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Nutrients, Foods, and Colorectal Cancer Prevention

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Abstract

Diet has an important role in the development of colorectal cancer. In the past few decades, findings from extensive epidemiologic and experimental investigation have linked consumption of several foods and nutrients to the risk of colorectal neoplasia. Calcium, fiber, milk, and whole grain have been associated with a lower risk of colorectal cancer, and red meat and processed meat with an increased risk. There is substantial evidence for the potential chemopreventive effects of vitamin D, folate, fruits and vegetables. Nutrients and foods may also interact, as a dietary pattern, to influence colorectal cancer risk. Diet likely influences colorectal carcinogenesis through several interacting mechanisms. These include the direct effects on immune responsiveness and inflammation, and the indirect effects of over-nutrition and obesity—risk factors for colorectal cancer. Emerging evidence also implicates the gut microbiota as an important effector in the relationship between diet and cancer. Dietary modification therefore has the promise of reducing colorectal cancer incidence.

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Keywords

diet; colorectal cancer; microbiota; prevention

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in the world¹. Although screening reduces the incidence and mortality from CRC²⁻⁴, the routine use of screening has been stymied, particularly in resource-limited settings⁵. Preventative measures, including dietary and lifestyle modifications, are therefore an attractive strategy to reduce the global burden of CRC.

In 1981, Doll and Peto “guestimated” that as many as 35% of cancer-related deaths and 90% of stomach and large bowel cancer-related deaths could be attributed to dietary factors⁶. Over the past several decades, numerous observational studies and randomized clinical trials (RCTs) have been conducted to identify potential dietary contributors to CRC risk^{7, 8}. However, data from these studies have shown either inconsistent or only modest associations. This is in contrast to the robust evidence linking diet with cardiovascular disease and diabetes and despite experimental data uncovering specific mechanisms relating diet to CRC. This perhaps should not be surprising given the complexity intrinsic to the etiopathogenesis of cancer. The intricate interactions of genetic, epigenetic and environmental determinants of risk⁹⁻¹¹, the prolonged latency period required for carcinogenesis^{12, 13}, as well as the etiologic heterogeneity of CRC as reflected by its anatomic, histologic, and molecular variability^{14, 15} pose inherent challenges to nutritional cancer epidemiology. Nonetheless, a critical appraisal of human data gathered thus far within the context of our mechanistic understanding of diet and CRC may serve as an initial step in realizing the promise of dietary chemoprevention.

Although there have been numerous reviews of diet and CRC, most have been specific to one or a few exposures¹⁶⁻²¹. Herein, we review all major dietary factors that may have a role in CRC, summarizing the most recent epidemiologic and clinical trial evidence, with a focus on potential mechanisms (Table 1). In addition, based on our synthesis of the evidence, we offer some recommendations, where possible, for clinicians to consider in their counseling of patients who may be interested in modifying their diet for the purpose of cancer prevention. Given the methodological limitations of retrospective case-control studies^{13, 22-24}, we focus on prospective studies and RCTs, prioritizing those with large size and robust design and analysis. Although RCTs are usually regarded as the gold standard for establishing causality, trials of dietary interventions have been challenging. Beyond issues of adequate compliance and enrollment of generalizable populations, dietary intervention RCTs have suffered from lack of knowledge regarding appropriate dose, form, and route of administration of dietary factors, the minimum duration of treatment, and optimal timing of exposure and endpoint ascertainment. Thus, we discuss data from RCTs within the context of observational studies as well as experimental evidence¹³, with a focus on those nutrients with the most compelling mechanisms. We emphasize mechanisms associated with inflammation and immune dysregulation given their established role in colorectal carcinogenesis^{25, 26} and the increasing appreciation of a role for the microbiota in CRC^{27, 28} (Figure 1).

Nutrients

Calcium

Calcium is an essential nutrient for bone and dental health. The ability of ionized calcium to form insoluble soaps with tumor-promoting free fatty acids and bile acids in the colonic lumen led to the hypothesis that calcium was anti-neoplastic²⁹. A prospective cohort study with nearly 20 years of follow-up observed an approximately 70% lower risk of CRC comparing the highest to the lowest quartiles of calcium intake³⁰. Fairly consistent but more modest inverse associations have subsequently been reported in most³¹⁻⁴⁶, although not all⁴⁷⁻⁵², cohort studies for CRC and colorectal adenomas. These findings prompted RCTs of calcium supplementation in which a significant reduction in adenoma recurrence^{53, 54}, particularly histologically advanced lesions⁵⁵, was observed. Additional mechanisms through which calcium might affect CRC risk include: inhibition of cell proliferation, promotion of cell differentiation and apoptosis⁵⁶⁻⁵⁹, suppression of oxidative DNA damage⁶⁰, and modulation of CRC-related cell signaling pathways⁶¹ (see reviews^{62, 63}). These effects are likely mediated by extracellular calcium-sensing receptor (CaR) signaling which contributes to the integrity of intestinal barrier function and homeostasis between gut microbes and the immune response⁶⁴ (Figure 2).

In contrast with adenoma recurrence RCTs, the Women's Health Initiative (WHI), the largest RCT with CRC incidence as a secondary outcome, did not find any reduction in CRC after a mean of 7 years of supplementation with calcium and vitamin D⁶⁵. However, several limitations may have contributed to the null findings, including: high calcium intake at baseline, poor compliance, complex factorial design, and insufficient duration of treatment and/or follow-up⁶⁶⁻⁶⁸. In a reanalysis, a 17% reduction of CRC incidence with calcium supplementation was observed among WHI participants not already taking calcium or vitamin D at randomization⁶⁹. Findings from other smaller trials have been similarly inconclusive^{70, 71}. Furthermore, contrary to prior adenoma RCTs, the initial results of another RCT of calcium and vitamin D supplementation failed to detect a reduction in risk of recurrent adenoma among 2,259 individuals, adding complexity to the calcium-CRC relationship⁷².

Several reasons may explain these discrepancies. A threshold effect of calcium on neoplasia risk may mask a benefit in an already calcium-replete population. In cohort studies, calcium intake beyond approximately 700–1000 mg/day was found to have minimal incremental effect on lowering CRC risk^{32, 36, 38, 46, 73, 74} and supplemental calcium did not further benefit participants with high dietary calcium intake^{31, 35, 36}. Also, the association between calcium intake and colorectal neoplasms may differ by anatomic location, with stronger associations observed for cancers in the distal colon or rectum^{36, 39, 41, 45, 52, 73, 75}.

Anatomic site heterogeneity may be driven by microbial composition or metabolic variation in the colonic lumen^{76, 77}. Calcium may have a differential effect based on other dietary factors or genetic background. The inverse association between calcium and colorectal neoplasms may be confined to individuals with a high vitamin D level^{35, 36, 78}, reflective of the regulation of calcium level by vitamin D^{62, 79}, or a low calcium/magnesium intake ratio^{80, 81}, due to competition between these metals for luminal absorption^{82, 83}. There is

also evidence for differential associations based on vitamin D receptor (VDR) polymorphisms⁸⁴⁻⁸⁶ or nonsteroidal anti-inflammatory drug use⁸⁵.

In summary, predominant evidence indicates an increased CRC risk among individuals with calcium intake lower than 700-1000 mg/day. It would therefore be reasonable to encourage individuals to increase their calcium intake to a level above this range, recognizing that data are inconsistent, including limited findings that calcium supplementation may be weakly associated with cardiovascular hazards⁸⁷. The potential modification of other factors on the calcium-CRC relationship warrants further investigation.

