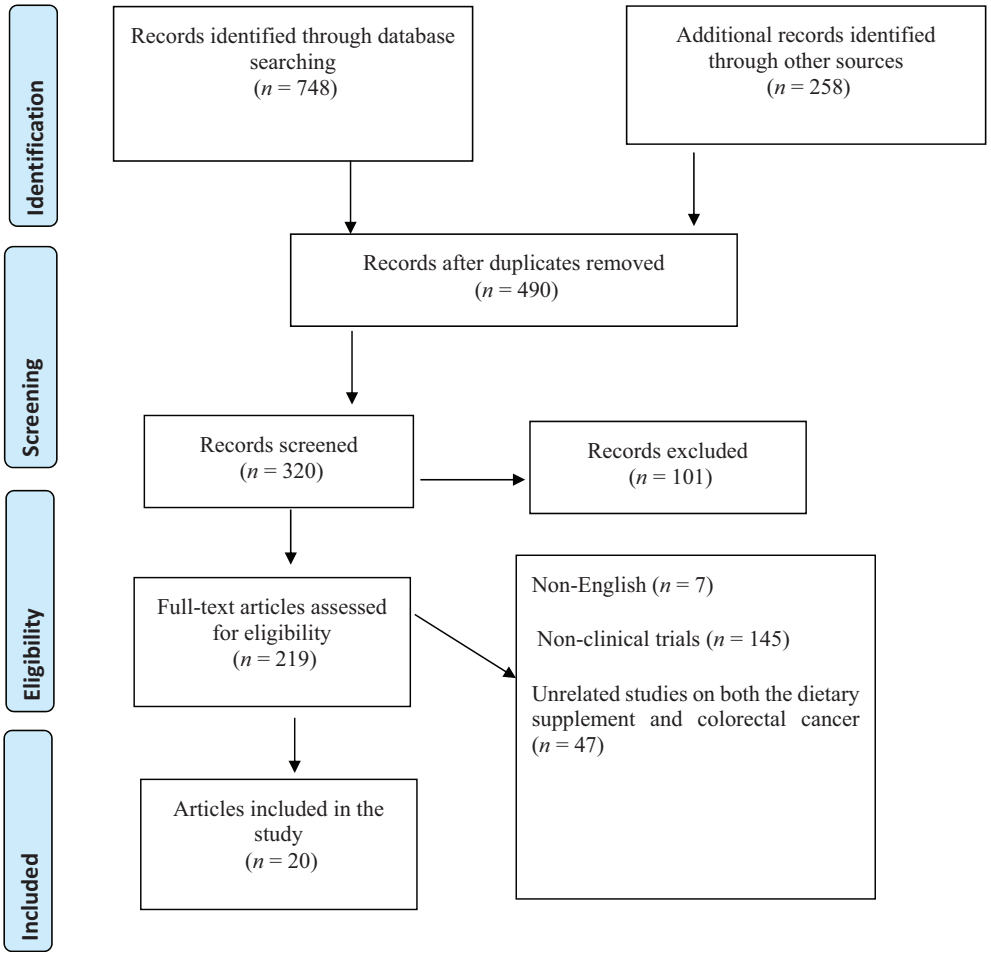

Figure 1 Flow chart of the included studies, including identification, screening, eligibility and the final sample included.

interact with nuclear receptors and transcription factors. This interaction has the potential to induce changes in cell proliferation and enhance apoptosis in cancer cells.[31] Moreover, as a result of improved immune function and increased microbial diversity, n-3 PUFAs can suppress the development of cancerous cells.[32]

Probiotics, prebiotics, and synbiotics. Totally, six studies were carried out on the effects of probiotics, prebiotics, and synbiotics on CRC, of which three observed a positive effect and three did not find any association between CRC and probiotics (Table 1). Probiotics are beneficial microorganisms that have health benefits and improve the gut flora. A prebiotic is a substance found in foods that promotes the growth of probiotics. Synbiotics can be created through the combination of probiotics and prebiotics.[14] Multiple studies have demonstrated that probiotics, prebiotics, and synbiotics have the potential to prevent CRC. An animal study conducted by Shang *et al*., for instance, demonstrated that a mixture of probiotics inhibited colon tumor cell proliferation.[14]

