Prevention of colorectal cancer and dietary management

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Objectives: This systematic review focuses on dietary and lifestyle risk factors for colorectal cancer (CRC) prevention and chemoprevention among high-risk populations.

Methods and materials: We searched PubMed for English-language articles about dietary components, lifestyle risk factors, and chemoprevention agents in relation to colorectal cancer and their references published from 1980 through 2013. We reviewed articles jointly for the most clinically important information, emphasizing randomized trials and meta-analyses where available.

Results: There is convincing evidence that intake of garlic, vitamin B6 and magnesium, active living, maintaining a healthy weight and waist, avoiding or reducing red meat, alcohol, and smoking, as well as hormone replacement therapy among women may significantly protect against developing colorectal cancer. There is less consistent evidence for fruit and vegetable intake (fiber and folate), fish and Omega-3 fatty acids, selenium, dairy, calcium and vitamin D. For high-risk populations, aspirin have been shown to protect against the development of colonic adenomas and CRC, while a minimal effective dose remains unclear.

Conclusions: Colorectal cancer can be prevented in general population through dietary and lifestyle interventions, and aspirin may be a good choice of chemoprevention agent among high risk individuals.

Key Words: Colorectal cancer (CRC); dietary; lifestyle; prevention; chemoprevention; aspirin; high risk individuals; meta-analyses

Introduction

Colorectal cancer (CRC) is among the most commonly diagnosed cancers, with about 1 million new cases and 600,000 deaths worldwide each year (1). Incidence rates vary markedly around the world, with the highest incidence in Australia and New Zealand, Europe and North America, and the lowest in Africa and South-Central Asia (*Figure 1*) (2). Because of the high incidence of colorectal cancer in Western countries, it is commonly regarded as a Western life-style disease. However, the incidence rates have been increasing in economically transitioning countries, including Eastern European countries, most parts of Asia, and select countries of South America (3).

The majority of CRCs are sporadic rather than familial, despite the striking increase in incidence that results from the form of the disease associated with inherited susceptibility (e.g., hereditary non-polyposis colon cancer, HNPCC, and familial adenomatous polyposis, FAP). The role of diet and lifestyle factors has long been suspected and investigated in CRC development, with specific dietary constituents, in addition to excessive caloric intake, weight gain, physical inactivity, smoking, and heavy alcohol intake all thought to result in elevated risk (4,5). The differences in rates by country, and elevated risk among immigrants from a low- to high-risk country (6), support that environmental factors are important in CRC risk. In one study, it was estimated that dietary factors contributed to nearly 50% of all CRC cases diagnosed, while the attributable risk was only about 10% for family history (7). Therefore, a healthy diet and lifestyle are seen as essential in primary prevention of CRC (8), and this review aims to summarize the most up-to-date evidence for these modifiable risk factors. With respect to additional risk modifying interventions,
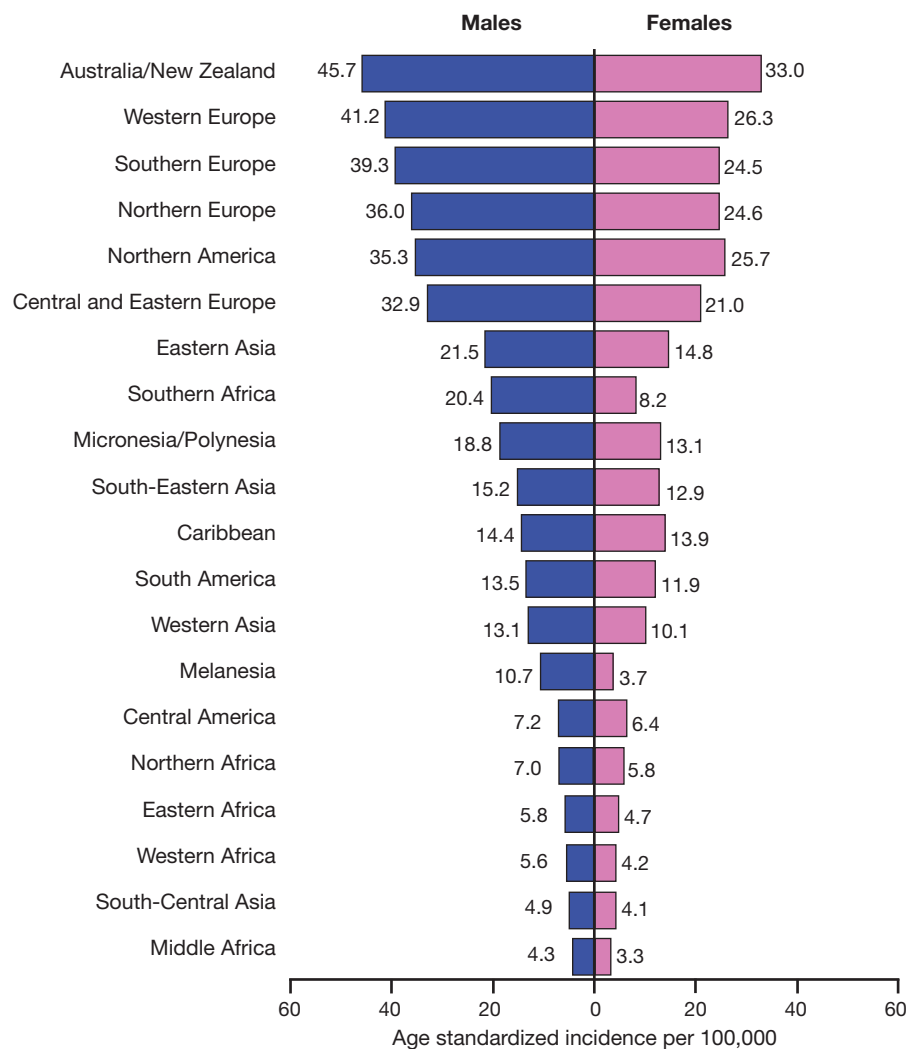
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Males | Females

