Review

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Dietary Intervention for Preventing Colorectal Cancer: A Practical Guide for Physicians

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Colorectal cancer (CRC) is a disease with high prevalence and mortality. Estimated preventability for CRC is approximately 50%, indicating that altering modifiable factors, including diet and body weight, can reduce CRC risk. There is strong evidence that dietary factors including whole grains, high-fiber, red and processed meat, and alcohol can affect the risk of CRC. An alternative strategy for preventing CRC is use of a chemopreventive supplement that provides higher individual exposure to nutrients than what can be obtained from the diet. These include calcium, vitamin D, folate, n-3 polyunsaturated fatty acids, and phytochemicals. Several intervention trials have shown that these dietary chemopreventives have positive protective effects on development and progression CRC. Research on chemoprevention with phytochemicals that possess anti-inflammatory and/or, anti-oxidative properties is still in the preclinical phase. Intentional weight loss by bariatric surgery has not been effective in decreasing long-term CRC risk. Physicians should perform dietary education for patients who are at high risk of cancer for changing their dietary habits and behaviour. An increased understanding of the role of individual nutrients linked to the intestinal micro-environment and stages of carcinogenesis would facilitate the development of the best nutritional formulations for preventing CRC.

Key Words Chemoprevention, Diet, Colorectal neoplasms, Calcium, Fatty acids, omega-3

INTRODUCTION

Colorectal cancer (CRC) is one of the major causes of death worldwide, with 1.8 million new cases and 880,792 deaths estimated in 2018 [1]. In the United States, it is the second leading cause of cancer-associated death, with nearly 6% of individuals predicted to suffer from this malignancy during their lifetime [2]. Both host and environmental factors are responsible for the risk of CRC. While there are non-modifiable factors such as age, predisposing genetic mutations, and a history of inflammatory bowel disease, several modifiable risk factors that we can control are also associated with development of colorectal polyps and CRC. The best known modifiable factors include diet, smoking, alcohol, physical activity, and excess body weight [3].

It is estimated that 50% of neoplasms including CRC are preventable [4,5]. Notably, two unique features in the pathogenesis of CRC provide opportunities to prevent this malignancy better. First, the progress of CRC is relatively slow compared with other malignancies. CRC has a long natural history. It is generally known that it takes, in general, at least five to ten years to develop CRC from a premalignant lesion [6]. During this period, patients normally have so-called 'benign precursor lesions' such as adenoma and serrated polyps that can be identified and removed [7]. Second, we can provide risk reduction measures for patients at higher risk of CRC by recognizing and modifying the aforementioned predisposed host and environmental factors during that period [8].

CRC prevention strategies include screening tools such as fecal occult blood test, colonoscopy, chemoprevention, lifestyle modification, and public health education [9]. In addition, novel blood tests detecting circulating tumor DNA [10] and protein biomarkers [11] have been developed, although they are still too early to be commercialized. Advanced screening modalities can lead to a reduction in CRC mortality [12]. However, CRC cases diagnosed by screening tools represent only a small portion of total diagnosed cases [13]. There

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are a number of interval CRC cases diagnosed between periods of screening colonoscopies. Therefore, it is difficult to successfully prevent CRC with screening alone. We should establish an improved CRC prevention strategy in more comprehensive ways.

This mini-review highlights the use of several chemopreventive agents such as re-purposed drugs, nutrients, and phytochemicals as a CRC prevention strategy and also addresses whether intentional body weight modulation such as bariatric surgery is effective for CRC prevention.

DIETARY AND LIFESTYLE RISK FACTORS FOR CRC

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has released an updated cancer prevention recommendation in 2018, the most comprehensive, detailed, objective guideline on dietary and lifestyle factors regarding CRC [5]. According to this guideline, there is convincing evidence that processed meat, alcoholic drinks (> 30 g daily), body fatness (marked by body mass index [BMI], waist circumference, or waist to hip ratio), and limited physical activity are factors affecting the incidence of CRC. The WCRF/AICR also recommends a diet rich in whole grains, fiber, and dairy products containing calcium.