Vitamin D

In 1980, Garland and colleagues proposed that vitamin D status accounted for the high mortality rate of CRC in populations with low solar UV-B radiation exposure⁸⁸. Subsequent cohort studies tested this hypothesis using a range of surrogates for vitamin D status, including solar radiation^{89, 90}, circulating 25-hydroxyvitamin D [25(OH)D] level^{45, 91-98}, dietary and supplement intake^{34, 35, 39, 47, 99-102}, and predicted 25(OH)D based on major determinants of vitamin D status¹⁰³. The predominant evidence from these studies supports an inverse association of vitamin D with adenoma incidence¹⁰⁴, CRC incidence, and mortality^{105, 106}. Based on a systematic review, one study suggested that the benefits associated with serum 25(OH)D may require at least 75 nmol/L (30 ng/mL), with optimal levels between 90-100 nmol/L (36-40 ng/mL) for multiple health outcomes including CRC¹⁰⁷. Because this level of sufficiency cannot typically be achieved with currently recommended vitamin D intake of 600 and 800 IU/d for younger and older adults¹⁰⁸, respectively, some authorities have called for an increase in recommended vitamin D intake to 1000 IU/d^{109, 110}.

Accumulating preclinical and clinical studies suggests an anticancer activity of vitamin D^{111, 112}. Vitamin D functions by binding to and activating the nuclear VDR. A polymorphism in VDR, *BsmI*, has been consistently associated with CRC¹¹³. Vitamin D may directly or indirectly regulate 3-5% of the human genome¹¹¹ and has been implicated in a wide spectrum of anticancer activities: anti-proliferation, induction of differentiation and apoptosis, anti-inflammation, inhibition of invasion and metastasis, and suppression of angiogenesis¹¹² (Figure 2).

Among these mechanisms, the anti-inflammatory and immune regulatory effects of vitamin D are particularly compelling and may mediate its role in vascular, neurologic, autoimmune, and infectious diseases¹¹⁴. In mice with colitis, a CRC risk factor, consumption of a high vitamin D diet attenuated inflammation, indicating that vitamin D may have an important role in inflammation-associated carcinogenesis¹¹⁵. High plasma 25(OH)D was strongly associated with lower risk of colorectal tumors with high lymphocyte counts, but not tumors with low counts¹¹⁶. Given the well-established role of vitamin D in immunity^{117, 118} and the ability of immune cells to generate biologically active vitamin D¹¹⁹⁻¹²¹, these data provide evidence for the importance of host immunity in vitamin D-mediated CRC prevention.

Despite this compelling epidemiologic evidence and biologic plausibility, the results of vitamin D supplementation have been disappointing in all ^{65, 71, 122} but one⁷⁰ RCT that

assessed cancer incidence as a secondary outcome. However, similar to calcium RCTs, limitations in study design still leave open the possibility that vitamin D may indeed have a chemopreventive role. A recent systematic review hypothesized that confounding by inflammatory processes involved in both CRC development and 25(OH)D deficiency might account for the inverse association between vitamin D and CRC in observational studies¹²³. However, we recently found that rigorous adjustment for inflammatory markers had little effect on the robust inverse association observed between 25(OH)D and CRC risk, indicating that confounding by inflammation was not a sufficient explanation¹²⁴.

In summary, compelling data from epidemiologic and experimental studies support the potential chemopreventive effects of vitamin D against CRC development, although the evidence from RCTs is inconclusive. A large ongoing RCT of vitamin D supplementation that includes cancer as a primary outcome, the VITamin D and Omega-3 Trial¹²⁵, will hopefully provide more direct data on this topic. Until then, it would be reasonable to ensure that patients obtain a sufficient level of vitamin D to maintain a plasma level of 25 (OH)D greater than at least 36 ng/mL.

Fiber

In the 1970s, Burkitt hypothesized that high fiber intake protected against CRC based on observations of the low CRC incidence among Africans who consumed a high fiber diet¹²⁶. Proposed mechanisms for this hypothesis included: reduced concentrations of intestinal carcinogens due to increased stool mass, decreased transit time, and bacterial fermentation of resistant starch to short-chain fatty acids (SCFAs)¹²⁶. Butyrate, the major SCFA produced by colonic fermentation, is the preferred energy source for colonocytes¹²⁷ and may enhance apoptosis and inhibit proliferation of cancer cells¹²⁸. In addition, SCFAs have immune modulatory and anti-inflammatory effects¹²⁹, acting to influence gastrointestinal and perhaps systemic health¹³⁰.

Despite substantial experimental evidence, human studies of fiber and CRC are equivocal¹³¹. Fiber intake was not associated with CRC risk in 14 cohort studies^{32, 46, 50, 132-140}, whereas in 9 other cohorts an inverse association was detected at least among some subgroups or for certain types of fiber¹⁴¹⁻¹⁵⁰. There are several explanations for this discrepancy. Given the close link of fiber intake with other behaviors, the fiber-CRC association may be confounded to a varied degree across studies. Indeed, adjustment for other dietary and lifestyle factors, such as intake of folate, red and processed meat and physical activity, substantially attenuated the inverse association between fiber and CRC in several^{137, 146, 151} but not all¹⁵² cohorts. Also, dietary sources of fiber vary enormously, with cereals as the major sources in European cohorts, and fruits and vegetables in American cohorts¹⁵¹. There is evidence that fiber from cereals may be more strongly associated with CRC^{146, 149-151}, although the mechanisms remain unclear. Large variations in fiber consumption across populations may also lead to inconsistent findings. Although a linear dose-response relationship was reported in a recent meta-analysis¹³¹, some studies support a threshold effect, with an increased risk for CRC among very low consumers of fiber and no apparent benefit of fiber intake among those with high consumption^{138, 144, 147, 151}. Measurement error in assessing fiber intake may also influence

results; dietary fiber intake assessed by food diaries, but not food frequency questionnaires, was inversely associated with CRC risk in a case-control study nested within 7 cohorts¹⁴⁸. Although food diaries may be more accurate compared to food frequency questionnaire, the 2 tools differ in assessment time frame (short term vs long term), range of covered food items, and sources of errors (recording/coding vs recall)¹⁵³. Other reasons for disparate results include: differences in study populations, definition of fiber, length of follow-up, and tumor site heterogeneity. Colon cancer, especially distal tumors, may be more strongly associated with fiber than rectal cancer^{142, 147-150}, although cereal fiber has been related to rectal cancer in some studies^{146, 150, 151}.

Six RCTs testing fiber supplementation among patients with a history of colorectal polyps^{54, 154-158} failed to detect any benefit except for a marginal reduction in adenoma recurrence among women in one small study¹⁵⁵. However, several limitations, including poor compliance with the intervention¹⁵⁹⁻¹⁶¹ and the relatively short follow-up period¹⁶², complicate interpretation. A resistant starch RCT in individuals with Lynch syndrome found no reduction in CRC incidence¹⁶³. However, the relevance of this finding to CRC prevention in the general population is unclear.

Given the biological plausibility and data from observational studies, fiber has been judged by the expert panel to protect against CRC with convincing evidence⁷. Recently, a meta-analysis summarized the prospective evidence and reported a 10% decreased risk of CRC per additional 10 g/day total dietary fiber intake¹³¹. In the absence of data to indicate any adverse consequences to a high fiber intake, it is reasonable to recommend individuals consume a high-fiber diet, particularly as it has been associated with other improved health outcomes^{164, 165}.