Region	Males	Females
Australia/New Zealand	45.7	33.0
Western Europe	41.2	26.3
Southern Europe	39.3	24.5
Northern Europe	36.0	24.6
Northern America	35.3	25.7
Central and Eastern Europe	32.9	21.0
Eastern Asia	21.5	14.8
Southern Africa	20.4	8.2
Micronesia/Polynesia	18.8	13.1
South-Eastern Asia	15.2	12.9
Caribbean	14.4	13.9
South America	13.5	11.9
Western Asia	13.1	10.1
Melanesia	10.7	3.7
Central America	7.2	6.4
Northern Africa	7.0	5.8
Eastern Africa	5.8	4.7
Western Africa	5.6	4.2
South-Central Asia	4.9	4.1
Middle Africa	4.3	3.3

60 40 20 0 20 40 60
Age standardized incidence per 100,000

Figure 1 Age-standardized colorectal cancer incidence rates by sex and region of the world. Source: Jemal *et al*. Global cancer statistics. CA Cancer J Clin 2011;61:69-90

chemoprevention has been a major goal in cancer, and colorectal cancer is seen as amenable to this approach through safe and cost effective agents. We also summarize evidence to date on chemoprevention of CRC.

This review evaluated and summarized scientific evidence on dietary, lifestyle, and chemo-prevention of colorectal cancer. We searched the PubMed database for studies published in English, for key epidemiological studies and animal studies, large case-control and cohort studies, randomized controlled trials (RCTs), and meta-analyses of studies of these different types in humans, with particular focus on studies from the past decade. We summarized the findings in the text and listed key points in *Table 1* by level and source of evidence.

Dietary and nutritional components

Red meat

Whether red meat is a culprit in causing CRC has been the subject of scientific debate. Extensive evidence suggests that long-term consumption of red meat or processed meats may increase CRC risk (9-11). A recent meta-analysis of 21 prospective studies showed that consumption of red and processed meats was associated with elevated CRC risk [relative risk, RR=1.22, 95% confidence interval (CI), 1.11-1.34, contrasting the highest versus lowest quartiles of intake], with a linear increase of CRC (RR=1.14, 95% CI, 1.04-1.24) associated with every 100 g/day increase of meat intake until a plateau was encountered at 140 g/day (12).

Table 1 Summary of evidence on diet and lifestyle risk factors for colorectal cancer