Over decades of research, investigations on diet and CRC have been motivated by a passive strategy to identify specific risk factors such as red meat and high-fat diet or preventive factors can reduce the cancer risk [14]. As our experience in the field increases, it is becoming clearer that a single nutrient or phytochemical over a range of usual intake would only modestly impact the incidence of cancer. Rather, a significant impact will result from an integrated diet and/or an exercise pattern, creating a stronger host-environment interactions or altered metabolic state, making coln epithelial cells less susceptible to the accumulation of incidental DNA alterations that lead to the carcinogenesis cascade.

It is methodologically challenging to test the effectiveness of a dietary intervention in reducing the CRC incidence. Combined dietary interventions with a low-fat/high fiber (18 g/4,184 kJ), resistant starch (30 g daily), and folic acid (0.5–5 mg daily) have been tested in polyp prevention trials [15,16]. In these trials, individuals at high-risk have undergone surveillance colonoscopy over five years after the initial diagnosis of colorectal neoplasia. However, these trials revealed a lack of effectiveness of a low-fat/high fiber diet or resistant starch in preventing recurrent colorectal adenomas. It is difficult to explain the discrepancy between results of previous epidemiologic studies and those of polyp intervention trials conducted in the early 2010s. Though these dietary formulations might not be effective in preventing colorectal adenoma or CRC, a more reasonable explanation is that interventions have been done in a 'too little (size and duration of intervention)' or 'too late (tested in individuals who have already started carcinogenesis cascade)' manner [6].

In contrast, effects of some nutrient-related 'nutraceutical' or 'pharmaco-nutrient' prophylactic efforts on CRC have been shown to be positive in some studies. These include calcium (1–2 g daily), vitamin D (400–1,100 IU daily), and n-3 polyunsaturated fatty acids (PUFA, 2 g daily).

CHEMOPREVENTIVE AGENTS

Nutritional or pharmacological interventions for CRC prevention, aside from population-based screening and endoscopic surveillance, are called chemoprevention. Chemoprevention includes administration of natural or synthetic compounds to block, delay, or even reverse the development of invasive neoplasms [17]. For instance, metformin and statin have been proven to be effective in preventing the development or recurrence of breast cancer [18,19] and hepatocellular carcinoma [20,21]. These multi-purposed drugs are known to modulate metabolic pathways and possess a wide range of positive pleiotropic effects including anti-inflammatory properties. In addition, dietary chemopreventive agents such as long-chain polyunsaturated fatty acids, vitamins and other minerals can also be used. There are debates whether these nutritional intervention should be included as a part of chemoprevention, but we believe that it should be considered as a part of chemoprevention strategy. In this section, we will introduce studies on various chemopreventive agents and their results.

Aspirin

Aspirin is not a type of nutrient, but it has been speculated that it can prevent CRC through its pleiotropic effects. Aspirin can attenuate tumor-promoting inflammation through inhibition of cyclooxygenase-2 activity and subsequently production of prostaglandin E_2 [22]. Numerous laboratory- and population-based studies have revealed the CRC preventive potential of aspirin [23,24]. However, in two major large-scale randomized studies, the Women's Health Study [25] and the Physicians' Health Study [26] have shown no preventive effect of aspirin on CRC development over ten years of follow-up.

The atmosphere then changed after an auxiliary study of four randomized clinical trials with 20 years of follow-up [27]. According to this report, taking aspirin for several years at a daily dose of at least 75 mg reduced both incidence and mortality of CRC. Subsequently, a randomized controlled trial on antineoplastic effects of aspirin in patients with Lynch syndrome was published [28]. In the latter study, 600 mg of aspirin per day substantially reduced the CRC incidence after 55 months of follow-up. Although the chemopreventive effect of aspirin has been recognized to some extent, it is difficult to recommend its intake on a routine basis due to a lack of risk-stratified analysis. There are several inevitable complications associated with aspirin overdose, such as gastroin-

testinal or systemic bleeding. In addition, its optimal dose for cancer prevention is not well established yet. In the United States, aspirin is currently recommended for limited indications, such as primary prevention of CRC only in patients aged 50 to 59 and post-diagnosis of CRC [29].