B vitamins and methionine

Genetic studies further support a role for folate in CRC. Individuals with high folate intake are less likely to develop tumors with hypomethylation either on a genome-wide level or at specific loci^{190, 191}. Consistent with the role of folate deficiency in promoting *p53* mutation, the inverse association between folate intake and CRC appears restricted to *p53*-mutated tumors¹⁹². In addition, a common mutation in the methylenetetrahydrofolate reductase (*MTHFR*) gene shows a folate-dependent association with CRC¹⁹³⁻²⁰¹. *MTHFR* converts 5,10-methylenetetrahydrofolate, the required cofactor for DNA synthesis, to 5-methyltetrahydrofolate, the predominant form of folate in the circulation and the primary methyl donor for DNA methylation. The ⁶⁷⁷C→T(Ala→Val) *MTHFR* mutation impairs enzymatic activity, leading to 5,10-methylenetetrahydrofolate accumulation and lower 5-methyltetrahydrofolate levels²⁰². When dietary methyl supply is high (i.e., no or low alcohol consumption, high folate and methionine intake), *MTHFR* mutation-positive individuals have a reduced CRC risk because higher levels of 5,10-methyltetrahydrofolate prevent imbalances of nucleotide pools during DNA synthesis. In contrast, when the methyl supply is low, there may be less compensation for the dysfunctional *MTHFR* enzyme and increased susceptibility to impaired DNA methylation that contributes to increased CRC risk¹⁹³⁻²⁰¹.

B vitamins, including folate (vitamin B9), riboflavin (vitamin B2), pyridoxine (vitamin B6) and cobalamin (vitamin B12), and methionine are essential for DNA methylation, synthesis,

stability and repair. Folate has received the most investigation as a cancer preventive agent. In addition to being consumed through diet or supplement use, large quantities of folate can also be produced by gut bacteria^{166, 167}. Folate deficiency results in genomic hypomethylation and defects in DNA synthesis, both of which can contribute to colonic carcinogenesis¹⁶⁸⁻¹⁷² (Figure 3). Dietary intake and circulating levels of folate have been inversely associated with CRC¹⁷³⁻¹⁸² and adenoma¹⁸³⁻¹⁸⁵ risk in observational studies. This association appears more marked among alcohol drinkers^{173, 175, 177, 183, 186-188} and low-methionine consumers^{182, 189}, consistent with alcohol's impairment of one-carbon metabolism and methionine's role in folate-mediated DNA methylation.

A potential dual-modulator role of folate adds more complexity to its relationship with CRC²⁰³. Contrary to the antineoplastic role in healthy tissues, folate may induce growth and progression of preexisting neoplasms through enhanced DNA synthesis in rapidly replicating neoplastic cells^{204, 205} and stimulation of inflammatory immune response pathways^{206, 207}. This idea has fueled debate about whether mandatory folic acid fortification introduced in the US and Canada in 1996–1998 is responsible for the transient increase in CRC incidence from 1996–1998²⁰⁸. However, the short temporal proximity between fortification and the uptick in CRC incidence, as well as unchanged mortality, argues against this hypothesis²⁰⁹. Moreover, in 2 large cohort studies, high folate intake during the post-fortification period was still associated with lower CRC risk^{175, 176}. In a recent meta-analysis of 13 RCTs, neither overall nor CRC-specific incidence was increased by daily 2.0 mg folic acid supplementation, an order of magnitude greater than the dose typically delivered by fortification²¹⁰. Given the potential dual role of folate in normal tissues and neoplasms, the timing of folate introduction may be a critical determinant of anti-cancer benefit^{211, 212}. Indeed, folate intake 12–16 years before diagnosis rather than recent intake was associated with lower CRC risk and a strong inverse association with adenoma was observed for folate intake 4–8 years before diagnosis in 2 large cohorts²¹³. This may also explain the largely null effects²¹⁴⁻²¹⁶, or an even increased risk of advanced lesions²¹⁶ in RCTs of folic acid supplementation among patients with a history of adenoma. Another important determinant of folate's effects might be the baseline intake. Some RCTs have found that folic acid supplementation reduces adenoma recurrence only among individuals with low baseline folate levels^{214, 217}.

In summary, the investigation of the folate-CRC relationship provides an excellent example of the complex role of nutrients in human health and disease. Despite the inconsistent evidence, recommending adequate folate intake may abrogate the increased risk of CRC consistently observed with folate deficiency. In contrast to folate, data regarding other B vitamins and CRC are scant. Vitamin B6 as assessed by dietary intake and blood pyridoxal 5'-phosphate, the major circulating form, has been associated with lower CRC risk in a meta-analysis²¹⁸. Vitamin B2 and B12 remain inconclusive^{32, 187, 189, 219-227}. For methionine, high intake has been associated with lower risk of CRC in a recent meta-analysis of 8 cohort studies²²⁸. Similar findings have also been reported for circulating methionine^{220, 229}. In addition to a role in one-carbon metabolism, metabolites of methionine may block mitogenic signaling in colon cancer cells²³⁰ and reduce inflammation-associated colon tumorigenesis through multiple signaling pathways²³¹.

Antioxidant nutrients

Antioxidants, reactive oxygen species scavengers, protect cells from oxidative stress that can initiate and promote carcinogenesis by inducing gene mutations, DNA damage, genome instability, cell proliferation, and inflammation²³². Carotenoids (e.g., beta carotene, vitamin A precursor, and lycopene), vitamin C, and vitamin E have potent anti-oxidative and anti-inflammatory properties. Selenium has no such action itself but is required for the anti-oxidative activity of selenoenzymes. Therefore, these vitamins and minerals are referred to as antioxidant nutrients.

Early ecologic²³³⁻²³⁵, case-control^{226, 236, 237} and small prospective studies^{141, 238-241} have shown that antioxidant nutrient intake is inversely associated with CRC risk. These data prompted small RCTs in which supplementation with antioxidant vitamins reduced adenoma recurrence^{154, 242-244}. However, these data were not corroborated in subsequent cohort studies that assessed dietary intake^{32, 219, 245-248}, supplemental use^{249, 250} or biomarker levels^{35, 245, 248, 251-253} of antioxidants. In pooled analyses of more than 10 cohort studies, dietary intake of carotenoids²⁵⁴, and vitamins A, C and E were not significantly associated with CRC risk, and any inverse association for total intake of vitamins A, C and E were attenuated after accounting for folate intake²⁵⁵. Larger RCTs that tested tumor chemopreventive efficacy of antioxidant supplementation also yielded null results^{156, 256-266}, although a potential benefit of beta-carotene was detected in one trial among a subgroup who neither smoked cigarettes nor drank alcohol²⁶⁷. Selenium supplementation reduced CRC incidence by 61% in the secondary analysis of a RCT among patients with a history of non-melanoma skin cancer (the National Prevention of Cancer (NPC) study)²⁶⁸. However, no such benefit was observed in the large Selenium and Vitamin E Cancer Prevention Trial (SELECT)²⁶⁴. In addition to the different formulations of selenium used in the 2 trials, the lower baseline selenium level among participants of the NPC study may have contributed to the observed benefit. There is evidence for a U-shaped relationship between selenium status and protection from cancer, with an optimal circulating level of selenium within the range of 130–150 µg/L²⁶⁹⁻²⁷¹. Selenium requirements may vary among individuals due to genetic variation in selenoenzymes^{272, 273}. Although some genetic mutations in selenoproteins have been associated with colorectal neoplasm risk²⁷⁴⁻²⁷⁶, the findings remain inconclusive^{253, 277, 278} and require replication in larger studies.