The efficacy of prebiotic fibers in reducing the risk of CRC was assessed in a randomized controlled trial and two prospective cohort studies. Castro-Espin *et al*. conducted a subanalysis of the EPIC Oxford Cohort Study, examining a total of 53 700 adult respondents, among whom 574 cases of CRC were identified.[20] The study participants were requested to complete semi-quantitative food frequency questionnaires (FFQs) to assess their consumption of prebiotic fibers, including galacto-oligosaccharide (GOS), fructan, and total prebiotic fiber. Their results showed that ingestion of prebiotic fiber, fructan, and GOS was not associated with an increased risk of CRC.[33] A prospective cohort study involving 160 195 US women investigated the relationship between prebiotic fiber consumption and the risk of CRC. During the study, the women were followed for 15 years. The prevalence of prebiotic and fiber supplement use was approximately 3.7% ($n = 5944$), which could be separated into psyllium (73.74%), polycarbophil (13.43%), methylcellulose (9.27%), wheat bran (2.15%), pectin (0.62%), resistant starch (0.42%), soy fiber (0.24%), guar gum (0.08%), and β-glucan (0.05%). There was no overall association between the use of any prebiotic supplements and CRC mortality in unadjusted and adjusted models in this study; but interestingly, an association between the consumption of insoluble fiber supplements and an increased risk of mortality related to CRC was observed in comparison to individuals who did not use such supplements.[15]

Table 1 Association between dietary consumption and colorectal cancer

Reference	Study design	Country	Supplement	Sample characteristic	Examined components	Results
Murff *et al.* (2022)	Placebo-controlled trial	USA	n-3 Long-chain polyunsaturated fatty acids	$n = 70$ in the supplement group/ $n = 72$ in the placebo group	2.5 gof n-3 LCPUFA per day compared to olive oil	n-3 LCPUFA supplementation had no proliferative or prapoptotic effects on rectal mucosa in our study
Ayako Kato *et al.* (2023)	Cohort	Japan	n-3 PUFA (combined EPA, DPA, DHA, and ALA)	699 cases/42546 controls	Quartile 1 compared to quartile 4 of n-3 PUFA intake	A high intake of ALA may lower the risk of distal colon cancer, according to our findings.
Willemsen *et al.* (2021)	Cohort	Canada	Fish intake	14 500 cases/27200 controls	Quartile 1 compared to quartile 4 of n-3 PUFA intake	Diet high in vegetables, fruits, fish, and whole grains prevents CRC
Shin *et al.* (2020)	Cohort	Sweden	Omega-3 and -6 fatty acids	344 cases/ 47 950 controls	Quartile 1 compared to quartile 4 of n-3 PUFA intake	Consuming high level of docosahexaenoic acid from fish oil was linked with decreased risk of rectal cancer
Aglago *et al.* (2020)	Cohort	10 European countries	Long-chain n-3 polyunsaturated fatty acids	6291 cases/515.321 controls	<9.07 g/day > 51.3 g/day Q1 *versus* Q5	Total intake of fish was inversely associated with CRC incidence
Engeset *et al.* (2007)	Cohort	Norway	Fish consumption focused mainly on lean fish	254 cases/6914 controls	70.8 g/day *versus* 117 g/day, T1 *versus* T3	Eating poached lean fish in the third tertile was associated with a lower risk of colon, but there was no overall association between fish consumption and colon cancer risk. (relative risk [RR] = 1.46, 95% CI 1.04–2.06)
Hall *et al.* (2008)	Cohort	USA	Fish or shellfish intake of fish and n-3 fatty acids	500 cases/21406 controls	Once per week *versus* 5 times/ week	Intake of fish was linked to reduced risk of colorectal cancer
Lee *et al.* (2009)	Cohort	China	Fish consumption	394 cases/ 73 224 controls	Quartile 1 (20 g/day) *versus* Quartile 5 (74 g/day) of fish consumption	No association was found between the risk of CRC and intake of total fish, but Eel, shrimp, and shellfish consumption were positively associated with CRC risk
Bradbury *et al.* (2020)	Cohort	UK	Fish consumption	2609 cases/175 402 controls	Once/week. *versus* 3 times/week	There was no association between intake of fish and CRC
Daniel *et al.* (2009)	Cohort	USA	Omega-3 fatty acids	896 cases/ 99 080 controls	Quartile (<0.78 g/day) *versus* Quartile 4 (≥1.199 g/day) of omega-3 fatty acids	Women who consumed more α-linoleic acid had higher risk of colorectal cancer
	Cohort		Fish oil supplementation	72 169 cases/54402 controls		