		Source of evidence	Summary points
Convincing/rather consistent	Red meat	Meta-analysis of observational studies (mostly prospective studies)	Red and processed meat intake significantly increase CRC risk by ~20%, contrasting highest *vs.* lowest intake, with a dose-response relationship until 140 g/day; association is strong in men; frequency of consumption may matter more than total amount consumed; avoid burned meat
	Vitamin B6	Meta-analysis of prospective studies	Vitamin B6 intake (statistically nonsignificant) and blood PLP levels (statistically significant) were inversely associated with CRC risk
	Garlic	Small randomized trial	Significant suppression of adenoma in CRC patients with 12-mo high-dose of aged garlic extract; 29% reduction in developing new adenoma
		Meta-analysis of observational studies	Approximately 30% reduction in CRC risk, contrasting high *vs.* low (16 g/wk average difference across studies) consumption of garlic
	Magnesium	Meta-analysis of large cohort studies	10% risk reduction contrasting the highest *vs.* lowest category of magnesium intake, with dose response
	Alcohol	Meta-analysis of 60 observational studies	Significant increase in CRC risk with dose-response; 21% risk increase for moderate drinkers (2-3 drink/d) and 52% risk increase for heavy drinkers (4+ drink/d), compared to never drinkers
	Obesity	Meta-analysis of 31 observational studies	CRC risk increases by 7% (4-10%) with a 2 kg/m^2 increase in BMI; CRC increases by 4% (2-5%) with a 2-cm increase in waist circumference
	Physical activity	Meta-analyses of observational studies	Approximately 20% risk reduction, contrasting physically active individuals *vs.* inactive
	Smoking	Meta-analyses of 100+ observational studies	18% risk elevation contrasting smokers *vs.* nonsmokers, with dose-response; Risk may reduce immediately following cessation of smoking
	Hormone replacement therapy	Meta-analysis of observational studies	A 33% risk reduction for recent users, compared to nonusers; Protective effect may be short lived and disappear following cessation of use
		Randomized trial	A 44% reduced CRC risk (95% CI, 19-62%), comparing the E+P arm *vs.* placebo arm
Probable/less consistent	Fruit and vegetables (Dietary fiber)	Observational studies	Many reported an inverse association but a few large cohort studies reported null association
		Meta-analysis of large cohort studies	Inconsistent. The inverse association is weak, about ~10% risk reduction
		Randomized trial	No association
	Fruit and vegetables (folate)	Case-control study	Minimal essential serum folate should be above 8.0 ng/mL for reduced risk of developing colorectal adenoma
		Cohort studies	Approximately 40% risk reduction contrasting highest *vs.* lowest quartile of intake; both long- and short-term intake may reduce risk
		Meta-analysis of randomized or pseudo-randomized trials	Evidence inconsistent; most meta-analyses reported null results
	Fish and Omega-3 fatty acids (FA)	Longitudinal cohort study	(Omega-3 FA) Significant risk reduction over 22-year follow-up
		Observational studies	(Fish) Evidence inconsistent
		Meta-analysis of observational studies	(Fish) A significant 12% reduction in CRC risk contrasting highest *vs.* lowest fish consumption
		Randomized trial	(Fish) No marked change of apoptosis and mitosis within the colonic crypt with 6-mo intervention with oil-rich or lean fish

Table 1 (*continued*)

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Table 1 (continued)

		Source of evidence	Summary points
Probable/ less consistent	Selenium	Randomized trial	Selenium supplementation reduced CRC risk but results were attenuated and insignificant after additional years of follow-up
		Meta-analysis of observational and clinical trials	No association in women but significant inverse association in men
	Dairy/ calcium	Meta-analysis of observational studies	Inverse association, reduced risk with greater intake
		Meta-analysis of randomized trials	Inverse association among individuals with a history of adenomas, but no association otherwise
	Vitamin D	Meta-analysis of longitudinal studies	Inverse association yet studies were limited to small sample sizes

Another meta-analysis of 25 prospective studies that same year found the association was similar by tumor site (colon cancer: RR=1.11, 95% CI, 1.03-1.19, and rectal cancer: RR=1.19, 95% CI, 0.97-1.46) but differed between men (RR=1.21, 95% CI, 1.04-1.42) and women (RR=1.01, 95% CI, 0.87-1.17) (13). Another meta-analysis of both cohort and case-control studies (22 in total) reported that the frequency of red meat consumption rather than total amount of consumed meat is associated with a higher CRC carcinogenesis (14). In addition, the processing method may matter. Very well-cooked meat or meats cooked in direct contact with flames were reported to raise the CRC risk, which may be explained by the carcinogenic heterocyclic amines produced during cooking (15,16). Other plausible biological mechanisms include endogenous formation of nitroso compounds in the gastrointestinal tract by red meat intake, but not by white meat intake (17).

Fruit and vegetables (fiber and folic acid)

Many observational studies have reported an inverse association between dietary fiber and CRC risk, with a relative reduction of up to 40% (18-22), although a few large cohort studies reported small, statistically null associations (23-25). A large pooled analysis of thirteen prospective cohorts suggested that dietary fiber intake was inversely associated with CRC risk in age-adjusted analyses, but no association remained after accounting for other dietary risk factors, including red meat, alcohol, folate, and total milk (26). A recent meta-analysis reported a dose-response analysis indicating that for each 10 g/day total dietary fiber, the relative risk of developing CRC was 0.90 (95% CI, 0.86-0.94) (27). However, two randomized trials

found that high dietary fiber did not affect the recurrence of colorectal adenoma (28,29).