Calcium and vitamin D

As aspirin and other non-steroidal anti-inflammatory drugs have a certain range of side effects, they could not be recommended for the purpose of cancer prevention. However, dietary supplements can also achieve chemoprevention with less concerns of side effects. This strategy is called a 'nutraceutical' or 'pharmaconutrient' approach. Nutraceutical is a product that is ingested in the form of tablets, capsules, powders or soft-gels containing natural plant extracts, vitamins, and minerals as main ingredients. It has the advantage of virtually no harmful side effects. The frontrunner of nutraceutical prevention for CRC is supplementation with calcium [30]. The WCRF/AICR underlines that calcium supplement can decrease the CRC risk [31].

Dietary calcium supplementation offers a benefit for preventing development of adenomatous polyps. Based on observational studies, there have been suggestions that dietary calcium may protect against CRC. Calcium is thought to bind fatty acids and bile acids in the colon, thus inhibiting fat-induced uncontrolled hyperproliferation of colonic epithelium [30]. Dose-response meta-analysis of prospective observational studies has found that an increase in calcium intake by 300 mg per day could reduce CRC risk (relative risk [RR], 0.91; 95% confidence interval [CI], 0.86 to 0.98). Intake of more than 1 g of calcium per day had an even greater risk-reducing effect (RR, 0.82; 95% CI, –0.71 to –0.95) [32].

Both dietary and supplementary calcium provide similar prevention benefits. Interestingly, co-administration of calcium and vitamin D better prevented damage to colonic mucosa by maintaining a healthy mucosal barrier function than calcium alone. $1,25(OH)_2D_3$, an active form of vitamin D, is considered to make a synergistic work as a key regulator in tight junction proteins and increase epithelial barrier integrity as proven in multiple animal and cell line models [33,34]. A case-control study on additive protective effects of these two nutrients showed that higher dietary calcium and vitamin D intake was associated with 43% and 52% reductions in colorectal cancer risk respectively, which was also supported by other systematic reviews and meta-analyses [35,36].

Although calcium intake has a dose-dependent protective effect on CRC, it is still unlikely to have a distinct impact on the risk of colorectal adenoma, a precancerous lesion. In a randomized controlled trial to determine whether 1,000 mg of elemental calcium and 400 IU of vitamin D3 supplementation could help prevent CRC, there was no significant risk reduction after 7 years of follow-up [37].

Folate

Folate (folic acid), a water-soluble vitamin B that plays an important role in DNA synthesis and methylation, is a nutrient that might modulate the development of CRC. Several observational studies have suggested that a diet low in folate is associated with an increased risk of colorectal neoplasia [38,39]. Collectively, these retrospective studies suggest a ~40% reduction in the risk of colorectal neoplasms in subjects with the highest dietary folate intake compared with those with the lowest intake. Several animal studies have tested the role of folate in preventing colorectal carcinogenesis, which was verified in genetically predisposed rodent models of CRC [40,41]. In animal studies, a moderate degree of folate deficiency was found to enhance colorectal carcinogenesis whereas modest levels of folate supplementation above the basal dietary requirement were suppressive [40,42].

Although folate has the potential as a useful chemopreventive agent for CRC, determining the appropriate dosage of this critical vitamin for DNA synthesis is an important but unsolved issue [43]. A recent systematic review and meta-analysis of 24 cohort studies has demonstrated that high folate intake is associated with a reduced risk of CRC with combined relative risk for the highest intake group compared with the lowest (RR, 0.88; 95% CI, 0.83 to 0.92) and the effect is different depending on the patient's alcohol consumption [44]. Notably, the protective effect was consistently observed for total (dietary and supplement) folate intake. However, supplementation (0.4 mg/d to 2.5 mg/d) of folic acid had no significant effect on CRC [45-47]. In contrast, in large-scale trials, including the Aspirin/Folate Polyp Prevention Study and another meta-analysis report, there was no evidence that folic acid supplementation was beneficial in preventing colorectal adenomas [48,49]. Therefore, it is still early to call that there is a protective efficacy of folate in CRC prevention.