(*Continues*)

Table 1 (Continued)

Reference	Study design	Country	Supplement	Sample characteristic	Examined components	Results
Liu *et al.* (2020)		European country			n-3 fatty acid supplementation (daily)	Taking regular fish oil supplements was associated with lower overall cancer risk in people who did not consume enough dietary fish oil
Manson *et al.* (2019)	Placebo-controlled trial	USA	Omega-3 fatty acids	12 933 in the supplement group/12936 in the placebo group	1 g/day of n-3 fatty acid supplementation	There was no association between intake of fish and CRC
CastroEspin *et al.* (2020)	Cohort	UK	Probiotics	574 cases/53.700 controls	Prebiotic fiber (fructan, GOS)	Total prebiotic, fructan, and GOS intake was not significantly associated with CRC risk.
Skiba *et al.* (2019)	Cohort	USA	Probiotics	3032 cases/160.195 controls	Prebiotic fibers (soluble and insoluble)	CRC risk and mortality were not associated with total prebiotic supplement use
Ishikawa *et al.* (2005)	Placebo-controlled trial	Japan	Probiotics and prebiotic	398 CRC patients	Probiotic (*L. casei*) 1 g per meal/ prebiotic 25 g per day	No significant difference was found in the risk of new CR tumors among the randomized groups
Liu *et al.* (2015)	Placebo-controlled trial	China	Probiotics	68 in the supplement group/66 in the placebo group	Mixture of three PRO bacteria 2 g/day	Probiotic supplementation could decrease serum zonulin level in patients with colorectal liver metastases surgery
Rafter *et al.* (2007)	Placebo-controlled trial	Ireland	Probiotics	37 supplement group/43 placebo group polypectomized patients	*Lactobacillus Bifidobacterium Enterococcus*	12 weeks supplementation with synbiotics decreased colorectal proliferation, increased epithelial barrier function and necrosis in colonic cells. Synbiotics increased *Bifidobacterium* and *Clostridium* perfringen in patients
Chong *et al.* (2019)	Placebo-controlled trial	Malaysia	Probiotics	53 in the supplement group/56 in the placebo group polypectomized patients	*Lactobacillus plantarum*	12-week administration of *Lactobacillus plantarum* DR7 in subjects increases anti-inflammatory cytokines such as IL-10 and decreased cytokines IL-1.
Song *et al.* (2021)	Placebo-controlled trial	China	Vitamin D	12 927 participants in the vitamin D group, 12 944 participants in the placebo group	Vitamin D (2000 IU) in combination with n-3 fatty acid (1 g) dietary supplement	The supplementation was not linked to the risk of colorectal cancer

(*Continues*)

Table 1 (Continued)

Reference	Study design	Country	Supplement	Sample characteristic	Examined components	Results
Kwan *et al.* (2019)	Placebo-controlled trial	Georgia	Vitamin D	104 CRC patients	The 104 CRC received 1000 IU vitamin D3 in combination with calcium 1200 mg for 1 year	The supplementation group have higher MSH2 (plays an essential role in repairing DNA)/mib-1 ratio, TGF β1 (growth inhibitor) expression, and lower TGFα (growth promoter)/TGFβ1
Abbadi *et al.* (2012)	Placebo-controlled trial	UK	Folate	15 in the supplement group/14 in the placebo group	400 μg/day folic acid or placebo for 10 weeks	Folate intake may reduce homocysteine but has no impact on ESR1 and MLH1 methylation. ESR1 and MLH1 increased methylation in tumor cells

Ishikawa *et al*. conducted a randomized controlled trial to investigate the impact of supplementing fibers as prebiotics and *Lactobacillus casei* as probiotic on Japanese adults with a history of CRC tumors. The study included a total of 398 participants categorized into four intervention groups: the control group, prebiotic fiber (dietary wheat bran) at a rate of 25 g/day, probiotic (*L. casei*) at a rate of 1 g/meal, and dietary wheat bran + *L. casei*. Participants were evaluated at baseline and at the end of 4 years, and the incidence of colorectal tumors was assessed. Tumor occurrence in the group administered both wheat bran and *L. casei* was higher than that in the groups administered wheat bran or *L. casei* and lower than that in the control group.[34]