Given differences in selenium metabolism²⁷⁹⁻²⁸³ and the modifying impact of estrogen²⁸⁴, a sex difference hypothesis emerged for the selenium effect on neoplasia. Some data including a CRC meta-analysis²⁵³, a prospective adenoma study²⁸⁵, a pooled analysis of 3 RCTs²⁸⁶, and the NPC study²⁸⁷, indicate that any selenium benefit in colorectal tumors may be restricted to men. However, these findings seem at odds with the null results of the SELECT trial, which only included men²⁶⁴, and a recent analysis of the large cohort in which the inverse associations with CRC for serum selenium and selenoprotein P levels were more apparent in women than in men²⁸⁸.

In summary, although adequate antioxidant intake may be essential for overall health, recommending routine use of antioxidant supplements is unlikely to prevent CRC, particularly in populations without significant nutrient deficiencies.

Fats

The hypothesis that high-fat diets cause CRC derives from the striking correlation between per capita consumption of meat or animal fat and national rates of the disease^{289, 290}. High-fat diets increase the intestinal excretion of bile acids, which can be metabolized by the gut bacteria to cancer-promoting agents²⁹¹⁻²⁹³. A high-fat diet can also induce marked changes in microbial community composition and function with concomitant or subsequent changes in gut immune and inflammatory effectors²⁹⁴⁻²⁹⁷ implicated in the intestinal tumorigenesis²⁹⁸. In 1990, findings from the Nurses' Health Study (NHS) indicated that high intake of total fat, specifically animal saturated and monounsaturated fat, but not vegetable fat, linoleic acid or cholesterol, increased colon cancer risk²⁹⁹. However, these results were not consistently replicated in subsequent studies^{46, 50, 300-306}. A meta-analysis of 13 prospective studies found that neither total fat nor specific types of fat was associated with CRC risk³⁰⁷. In accordance with the observational findings, the WHI RCT did not detect any reduction in CRC incidence after over 8 years of low-fat (20% of energy intake) dietary modification³⁰⁴.

Among specific types of fat, omega-3 polyunsaturated fatty acids (PUFAs) have garnered particular attention due to their potent anti-inflammatory effects in experimental models³⁰⁸⁻³¹¹. A placebo-controlled RCT showed that omega-3 PUFA administration of 2 g daily for 6 months decreased polyp number, size and overall burden in patients with familial adenomatous polyposis³¹². A larger RCT, the seAFOod Polyp Prevention Trial, is currently underway to investigate the effect of omega-3 PUFA supplementation alone or in combination with aspirin on adenoma recurrence³¹³. Despite these promising data, findings from epidemiologic studies are inconclusive³¹⁴. Some studies suggest that the inverse association between omega-3 PUFAs and CRC is restricted to aspirin nonusers^{315, 316}, although the results are mixed³¹⁷⁻³¹⁹. Recent studies also suggest that the omega-3-PUFA-CRC association may vary by tumor site, with an inverse association for proximal colon or rectal cancer, but a positive association for distal colon cancer^{318, 320}. Differential associations are plausible given the considerable anatomic variation in biochemical milieu (e.g., pH), molecular features, and gut microbiota observed throughout the colon³²¹⁻³²³. Several lines of evidence also support that omega-3 PUFAs may exert their effects only in the early stages of carcinogenesis. Dietary intake of omega-3 PUFAs more than 10 years before cancer diagnosis, but not recent intake, has been associated with a lower risk of CRC^{318, 324}. Similarly, high levels of omega-3 PUFAs in the circulation or erythrocyte membranes have been associated with lower adenoma risk³²⁵⁻³²⁷.

Laboratory data indicate that omega-6 PUFAs have pro-inflammatory effects; these are attributed to antagonism of omega-3 PUFAs. However, human studies have not provided convincing data for the detrimental effects of omega-6 PUFAs on cancer outcomes, including CRC^{305, 306, 315-317, 328}, and heart disease³²⁹, raising questions about the plausibility of this hypothesis^{330, 331}. Another fatty acid, *trans* fat, has been associated with an increased risk for cardiometabolic diseases³³². Some of the postulated mechanisms of *trans* fat also involve cancer risk, such as systemic inflammation, insulin resistance, and adiposity³³³. However, findings from epidemiologic studies have been inconsistent on the association between *trans*-fat intake and increased CRC risk³³⁴⁻³³⁷.

In summary, there is limited evidence that total fat or specific types of fat are associated with CRC risk. Thus, recommendations to alter one's fat intake for the specific purpose of CRC prevention do not appear warranted without additional data—particularly the results of the RCT of omega-3 PUFA supplementation¹²⁵.

Sulfur

Sulfur in the diet can arise from inorganic sulfate used in the preservation of processed foods and beverages, and the sulfur-containing amino acids from protein, such as methionine, cysteine, and taurine³³⁸. These sulfur compounds are metabolized to hydrogen sulfide (H₂S) by gut bacteria through reduction and fermentation reactions³³⁹⁻³⁴¹ (Figure 4). H₂S has been implicated in inflammatory disorders associated with risk of CRC, such as ulcerative colitis,³⁴²⁻³⁴⁴ and directly with CRC³⁴⁵⁻³⁵¹. In a prospective study, high intake of sulfur and sulfate is associated with increased likelihood of relapse of ulcerative colitis³⁵². Dietary sources of sulfur, such as red meat, animal protein and wine, have also been associated with ulcerative colitis onset and relapse³⁵³⁻³⁵⁶. In the colon, excess chronic H₂S exposure is associated with factors that promote carcinogenesis, such as impaired colonocyte nutrition, DNA damage, epithelial hyperproliferation, inflammation, and alterations in immune cell populations and function^{341, 347, 357-359}.

Other sources of sulfur include the allyl sulfur components from garlic³⁶⁰ and sulfur-containing glycosides (mainly glucosinolates) found in cruciferous vegetables, such as cabbage, brussel sprouts, and broccoli³⁶¹. In contrast to the inorganic sulfur and sulfur-containing amino acids, allyl sulfur compounds and glucosinolates possess antineoplastic effects via multiple mechanisms including: inhibition of carcinogen-activating enzymes, detoxification of carcinogens, induction of apoptosis, arrest of cell cycle progression, modulation of inflammation, and suppression of angiogenesis³⁶²⁻³⁶⁶. High garlic intake has been associated with a modest reduction of CRC incidence in cohort studies³⁶⁷, although such findings were not replicated in a recent meta-analysis³⁶⁸. Animal studies also indicate a protective effect of garlic on CRC³⁶⁹. Cruciferous vegetables and their interaction with genetic variations may affect CRC risk as well³⁷⁰ (see fruits and vegetables section).

In summary, sulfur-containing foods may have divergent effects on CRC development depending on the specific sulfur-associated compounds. However, at present there is insufficient human evidence to recommend modification of sulfur intake for the prevention of CRC.

Foods

Because various nutrients are consumed in foods, investigation of foods accounting for the interaction among multiple nutrients may not only facilitate the formulation of public health recommendations, but also provide additional insight into the role of dietary factors in colorectal carcinogenesis. Here, we focus on foods with the greatest epidemiologic evidence in CRC (Figure 5).