n-3 PUFAs

Fatty/oily fish is assumed to have protective effect against CRC by the WCRF. As fatty and oily fish is almost exclusive dietary source of n-3 PUFAs, animal and in vitro studies have been conducted to investigate the association between dietary intake of n-3 PUFAs and CRC risk [50,51]. In an observational, prospective cohort study (EPIC) with 521,324 participants in ten European countries [52], total fish consumption, including fatty fish, lean fish, and shellfish, was inversely associated with CRC risk.

Overall, a weekly intake of 100–200 g of fatty or lean fish was associated with a 7% lower CRC risk. Similarly, dietary intake of all n-3 PUFAs was inversely associated with the risk for CRC, whereas the n-6 : n-3 PUFAs ratio was positively associated with CRC. Results of the seAFOod polyp prevention trial in which aspirin and 2 g of eicosapentenoic acid, a representative n-3 PUFA, were administered together daily for 12 months showed a significant reduction in the number of colorectal adenomas [53]. In addition, the VITAL random-

ized trial with 25,871 participants intaking mixed marine n-3 PUFAs (1 g daily) with vitamin D3 (2,000 IU daily) showed an overall negative outcome but demonstrated a significant reduction in colorectal polyp recurrence in groups with low baseline plasma n-3 PUFA levels or African-Americans [54].

Theoretically, n-3 PUFAs can produce anti-inflammatory 5-series leukotrienes and 3-series prostaglandins and act as competitive inhibitors of the actions of n-6 fatty acids that produce 4-series leukotrienes and 2-series prostaglandins and promote the synthesis of proinflammatory interleukins and tumor necrosis factor [55].

However, an epidemiologic study by Song et al. [56] showed that n-3 PUFAs did not affect overall CRC risk in the HPFS or NHS cohort of US adults. A randomized, double-blind, placebo-controlled trial with colon cancer patients revealed increased erythrocyte deformity and postoperative infectious complications [57]. Therefore, after decades of research, the anti-CRC efficacy of supplementing n-3 PUFAs remains inconclusive. There are several explanations for such inconsistency. One explanation is that the metabolism of n-3 PUFAs has various inter-individual capacities. Epoxy fatty acids produced during the metabolism of PUFAs are responsible for the anti-inflammatory effect of PUFAs. They are degraded at different rates as the level of soluble epoxide hydrolase (sEH) that breaks them down varies from from person to person.

It has been reported that increased sEH levels are associated with depression, Parkinson's disease, and maybe some cancers [58]. Another proposed reason is that the intake ratio of n-3 to n-6 PUFAs might be more important than the total amount of n-3 PUFAs. Therefore, increasing the intake of n-3 PUFAs alone may not sufficiently improve the anti-inflammatory function. Notably, the benefit linked to high marine n-3 PUFAs intake was restricted to colon cancers with wild-type *KRAS* (*Kirsten rat sarcoma viral oncogene homologue gene*) [59]. This suggests that host and tumor characteristics should also be considered when making the best nutritional risk reduction strategy.

Phytochemicals

Phytochemicals are chemical compounds produced by plants. This term is generally used to describe plant compounds that have not been scientifically defined as essential nutrients, such as vitamins and minerals. Phytochemicals represent a prominent source of novel compounds for drug discovery. Phytochemicals have been the focus of many studies due to their ability to modulate carcinogenic processes by altering multiple cancer cell survival pathways [60,61].