Liu *et al*. examined the effects of perioperative probiotic treatment on postoperative liver complications after colorectal liver metastases surgery in a double-center and double-blind randomized clinical trial. Patients in the probiotic group received encapsulated admixture of three probiotic bacteria composed of *Lactiplantibacillus plantarum*, *Lactobacillus acidophilus*-11, and *Bifidobacterium lactis*-88 every day. The result showed that supplementation with probiotics could inhibit the p38 MAPK signaling pathway, improved the positive rate of the blood microbial DNA, reduced postoperative intestinal infection related complications, promoted rapid recovery, and reduced the postoperative serum zonulin concentration. Zonulin serves as a marker for assessing the permeability of the intestines, and elevated levels of zonulin in the bloodstream have been observed in individuals with CRC. Owing to the significant variability observed, further research is required to make definitive recommendations of probiotics against CRC.[35]

The consumption of synthetic probiotics including *Lactobacillus rhamnosus* GG and *B. lactis* Bb12 by cancer patients resulted in two notable effects: an upregulation of interferon-gamma production, and an inhibition of interleukin (IL)-2 secretion by mononuclear cells.[36] In human trials, 12 weeks of supplementation with synbiotics decreased colorectal proliferation and increased epithelial barrier function and necrosis in colonic cells.[37]

The administration of *L. plantarum* DR7 to participants over a period of 12 weeks resulted in an increase in anti-inflammatory cytokines, specifically IL-10, while simultaneously decreasing the levels of IL-1.[38] Another study conducted by Golkhalkhali *et al*. aimed to examine the effects of omega-3 fatty acid and microbial cell preparation (MCP) supplementation on patients with CRC undergoing chemotherapy. MCP is a type of probiotic supplement containing live or inactive microorganisms.[39] The co-administration of omega-3 with MCP resulted in an improvement in the overall well-being of individuals, as well as a reduction in the levels of IL-6 and improvements of the adverse effects associated with chemotherapy treatment.[39]

The precise mechanisms behind the impact of probiotics, prebiotics, and synbiotics on CRC remain uncertain. Probiotics can balance intestinal microflora, reduce cancerogenic compounds, increase immune response, and regulate apoptosis.[40,41] Khaleel *et al*. in a review study on the role of probiotics against CRC reported that probiotics have the potential to reduce the risk of CRC through multiple mechanisms: (i) increase the expression level of the tight junction proteins and protect intestinal barriers; (ii) regulate the activity of immune cells and cytokines to inhibit the progress of pathogens; (iii) regulate cell proliferation and

apoptosis of tumor cells; and (iv) restore the equilibrium of gut bacteria, thereby promoting host homeostasis.[42]

The study conducted by Moreno *et al*.[43] found that yogurt consumption has the potential to reduce the levels of β-glucuronidase in mice afflicted with colon cancer.[43] Bacterial β-glucuronidase could deconjugate liver glucuronides and release aglycones. Bacteria found in yogurt may have an impact on the enzymes in the gut flora that are associated with the development of colon cancer.[44] Another trial study found that supplementing with *L. acidophilus* decreased β-glucuronidase activity after 10 days. Procarcinogens can be converted to proximal carcinogens by β-glucuronidase.[45] Furthermore, the production of short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, occurs as a result of the fermentation of indigestible foods by gut microorganisms. Butyrate is reported to have the potential to lower CRC risk through increased cellular differentiation and decreased proliferation.[46,47]

Vitamin D and calcium. Two clinical trials were carried out on the effects of vitamin D on CRC, of which one study reported positive effects while the other study did not find any association (Table 1). The production of vitamin D is primarily internal, triggered by UV radiation exposure on the skin. 1,25-Dihydroxyvitamin D [1,25(OH)2D] is the active variant of vitamin D that is synthesized in the kidney and other tissues such as the colon after being metabolized in the liver as 25-hydroxyvitamin D [25(OH)D]. Anticancer compounds may be vitamin D receptors, which are present in the majority of tissues. These receptors may regulate proliferation, induce apoptosis and differentiation, and suppress inflammation.[48] Participants with a higher quartile of vitamin D scores had a reduced incidence of CRC according to a cohort study of African American women.[49] A meta-analysis linked increased vitamin D consumption to a decreased incidence of CRC.[50]