Meat

In its systematic review of diet and cancer, the World Cancer Research Fund concluded that there is convincing evidence that red meat and processed meat increase CRC risk⁷. A recent meta-analysis indicated an approximately 20% higher risk of CRC per 100 g/day increase in red meat and 50 g/day increase in processed meat. The risk increases linearly with increasing intake of red and processed meats up to approximately 140 g/day; beyond this level, the risk increase is less pronounced³⁷¹. Similar findings have been reported for colorectal adenomas³⁷². Remote rather than recent intake of red meat may be significantly associated with CRC, suggesting an initiating role in colorectal carcinogenesis³⁷³. In addition, associations appear to be more pronounced for distal colon and rectosigmoid adenocarcinomas than other sites³⁷³⁻³⁷⁵.

Several mechanisms may underlie the relationship between red meat and CRC. Effects may be mediated through some of the nutrients already described. Meat is an abundant source of sulfur-containing amino acids, saturated fats and, in the case of processed meat, inorganic sulfur used as a preservative. Heme iron in red meat can induce oxidative stress³⁷⁶, colonocyte proliferation³⁷⁷ and the endogenous formation of *N*-nitroso compounds (NOCs), which are potent carcinogens in the gastrointestinal tract³⁷⁸. NOCs are also introduced exogenously in processed meats from nitrates and nitrites added in the preserving process³⁷⁹. Meat cooked at high temperature is also a source of other mutagens, including heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs)³⁸⁰⁻³⁸³. High consumption of heme iron (but not other forms of iron)³⁸⁴⁻³⁸⁶, NOCs^{385, 387, 388}, HCAs^{385, 389-391}, and PAHs^{385, 392} have all been associated with increased risk of colorectal tumors with a few exceptions^{393, 394}. Consistent with their mutagenic effects, processed meat and heme iron have been more strongly associated with the risk of colorectal neoplasia harboring somatic mutations in *KRAS* and *APC*³⁹⁵⁻³⁹⁷. Genetic variations in NOC and HCA metabolism may modify the relationship between red meat intake and CRC risk as well^{391, 398-401}. Individuals with genotypes that lead to rapid activation of *N*-acetyltransferases 1 and 2, important enzymes for carcinogen activation, have greater risk associated with high red meat intake, compared to those with slow activation genotypes^{391, 398-401}, although the evidence is inconclusive^{402, 403}.

Poultry⁴⁰⁴ and fish⁴⁰⁵ has been associated with a modest reduction of CRC incidence in contrast to red meat. This is concordant with the notion that components other than fat and protein in red and processed meat contribute to the carcinogenic effects^{304, 406}. Thus, based on current evidence it would be reasonable to recommend substitution of poultry or fish for red and processed meat as a strategy for CRC prevention^{299, 407}.

Dairy products

Dairy products may protect against colorectal neoplasia because of their high content of calcium, other micronutrients and bioactive constituents^{56, 408, 409}. However, epidemiologic evidence is inconsistent^{33, 34, 44, 48, 51, 52, 73, 101, 102, 406, 410-418}. In a pooled analysis of 10 cohort studies, milk consumption was associated with lower risk for CRC—particularly for distal colon and rectal cancers. Despite the moderate-to-high correlation between milk and calcium intake (*r* ranges 0.38-0.78), accounting for calcium only partially attenuated this

association, indicating calcium-independent and -dependent mechanisms of cancer prevention⁷³. A recent meta-analysis of 19 cohort studies indicate a nonlinear, inverse association between milk intake and CRC risk, with no substantial change in CRC incidence below ~200 g/day and the greatest reduction over consumption of 500-800 g/day⁴¹⁹. Constituents in milk other than calcium may also contribute to the antineoplastic activity, including conjugated linoleic acid (CLA) that has antioxidant, anti-inflammatory and immune modulatory properties⁴²⁰⁻⁴²⁴. CLA supplementation has been shown to inhibit colorectal carcinogenesis in animal models⁴²⁵⁻⁴²⁷. The first human evidence in support of beneficial CLA effects was reported in a Swedish cohort in which high CLA intake was associated with lower CRC risk and partly accounted for the inverse relationship between high-fat dairy food consumption and CRC incidence⁴¹⁴. Butyric acid, a SCFA, present in or generated by consumption of dairy products may also have a protective effect against CRC possibly through its diverse effects on cellular function^{428, 429}.

Contrary to adult dairy consumption, high childhood dairy intake was associated with 3-fold increase of CRC risk in a longitudinal study⁴³⁰. This association may be mediated by attained adult height which is positively associated with both childhood dairy intake and CRC risk⁴³¹, or may be a marker of a programming effect of early-life nutrition on host growth signaling pathways⁴³² and the gut microbiome⁴³³. Given the paucity of data, further investigation is needed to confirm these observations and elucidate the mechanisms whereby early- and later-life nutritional exposures may influence CRC risk⁴³⁴.

Fermented dairy products, such as yogurt, have also been associated with CRC. The lactic acid bacteria of fermented milk products may alter the composition or function of a host's endogenous gut microbiota⁴³⁵, reduce absorption of mutagens from cooked foods⁴³⁶, inactivate intestinal carcinogens⁴³⁷, and dampen intestinal inflammation⁴³⁸. However, epidemiologic evidence relating yogurt consumption to CRC risk is conflicting^{33, 48, 418, 439, 440}. Possible reasons include the challenge of adequately accounting for confounding by lifestyle factors associated with yogurt consumption, limited variation in the amount of intake, and varied bacterial and nutritional yogurt composition in different populations. For example, yogurt was weakly associated with lower CRC risk in a pooled analysis of studies mostly from the U.S.⁷³, where yogurt may be heat treated after fermentation to destroy most microbes and extend shelf-life. In contrast, a strong inverse association was reported in European countries where yogurt typically contains high counts of live lactic acid bacteria^{418, 440}. Similarly, an inverse association with CRC was reported for high lactose intake⁵¹, a sugar present in milk that can be fermented by gut bacteria to produce butyrate⁴⁴¹. Genetic variation associated with lactase persistence has also been shown to influence CRC risk⁴⁴². There are limited data on other dairy products, including cheese^{33, 38, 48, 51, 52, 136, 414, 418}, high-fat dairy products^{34, 305, 414}, low-fat dairy products^{101, 305}, cottage cheese^{33, 38, 51, 413}, non-yogurt fermented dairy products (e.g., kefir)^{46, 48, 52, 101, 102} and butter^{51, 414}. No association with CRC risk was reported for any of these dairy products in the meta-analysis⁴¹⁹.

In summary, there is probable evidence that milk consumption protects against CRC. The potential anti-CRC effect of yogurt also deserves further investigation. Thus, it may be reasonable to encourage intake of milk, and possibly yogurt, for CRC prevention.