Curcumin is a widely investigated anti-inflammatory and anticancer phenolic compound. It has multiple health benefits, including improved syndrome, chronic pain, and degenerative eye conditions [62,63]. It is used in several other formulations, including capsules, energy drinks, and even cosmetics. It has been reported that curcumin can induce apoptosis

Table 1. Major randomized clinical trials on efficacy of dietary prevention in colorectal cancer

Author (year)	Goal(s)	Intervention	Dosage/d	Follow-up (yr)	Primary outcome	Results
Cook et al. (2005) [25]	To examine the effect of aspirin on the risk of cancer among healthy women	Aspirin	100 mg	10.1	Incidence of cancer or CV events	HR 0.80 (95% CI, 0.67 to 0.97)
Burn et al. (2011) [28]	To investigate the antineoplastic effects of aspirin and a resistant starch in carriers of Lynch syndrome	Aspirin	600 mg	4	Development of CRC	HR 0.63 (95% CI, 0.35 to 1.13)
Wactawski-Wende et al. (2006) [37]	To determine whether calcium and vitamin D supplementation would help prevent CRC	Calcium and vitamin D	1,000 mg of elemental calcium and 400 IU of vitamin D_3	7	Incidence of CRC	HR 1.08 (95% CI, 0.86 to 1.34)
Cole et al. (2007) [47]	To assess the safety and efficacy of folate supplementation for preventing colorectal adenomas	Folate	1 mg of Folic acid supplementation	3	Occurrence of at least 1 colorectal adenoma	HR 1.04 (95% CI, 0.90 to 1.20)
Song et al. (2019) [59]	To assess the effect of daily marine n-3 PUFA supplementation on the risk of CRC precursors	Marine n-3 PUFA	1,000 mg (which included 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid)	5.3	Risk of conventional adenoma or serrated polyps	Conventional adenoma multivariable HR 0.98 (95% CI, 0.83 to 1.15) serrated polyp HR 1.05 (95% CI, 0.84 to 1.29)

CV, cardiovascular; HR, hazard ratio; CI, confidence interval; CRC, colorectal cancer; PUFAs, polyunsaturated fatty acid.

in human colon cancer HT29 cells [64]. In chemo-resistant CRC cells, curcumin can enhance the therapeutic potential of conventional chemotherapeutic drugs by inhibiting proliferative targets, including cyclin D1, NF-κB, phosphoinositide 3-kinase and Src [65].

Resveratrol, a natural stilbene found in wine and grapes, has been reported to inhibit signaling pathways involved in [66]. A combination of resveratrol and grape seed extract suppressed Wnt/β-catenin signaling and induced mitochondria-dependent apoptosis in in vitro and in vivo models [67].

Despite an extensive number of studies to identify molecular pathways and interest in the clinical potential of specific phytochemicals, it is still primarily done in preclinical trials. So far, few phytochemicals have been tested in clinical settings.

INTENTIONAL WEIGHT REDUCTION

There are multiple lines of evidence supporting the association between obesity and CRC [68]. Of note, visceral fatness, waist circumference, and waist to hip ratio are also closely related to CRC risk [69]. Excess body weight is linked to colorectal polyps, which are precancerous lesions of CRC [70]. Thus, it is important to avoid excess body weight in CRC prevention. However, research on how much CRC risk can be reduced by intentional weight reduction is still lacking. Planning randomized clinical trials is quite difficult as it is challenging to monitor body weight over long periods in a large cohort. In addition, biases such as recall bias and reverse causation might be involved. Moreover, it is very unlikely that interventional randomized clinical studies will be conducted due to ethical factors. Nevertheless, it is possible to see long-term effects of rapid and significant weight loss intervention at a specific time point, which is possible through bariatric surgery (BS). BS has been proven to produce weight loss in patients with severe obesity in both short and long-term periods [71]. We can indirectly examine the relationship between intentional weight loss and cancer risk through BS cohorts.

A meta-analysis of large cohort studies using data of more than 304,516 patients with obesity showed that BS was protective against breast and endometrial cancer risk. In contrast, colorectal cancer risk was not statistically different (odd ratio [OR], 0.82; 95% CI, 0.41 to 1.64) [72]. This suggests that there are independent differences between mechanisms of carcinogenesis, even among obesity-related cancers, probably due to altered fat and bile metabolism, gut hormonal change, and shifts in gut microbiota [73]. Further studies are required to determine the risk of colorectal adenoma and neoplasia using a larger number of individuals receiving BS at an early age.