Kwan *et al*. investigated the impact of vitamin D and calcium on the expression tumor cells in patients with CRC. Totally, 104 patients with CRC received 1000 IU vitamin D3 in combination with calcium 1200 mg/day for 1 year. Expression of transforming growth factor alpha (TGFα) as a growth promoter decreased in the supplementation group, whereas the ratio of MutS Homolog 2 (MSH2) as an essential factor in DNA repair increased.[51]

In addition, some studies found that calcium intake decreased adenomatous polyps.[52] In one study conducted by Davenport *et al*., a negative association was found between calcium consumption and hyperplastic polyps ($P = 0.03$).[53] According to a study carried out by Keume *et al*., a daily intake of 300 mg of calcium supplements resulted in a reduced risk of adenoma recurrence compared to the control group.[54] A meta-analysis indicated that dietary intake of vitamin D (160 IU/day) was related to lower CRC,[50] and another meta-analysis found that intake of vitamin D (1000–2000 IU/day) decreased colon cancer risk.[55] Yet other study indicated that CRC mortality decreased by 12% for each 20 nmol/L increment of 25(OH)D concentration.[56] A single clinical trial revealed an association between the administration of vitamin D supplements at a dosage of 400 IU and the prevention of CRC.[57]

Conversely, an additional clinical trial found no relationship between 2000 IU of vitamin D and CRC.[58] In a clinical trial, 25 871 participants without cancer received vitamin D (2000 IU/day) in combination with n-3 fatty acids (1 g/day) or received placebo. Supplementation did not change the risk of CRC compared to the control group.[48] The impact of vitamin D and calcium supplementation on the risk of serrated polyps (SSA/Ps) was examined by Crockett *et al*. Their results showed that the intake of calcium and vitamin D supplements was associated with a higher SSA/Ps. No association was found between vitamin D and the risk of SSA/Ps.[59]

The exact mechanisms underlying the effects of vitamin D on CRC remain unknown. Vitamin D may act as a modulator of cell differentiation in CRC. Vitamin D suppresses β-catenin signaling and genes involved in cell development including vinculin (a cytoplasmic actin-binding protein enriched in focal adhesions and adherens junctions), occludin (a transmembrane protein that regulates the permeability of epithelial and endothelial barriers), and E-cadherin. Other mechanisms by which vitamin D may influence cell differentiation include modulating the expression of the vitamin D receptor (VDR), cytochrome p450 enzymes, and other enzymes involved in the synthesis of active metabolites of vitamin D.[60,61] The active metabolites of vitamin D [1,25(OH) 2D3] were shown in a meta-analysis to promote apoptosis and decrease proliferation.[50]

Moreover, calcium affects the expression of Annexin A10 (family of calcium-regulated phospholipid binding proteins). ANX A10 belongs to a group of proteins called the ANX family, which consists of 13 members. ANX A10 proteins are increased in SSA/Ps. These proteins bind to calcium and phospholipids and play various roles in membrane transport, calcium signaling, cell differentiation, and proliferation. ANXs have gained significant attention due to their link with tumor development and progression, as they frequently had irregular regulation in neoplasia.[62] Calcium supplementation can affect cancer progression through the regulation of ANX A10 levels.[59]

Folate. Folate, known as vitamin B_9, may play a dual role in colon carcinogenesis. An increase in dietary folate has a protective effect against CRC prior to the onset of neoplastic foci, while, after the initial lesions, the consumption of dietary folate may increase tumorigenesis.[63] Folate metabolism can affect methyl distribution and alter DNA methylation and DNA synthesis. Some studies have indicated that dietary folate deficiency increased CRC risk,[64] but folate may protect only folate-deficient individuals against the risk of CRC.[65] The Nurses' Health Study (NHS) indicated that women who received folate (400 μg/day) had a lower risk of CRC.[66]

Folate may reduce the risk of CRC, according to a systematic review, but only when consumed in the form of foods and not supplements.[67] Abbadi *et al*. explored the impact of folate supplementation (400 μg) on the methylation of ESR1 (estrogen receptor 1) and MLH1 (mutL homolog 1) in the colonic mucosa. The results of their research revealed that the intake of folate may potentially decrease homocysteine levels; however, no significant impact was found on the heightened methylation of ESR1 and MLH1 in cancer cells.[68] Folic supplementation (5 mg/day) was shown to reduce the recurrence of colonic adenomas in another investigation. In individuals with advanced adenomas, folic acid treatment decreased the risk of adenomas recurring.[69] The potential mechanism by which folate can reduce the risk of