Fruits and vegetables

Fruits and vegetables may protect against CRC because of high levels of several potential anticarcinogenic compounds that we have already discussed, including: fiber, folate, other B vitamins, minerals, and antioxidants⁴⁴³. However, epidemiologic studies have yielded inconsistent findings, possibly because of the large variations across studies in consumption amount, production methods, storage conditions, nutrient content, and cooking and preparation as well as variation in accounting for confounding factors^{444, 445}. In 11 of 21 cohort studies^{134, 136, 142, 413, 446-452}, a weak inverse association was reported between fruit or vegetable intake and CRC; in other studies no association was detected^{46, 133, 417, 453-459}. The relationship seems more evident for distal colon cancer than for other anatomic sites⁴⁶⁰. In some studies, a stronger association was observed among certain subgroups, such as obese or physically inactive individuals⁴⁵², never and former smokers⁴⁵¹, nondrinkers of alcohol⁴⁶⁰, and low consumers of red meat⁴⁶⁰. As suggested by some studies^{134, 144, 449}, a recent meta-analysis found a significant nonlinear relationship between fruit and vegetable intake and CRC incidence, with the greatest risk reduction associated with increasing fruit intake up to about 100 g/day and vegetable intake to about 100-200 g/day, with little evidence for further reduction with higher intake⁴⁴⁴. These findings agree with the results of the Polyp Prevention Trial in which extremely high consumption of fruits and vegetables (as well as high fiber and low fat) did not result in appreciable reductions in adenoma recurrence¹⁵⁸. This nonlinear relationship may explain the discrepant findings, as in some studies the lowest level of intake was already above the beneficial effect range^{448, 452, 456}. In addition, there is some evidence that high fruit and vegetable intake during adolescence and mid-life, independent of adult diet^{461, 462}, may confer additional benefit, suggesting that exposures over the life cycle plays a role in CRC development.

Of all vegetables, cruciferous vegetables are of particular interest given their high glucosinolate content that can be metabolized to isothiocyanates (ITCs) and indole-3-carbinol (I3C) by myrosinase-expressing colonic bacteria³⁶⁶. The multifaceted antineoplastic activities of ITCs and I3Cs have been suggested in animal studies³⁶⁵ (see Figure 4 and the sulfur section). A potential benefit of high cruciferous vegetable intake or high ITC levels on colorectal neoplasms has also been noted⁴⁶³. A recent meta-analysis reported 16% reduction of CRC risk comparing the highest to the lowest categories of cruciferous vegetable intake³⁷⁰. Genetic studies offer supporting evidence, in which genetic variations in glutathione S-transferase, a critical enzyme in ITC metabolism, modify the association of cruciferous vegetables or ITCs with colorectal tumors⁴⁶⁴⁻⁴⁷⁰. Given the importance of gut microbiota in glucosinolate metabolism, further investigation is needed to uncover the potential interplay between genetic susceptibility, gut bacterial composition, and dietary intake in determining CRC risk.

In summary, there is limited evidence that high intake of fruits and vegetables protects against CRC. However, considering the well-established cardiometabolic benefits of adequate fruit and vegetable intake^{471, 472}, it would be reasonable to recommend increasing intake among populations with very low consumption.

Whole grain

In contrast with refined grains that retain only the endosperm, whole grains contain germ and bran, which are rich sources of various substances with anticancer properties, including fiber, antioxidants, and phytochemicals⁴⁷³. High intake of whole grain has been related to lower CRC risk in all^{146, 474-480} but 2 cohort studies^{46, 144}. Of note, a particular challenge of studying whole-grain intake is the difficulty of accurate measurement owing to the wide variation in whole grain content among products and absent universal standards for whole grains or whole-grain products⁴⁸¹. To address this issue, a circulating biomarker of whole grain intake, alkylresorcinol, has been developed. Alkylresorcinols, phenolic lipids found exclusively in the bran part of wheat and rye⁴⁸², are not affected by food processing⁴⁸³ and can be measured in blood plasma with moderate validity and reproducibility^{484-489, 490}. In a large nested case-control study, the highest quartile of plasma alkylresorcinol was associated with decreased risk of distal colon cancer, but not proximal colon or rectal cancer⁴⁹¹. In another study, plasma alkylresorcinol, but not whole grain intake assessed by food frequency questionnaires, was associated with CRC, particularly of the distal colon⁴⁸⁰.

In summary, based on convincing evidence, it would be reasonable to recommend increasing intake of whole grains to help reduce risk of CRC. In addition to the high content of bioactive compounds, whole grain also represents a source of high-quality carbohydrate, as assessed by a low glycemic index, due its slow digestion and absorption⁴⁹². Although the epidemiologic evidence on glycemic index and CRC is inconclusive⁴⁹³, consumption of whole grains has been associated with decreased fasting insulin level and improved insulin sensitivity⁴⁹⁴. Given the well-established role of insulin in promoting colonic growth⁴⁹⁵, whole grain may exert its beneficial effect on colorectal carcinogenesis by lowering insulin.

Dietary Pattern

Emerging data suggest that consideration of a combination of nutrients and foods may demonstrate stronger associations with CRC risk compared with specific nutrients or food types. This may reflect the interplay of various components of diet, and that not only the addition of beneficial dietary factors but the substitution of detrimental dietary constituents with such factors is critical. For example, in accordance with vitamin D's regulatory role in calcium metabolism, there is evidence that high intake of calcium and vitamin D interact to influence CRC risk^{35, 36, 78}. In addition, increasing folate consumption may mitigate alcohol-induced folate deficiency⁴⁹⁶ and exert stronger protection among alcohol drinkers^{173, 177, 187, 188}. Given the importance of inflammation in CRC development, various nutrients with either pro- or anti-inflammatory activities may work together to influence CRC risk through intertwined pathways, including gut microbiota co-metabolism²⁹⁴.

Human studies have also focused on dietary patterns, which represent the combination of highly correlated foods consumed in a certain population that can be derived from either an *a posteriori* (data-driven) approach by factor or cluster analysis, or *a priori* approach based on dietary recommendations^{497, 498}. The data-driven approach has identified at least two general patterns: the western pattern, featuring high consumption of processed and red meats, refined grains, soda and sweets, and the prudent pattern featuring high intakes of

fruits, vegetables, fish, poultry and whole-grain products. The western pattern has been associated with increased CRC risk^{474, 499-503}, whereas the prudent pattern, has been less consistently associated with lower risk^{140, 474, 499, 503-508}. In addition, a prudent pattern during adolescence, independent of adult dietary pattern, was associated with lower risk of rectal adenomas, whereas a western pattern was associated with higher risk⁴⁶¹. Among CRC patients, higher intake of a western dietary pattern after diagnosis may increase the risk of cancer recurrence and mortality⁵⁰⁹.

Several *a priori* dietary patterns have also been assessed. A Mediterranean diet has been associated with lower cancer mortality⁵¹⁰ and lower CRC risk⁵¹¹⁻⁵¹³. The Dietary Approaches to Stop Hypertension (DASH) diet, originally designed for blood pressure control⁵¹⁴, has been associated with a lower CRC risk^{478, 515}. Other indexes, such as Healthy Eating Index-2005, Alternate Healthy Eating Index, and Recommended Food Score, have also been related to CRC risk⁵¹².

Energy Balance

Given the critical role of diet in energy balance, nutritional factors may influence the development of CRC through their effects on adiposity and its associated metabolic derangements. Long-term energy imbalance, represented by an excess of energy intake over expenditure, leads to overweight and obesity⁵¹⁶. An extensive body of literature has implicated overweight and obesity, especially abdominal adiposity, as one of the critical factors, if not the most important factor, for CRC. The risk increases by 2-3% per unit increase of body mass index and per inch increase of waist circumference⁷.