DIETARY MONITORING AND GUIDANCE BY PHYSICIANS

As mentioned above, diet influences the onset of CRC. Thus, clinicians need to provide a good dietary advice to patients at risk. In particular, providing dietary education and changing patients' nutritional habits at a 'reversible' moment (which is not too late) is more likely to reduce the occurrence of colorectal adenoma. This 'preventionist' approach to CRC is expected to be particularly useful during a screening colonoscopy. Subjects with adenomas who had been educated to maintain optimal body weight and dietary habit showed significantly smaller waist circumference and BMI at 12 months after endoscopy than those who did not receive a proper education [74]. In particular, counseling at this optimal point is expected to be useful because it can bring the high-

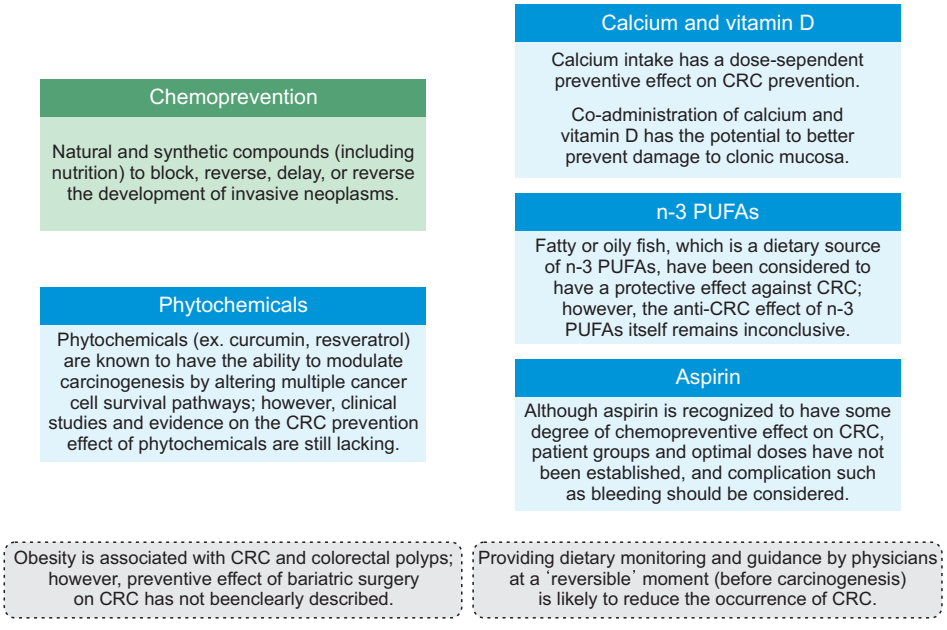

Figure 1. Recommended interventions and clinicians' guidance for colorectal cancer prevention. CRC, colorectal cancer; PUFAs, polyunsaturated fatty acids.

est motivation to the patient and leads to a substantial habit change. However, it should be recognized that these dietary changes do not necessarily prevent all colorectal neoplasia. It should be explained to patients that there are several other non-modifiable factors (e.g., age, sex, and genetic predisposition). On the other hand, long-term national surveillance is needed to verify the CRC prevention effect of regular dietary education within a large cohort. A nationwide surveillance could improve public health and better allocate limited medical resources for preventing CRC.

Although CRC has a high incidence and mortality, it is a preventable disease. Among several prevention strategies, dietary intervention has been proven to be able to reduce CRC risk after decades of research. It has been suggested that chemopreventive agents such as aspirin, calcium, vitamin D, n-3 PUFAs, and phytochemicals can effectively prevent CRC (Fig. 1). Due to methodological barriers of dietary nutritional studies, randomized controlled clinical trials are lacking (Table 1). There are only few randomized clinical trials on efficacy of 'nutrition-level' dietary prevention in colorectal cancer. Further understanding of the optimal nutritional composition and determining the optimal dose and duration could decrease CRC incidence. Future research will require a multi-disciplinary approach by basic scientists, clinical doctors, and nutritionists.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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