Table 2 Number of studies with benefit and studies with no benefit

No of studies (for each supplement)	Nutrition supplement	Studies with benefit (*N*)	Studies with no benefit (*n*)
12	n-3 Long-chain polyunsaturated fatty acids and fish intake	9	3
6	Probiotics	4	2
1	Vitamin D	1	1
1	Folate	—	1

CRC involves alterations in normal DNA methylation patterns, imbalances in DNA precursor levels, and modifications to chromosomal and chromatin structures.[70]

Other nutrients. A few studies have examined the impact of trace elements on CRC. One study found that zinc deficiency may increase CRC risk.[71] A negative association has been reported between zinc and CRC risk.[72,73] Another study, however, found no association between zinc consumption and CRC.[74]

Supplementation with zinc may improve the anticancer drug response through the regulation of gene expression.[75] Zinc supplementation (70 mg/day for 16 weeks) enhanced the quality of life and decreased fatigue in CRC patients.[76] A cohort study involving 34 708 postmenopausal women found that dietary zinc had a negative association with CRC, while dietary heme iron intake was positively associated.[73] Free iron is considered to be carcinogenic, especially in heavy alcohol drinkers.[77]

Several studies have indicated that taking selenium supplements can potentially lower the risk of developing colorectal cancer.[78,79] In the Nutritional Prevention of Cancer (NPC) trial, 1312 participants were given 200 μg of selenium and the results showed a decrease in overall cancer rates, including lung, colon, and prostate cancer.[78] Se decreases oxidative stress, regulates immune response, and has a beneficial effect on the repair of DNA damage[78] (Table 2).

Discussion

Dietary intake has been frequently reported to have an important role in the development of CRC.[79] The modification of diet and lifestyle may modify the risk of CRC and prevent neoplasia in up to 50% of cases.[80] The present systematic review has indicated that results have been inconclusive in previous studies regarding the effects of dietary supplements on CRC. n-3 fatty acids may potentially reduce the risk of developing cancer, particularly CRC.[81] In some studies, however, n-3 PUFAs were not associated with CRC risk.[11] One of the most prominent mechanisms for the anticancer activity of n-3 PUFAs is inhibition of the production of arachidonic acid-derived eicosanoids, which are positively associated with inflammation and carcinogenesis.[82] A cohort study was conducted by Liu *et al.* to examine the impact of fish oil supplementation on cancer risk.[22] There are many health benefits associated with the dietary intake of n-3 PUFAs, including prevention of inflammatory diseases. Numerous studies have demonstrated an inverse relationship between omega-3 intake and a variety of cancers including colon, prostate, and breast cancer. In addition, a prospective analysis of approximately half a million participants reported that intakes of total fish, including fatty fish, lean fish, and shellfish, were inversely associated with CRC risk.[20] In this regard, a study indicated that omega-3 PUFAs were safe and effective in lowering TNF-α and IL-6 levels and shortening the length of hospital stay for patients with CRC undergoing adjuvant therapies.[83] An anticancer effect of EPA and DHA was reported through a reduction in the proliferation, metastasis, and inflammation of cancer cells.[27]

CRC may be suppressed by some other dietary components such as probiotics, prebiotics, and synbiotics.[15,42] Supplementation with probiotics in patients with CRC was found to improve their quality of life, enhance gut microbiota diversity, reduce postoperative infection complications, and inhibit pro-inflammatory cytokine production.[84] Probiotic intervention improves the microbiota, releases antimicrobials and anticarcinogenic agents, helps to remove carcinogens, and improves the intestinal permeability, tight junction function, and enzyme activity in CRC patients.[85] Supplementation with oral probiotics may also have a positive effect on zonulin levels, a measure of intestinal permeability.[35] Probiotics may also reduce aberrant crypt foci[86] and increase the activity of natural killer cells and IL-10.[36]

CRC may also be prevented by diets high in vitamin D, folic acid, zinc, and Se.[87] Vitamin D3 plus omega-3 fatty acid supplementation in CRC patients has beneficial impacts on inflammation and nutritional status.[88] The active metabolite of vitamin D, 1,25(OH)2D3 (calcitriol), inhibits proliferation, induces apoptosis, and promotes epithelial differentiation of human colon cancer cells through the modulation of key genes in the carcinogenesis signaling pathways.[89] Zinc and selenium may protect against CRC progression through their anti-oxidative effects.[90] In this regard, blood selenium participates in oxidoreduction as a component of selenoproteins, and thus may have a beneficial effect against the risk of developing CRC.[91]