Although the exact mechanisms that underlie this association remain unclear, several lines of evidence indicate that insulin resistance and increased signaling of insulin and insulin-like growth factor (IGF) may mediate the effect^{495, 517}. Adipose tissue itself is a metabolically active organ, producing molecules that potentially modulate carcinogenesis, including: inflammatory cytokines, adipokines and sex hormones^{518, 519}. Interested readers are encouraged to refer to other excellent reviews on the mechanisms underlying the relationship between obesity and cancer^{518, 519}, in particular CRC⁵²⁰. Several components of a western diet have been associated with obesity and weight gain, including high intake of red meat and processed meat, and low consumption of fruits, vegetables, fiber, and whole grains⁵²¹. Greater intake of red and processed meat has been related to increased levels of inflammatory and dysregulated metabolic biomarkers⁵²². Fruits and vegetables, or biomarkers of their intake, have been inversely associated with metabolic syndrome⁵²³ and concentrations of fasting insulin and glucose⁵²⁴⁻⁵²⁶. Similarly, higher fiber and whole grain intake has been associated with improved insulin sensitivity^{527, 528}.

In contrast to the equivocal findings on individual nutrients or foods, the strong, consistent association between obesity and CRC (at least in men) further underscores the predominant importance of combined, integrated effects of nutrients/foods over their individual effects. These effects probably reflect both the excess quantity of energy intake over expenditure, and the suboptimal quality of the diet associated with obesity.

Interaction between Diet and the Gut Microbiota

The explosion of research in host-microbe interaction supports a potential role of gut microbiota and their interplay with diet in human health and disease, through regulation of host metabolism and immune function^{294, 529-535}. An altered microbial community as well as enrichments of select bacteria, such as *Fusobacterium nucleatum*, have been implicated in the development of colorectal adenomas and adenocarcinomas⁵³⁶⁻⁵⁴⁵. Studies have also associated changes in relative proportions of gut bacterial clades with obesity^{530, 546, 547}, metabolic syndrome⁵⁴⁸ and type 2 diabetes^{549, 550}, all of which are conditions that increase CRC risk. Accumulating evidence suggests a profound effect of diet on gut microbiota^{296, 531, 551-553}. Dietary fiber can favor the growth of butyrate-producing bacteria over other bacteria, beneficially shaping the structure of the human gut microbiota⁵⁵⁴. Children from rural Africa, where diet is high in fiber, have a strikingly different composition of gut microbiota than those from urban Europe characterized by a western diet⁵⁵². Switching from a low-fat, plant-rich diet to a western diet changed microbial composition, and metabolic pathways and gene expression in the gut microbiome⁵⁵³.

The progressive maturation and balanced composition of intestinal microbes may be important for establishment and regulation of immune and inflammatory responses through bacteria-derived products, such as SCFAs, bile acids and vitamins. Decreased levels of such products because of either dysbiosis or an imbalanced diet may contribute to inflammation and subsequent disease development in the host^{130, 294, 555}. Synbiotic intervention with prebiotic resistant starch and beneficial bacteria has been shown to lower the incidence of colonic neoplasms in rats⁵⁵⁶.

However, more research in animal models as well as robust epidemiologic and well-controlled interventional studies in human are required.

Conclusion and Future Directions

Although there are few conclusive data from RCTs to support the efficacy of dietary modification or nutrient supplementation for CRC prevention, several foods and nutrients, including red meat and processed meat, fiber, milk, calcium, and whole grains, have been related to CRC with reasonable consistency in prospective cohort studies. Taken together with biological mechanisms derived from experimental studies linking these factors with CRC, there is a strong rationale to continue investigation into dietary strategies for CRC prevention.

Several questions remain to be addressed. Given evidence supporting clear anatomic and molecular heterogeneity of colorectal tumors, how do nutritional factors differentially influence the risk of cancers that arise from distinctive etiologic pathways? What are the optimal dose, formulation, and time window for exposure to specific nutrients, foods, or dietary patterns to interrupt or reverse carcinogenesis? How do dietary components interact with the gut microbiota as well as other host factors to influence CRC risk? Although we remain at an early stage of addressing these questions, technologic advances in the form of novel experimental models and methodologic tools (e.g, metabolomics, microbial

meta'omics) will undoubtedly yield mechanistic and causal insights that can be used to inform public health recommendations⁵⁵⁷ and curtail CRC incidence and mortality⁵⁵⁸.

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Figure 1. Proposed canonical and non-canonical inflammatory mechanisms relating nutrients to colorectal cancer

Consumption of saturated or *trans*-fats increases free fatty acids and bile acid levels. Bile acids are metabolized by gut microbes to generate secondary bile acids, which can promote colorectal carcinogenesis through increased pro-inflammatory effectors and oxidative stress mediated via engagement of nuclear factor-κB (NFκB) and cyclooxygenase-2 (COX2/prostaglandin synthase-2) pathways. Sulfur-containing amino acids and inorganic sulfur are also metabolized by gut microbes to produce hydrogen sulfide (H₂S), which can be toxic to the colorectal mucosa and induce oxidative stress. As reactive oxygen species scavengers, antioxidant nutrients can protect colonocytes from oxidative stress. B vitamins also counteract oxidative stress through lowering homocysteine. Calcium may inhibit colorectal carcinogenesis through direct effects on cell proliferation, differentiation and apoptosis, and binding to free fatty acids and bile acids. Vitamin D exerts anti-inflammatory effects through bile acid catabolism, suppression of NFκB and COX2 signaling, and enhanced production of interleukin-10 (IL10). Omega-3 fatty acids can inhibit inflammation and promote resolution through lipid mediators (i.e., lipoxin, resolvins and protectins) and directly via G protein-coupled receptor 120 (GPR120) signaling.

Figure 2. Metabolism and antineoplastic pathways of calcium and vitamin D

Vitamin D signaling via vitamin D receptor (VDR) and retinoid X receptor (RXR) regulates the transcription of numerous genes involved in carcinogenesis through effects on inflammation, cell proliferation, differentiation, apoptosis and angiogenesis. Elevated intracellular calcium, together with diacyl glycerol (DAG), results in the activation of protein kinase C (PKC) that can inhibit cell proliferation and promote differentiation through multiple downstream signals. CaR signaling may also inhibit cell proliferation through inactivation of the β -catenin pathway. Vitamin D is an essential regulator of calcium homeostasis through the negative feedback system involving parathyroid hormone (PTH). The secretion of PTH is enhanced as circulating calcium concentration decreases, resulting in increased synthesis of $1,25(\text{OH})_2\text{D}_3$. Elevated $1,25(\text{OH})_2\text{D}_3$ in turn promotes calcium absorption in the intestine and calcium release from bone, which suppresses PTH production.

Figure 3. Folate, methionine and other B vitamins in DNA methylation and synthesis

Folate from dietary intake, supplement use and synthesis by gut bacteria is converted to its predominant circulating form, 5-methyl tetrahydrofolate (THF), which can be metabolized by methionine synthase (MS) to form methionine from homocysteine. Vitamin B6 and B12 are also critical cofactors in DNA methylation and synthesis. Dysregulated DNA methylation and DNA synthesis contribute to colorectal carcinogenesis. Abbreviations: DNMT, DNA methyltransferase; MAT, S-adenosylmethionine synthase; SAH, S-adenosylhomocysteine; TS, thymidylate synthase; VDRE, vitamin D response element.