In summary, there is strong evidence that dietary factors affect CRC risk and can be considered as an alternative strategy for the nutritional prevention of CRC.[92] However, the results have been inconsistent.[93] Moreover, since dietary components interact with each other, the actual effect of diet on CRC risk may become apparent only when the components are considered as a whole.[80] This study has limitations including the small sample sizes of the studies and the limited number of studies included, which might have affected the accuracy and applicability of our results. Also, variations in the treatment of patients, the formula and dose of supplements, and the route and time of administration of nutrition supplements among the studies included might have resulted in heterogeneity. In addition, our study was limited to research published in English, introducing selection bias. More longitudinal research is needed in order to verify these findings and pinpoint how diet influences CRC risk.

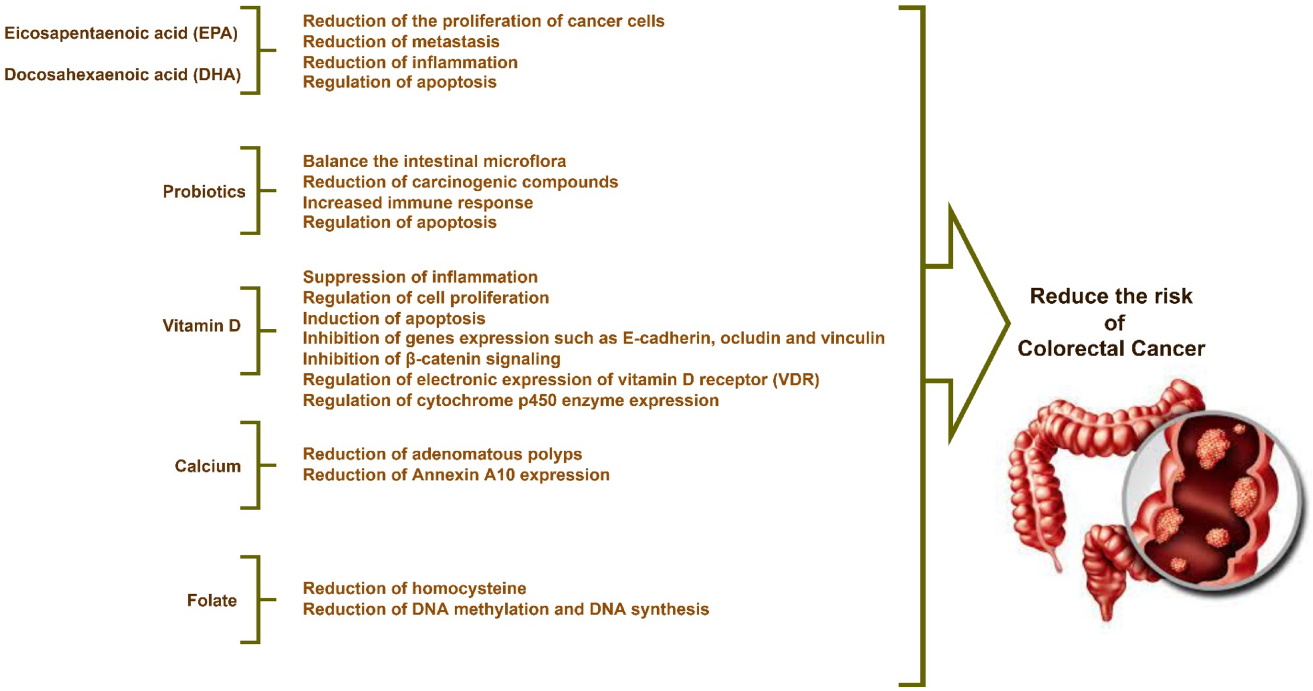

Figure 2 Protective effects of dietary components against colorectal cancer.

Conclusion

Dietary intake can influence the risk of developing CRC. Exploring the effects of nutritional supplements in patients with CRC may result in the discovery of novel approaches for preventing, managing, and treating CRC (Fig. 2). Further studies are warranted to verify these discoveries and pinpoint the fundamental mechanisms by which dietary components influence the risk of CRC.

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