Figure 4. Proposed mechanisms relating sulfur-containing foods to colorectal cancer

Sulfur-containing amino acids and inorganic sulfur may have procarcinogenic properties, whereas glucosinolates and allyl sulfur compounds possess antineoplastic activities. Gut bacteria can ferment sulfur-containing amino acids to produce hydrogen sulfide (H₂S). Gut sulfate-reducing bacteria can reduce inorganic sulfur in processed food and beverages to produce H₂S. Several mechanisms that may mediate the pro-carcinogenic effects of H₂S include: impaired fuel utilization of butyrate by colonocytes, increased cell proliferation, DNA damage, and inflammation. Cruciferous vegetables are rich in glucosinolates that can be metabolized by myrosinase-expressing gut bacteria to thiohydroxymate-O-sulfonate, which can be further converted to isothiocyanates, indole and nitrile. These metabolites and their downstream products have a wide diversity of anticarcinogenic effects. Allium vegetables have high levels of allyl sulfur compounds, mainly γ-glutamylcysteines, which can be converted to S-allylcysteine, or hydrolyzed and oxidized to form alliin. After processing, alliin decomposes to diallyl disulfide (DADS), diallyl sulfide (DAS), and diallyl trisulfide (DAT), which have been related to garlic's cancer-preventive effects.

Figure 5. Biologic mechanisms relating foods to colorectal cancer

Red and processed meat may contribute to CRC through generation of carcinogens, including *N*-nitroso compounds (NOC), heme iron, sulfur-containing amino acids, and saturated fat. Overweight or obesity as well as chronically increased levels of insulin may also have a critical role. Despite high saturated fat content and its role in increasing insulin-like growth factor 1 (IGF1), dairy products may inhibit colorectal carcinogenesis via a variety of bioactive constituents: calcium, vitamin D (when fortified), conjugated linoleic acid (CLA), butyric acid, lactose, and lactic acid bacteria in fermented milk products. Fruits and vegetables contain various components with antineoplastic potential: fiber, antioxidants, B vitamins, and glucosinolates (in cruciferous vegetables). Potential anti-cancer mechanisms of fiber include: binding or diluting secondary bile acids, increased stool weight, decreased transit time, and bacterial fermentation leading to reduced colonic luminal pH and production of butyrate which has antineoplastic properties. Fiber, fruits and vegetables may also influence carcinogenesis through decreased adiposity.

Table 1
Summary of evidence and mechanisms relating nutrients and foods to colorectal cancer

Nutrient or Food	Level of Evidence ^a	Estimate of Relative Risk (RR) ^b	Proposed Mechanisms
Nutrient			
Calcium	Probable	RR=0.92 (0.89–0.95) per 300 mg/day increase of total calcium intake [ref ⁷⁴]	Binding to fatty acids and free bile acids; suppression of cell proliferation; promotion of cell differentiation and apoptosis; inhibition of oxidative DNA damage; modulation of colorectal cancer-related cell signaling pathways
Vitamin D	Limited-suggestive	RR=0.95 (0.93–0.98) per 100 IU/day increase of dietary vitamin D intake; 0.96 (0.94–0.97) per 2.5 ng/mL (6.25 nmol/L) increase of circulating 25(OH)D [ref ⁷]	Anti-proliferation, pro-differentiation and apoptosis, anti-inflammation, inhibition of invasion and metastasis, and suppression of angiogenesis
Fiber	Convincing	RR=0.90 (0.86–0.94) per 10 g/day increase of dietary fiber intake [ref ¹³¹]	Increased stool weight, decreased transit time, dilution of colonic carcinogenic content, decreased adiposity, and anticancer properties of short-chain fatty acids produced by bacterial fermentation of resistant starch
Folate	Limited-suggestive	RR=0.99 (0.93–1.05) per 100 µg/d increase of dietary folate intake; 0.98 (0.94–1.03) per 100µg/day increase of total folate intake [ref ⁷]	Essential nutrient for DNA methylation and DNA synthesis, critical processes in carcinogenesis
Vitamin B6	N/A	RR=0.90 (0.75–1.07) comparing the highest to the lowest categories of vitamin B6 intake; 0.51 (0.38–0.69) per 100 pmol/mL increase of blood level of pyridoxal 5'-phosphate [ref ²¹⁸]	One-carbon metabolism, critical for DNA synthesis and DNA methylation
Methionine	N/A	RR=0.89 (0.79–1.00) comparing the highest to the lowest categories [ref ²²⁸]	One-carbon metabolism, critical for DNA synthesis and DNA methylation; inhibition of cell growth and reduced inflammation
Vitamin A, C, E	Limited-no conclusion	RR=0.93 (0.79–1.10) for total vitamin A, 0.86 (0.74–1.00) for total vitamin C and 0.83 (0.70–0.99) for total vitamin E, comparing the highest to the lowest categories [ref ²⁵⁵]	Antioxidative, inhibition of cell proliferation, pro-apoptosis, and reduced inflammation
Selenium	Limited-no conclusion	RR=0.81 (0.71–0.92) comparing the highest to the lowest categories of selenium concentrations in serum, plasma or toenails [ref ²⁵³]	Antioxidative, inhibition of cell proliferation, pro-apoptosis, and reduced inflammation
Total fat	Limited-no conclusion	RR=0.99 (0.89–1.09) comparing the highest to the lowest categories [ref ³⁰⁷]	Increased intestinal level of bile acids, which can be metabolized by bacteria to deoxycholic acid to promote CRC development
Omega-3 polyunsaturated fatty acids	Limited-no conclusion	RR=0.97 (0.86–1.10) comparing the highest to the lowest categories [ref ³¹⁴]	Reduced inflammation through inhibition of arachidonic acid-derived eicosanoid biosynthesis, and modulation of transcription factor activity, gene expression and signal transduction; improved insulin sensitivity; altered cell membrane fluidity
Food			
Red and processed meat	Convincing	RR=1.16 (1.04–1.30) per 100 g/day increase of red and processed meat intake [ref ⁷]	Carcinogenic effect of heme iron, N-nitro compounds, and heterocyclic amines generated during cooking at high temperature. Pro-neoplastic effect of increased adiposity and insulin

Nutrient or Food	Level of Evidence ^a	Estimate of Relative Risk (RR) ^b	Proposed Mechanisms
Milk	Probable	RR=0.91 (0.85–0.94) per 200 g/day increase of total milk intake [ref ⁴¹⁹]	Antineoplastic effect of calcium, vitamin D (for fortified milk), conjugated linoleic acid, butyric acid, and lactose
Fruits	Limited-suggestive	RR=0.97 (0.94–0.99) per 100 g/day increase of fruit intake [ref ⁷]	Anticarcinogenic compounds, such as folate, vitamins, fiber, minerals, and flavonoids; decreased adiposity
Non-starchy vegetables	Limited-suggestive	RR=0.98 (0.96–0.99) per 100 g/day increase of vegetable intake [ref ⁷]	Anticarcinogenic compounds, such as folate, vitamins, fiber, minerals, flavonoids, and glucosinolates contained in cruciferous vegetables; decreased adiposity
Whole grains	Convincing	RR=0.83 (0.78–0.89) per 3 servings/day increase of whole grains [ref ¹³¹]	Anticancer properties of fiber, antioxidants and phytochemicals; decreased adiposity; improved insulin sensitivity and decreased insulin level

^aSource: Continuous Update Project Report on Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer, World Cancer Research Fund/American Institute for Cancer Research, 2011⁷.

^bThe estimates are derived from the 2011 review by World Cancer Research Fund/American Institute for Cancer Research⁷, except for the nutrients that were not covered in that review (i.e., vitamin B6, methionine, total fat, and omega-3 polyunsaturated fatty acids), nutrients for which observational studies were not summarized in that review (i.e., vitamins A, C and E, and selenium), and exposures for which more recent meta-analyses were available (i.e., calcium, fiber, milk, and whole grain).