Dietary folate or folic acid (from dietary supplements and food fortification) is necessary to synthesize, repair and methylate DNA. It is especially important during periods of rapid cell division and growth such as pregnancy and infancy. Folate is also thought to help prevent changes to DNA that may lead to cancer, and its rule in CRC carcinogenesis has been extensively studied. Humans cannot synthesize folate de novo, and therefore folate has to be supplied through diet to meet their daily requirements, with fresh fruits and vegetables being the major sources. There are growing data and a continuing controversy over the effect of folic acid supplementation on cancer risk. Both the Nurse's Health Study and secondary analysis from the Wheat Bran Fiber randomized trial reported that high dietary folate was associated with 40% reduced risk of colorectal adenoma (highest *vs.* lowest quartile) (30,31). The Nurses' Health Study and Health Professionals Follow-Up Study further suggested that both long- and short-term intakes of total folate were associated with a lower risk of colorectal adenoma (32). With respect to dose, one case-control study based on suspected patients undergoing screening reported that the minimal essential serum folate concentrations should be above 8.0 ng/mL for reducing risk of developing colorectal adenoma (33). One meta-analysis summarized 3 randomized or pseudo-randomized trials and concluded that folate status was inversely related to the risk of developing CRC (34); however, a recently published larger meta-analysis of 15 randomized trials reported that folic acid supplementation has no significant effect on CRC risk (35). A meta-analysis of 3 large randomized trials of folic acid supplementation

among patients with an adenoma history also reported no association (36).

Garlic

Garlic is characterized by a high content in organo-sulfur compounds and flavonoids. The allyl sulfur constituents in garlic comprise about 1% of its dry weight and are responsible for its health benefits (37,38). Garlic also contains other constituents such as flavonoids and selenium that are considered to have antioxidant properties and anticarcinogenic activity. Preclinical investigations provide convincing evidence that garlic and related sulfur-containing compounds inhibit carcinogen-induced tumors in various organs (39). One RCT conducted within a small sample of 37 patients with CRC found (I) a significant suppression in both the total size and number of adenomas in CRC patients after 12-mo of high-dose aged garlic extract (40), and (II) a 29% reduction in developing at least one new adenoma (41). A meta-analysis of 4 case control and 3 cohort studies confirmed the inverse association between garlic intake and CRC risk, with an approximate 30% relative reduction in incidence contrasting high vs. low (16 g/wk average difference across studies) consumption of garlic (42).

Fish and Omega-3 fatty acids

Long-chain n-3 fatty acids have been suggested to play a protective role in colorectal cancer development in laboratory and animal studies, with the mechanism of action conjectured to be inhibition of the cyclooxygenase-2 (COX-2) enzyme and the production of arachidonic acid (n-6) derived eicosanoids (40-42). A long-term prospective study of U.S. men reported a significantly reduced CRC risk contrasting the highest versus lowest quartiles of n-3 fatty acids (odds ratio, OR=0.74, 95% CI, 0.57-0.95) (43). Fish is the main dietary source of the long-chain n-3 fatty acids. Some observational studies found an inverse association between fish consumption and CRC risk (10,43-45), while others did not (46-48). A recent meta-analysis pooled data from 22 cohort and 19 case-control studies, and reported a 12% (OR=0.88, 95% CI, 0.80-0.95) reduction in CRC risk contrasting highest vs. lowest fish consumption (49). However, a multi-center, randomized controlled trial investigated the effect of 6-month intervention with oil-rich or lean fish on apoptosis and mitosis within the colonic crypt, and found no marked change in these endpoints (50).

Vitamin B6

Vitamin B6 is widely distributed in foods, with good sources including meats, whole grain products, vegetables, nuts and bananas. Vitamin B6 is involved in almost 100 enzymatic reactions, among which one function involves transferring 1-carbon groups for DNA synthesis and methylation (51). Therefore, vitamin B6 deficiency may increase CRC risk through aberrations in DNA synthesis, repair, and methylation. Vitamin B may also suppress colorectal carcinogenesis by reducing cell proliferation, angiogenesis, oxidative stress, inflammation, and nitric oxide synthesis (52,53). A meta-analysis summarized evidence from prospective studies, with 9 studies on vitamin B6 intake and 4 studies on blood pyridoxal 5'-phosphate (PLP, the principal active coenzyme form of vitamin B6) levels, in relation to CRC risk. The pooled RRs of CRC contrasting highest vs. lowest category of vitamin B6 intake and blood PLP levels were 0.90 (95% CI, 0.75-1.07) and 0.52 (95% CI, 0.38-0.71), respectively (54).

Dairy, calcium and vitamin D

In vitro and in vivo studies have suggested that high dietary intake of calcium and vitamin D may reduce CRC risk by a variety of mechanisms, such as reducing epithelial cell exposure to toxicity, inhibiting proliferation of intestinal mucosa and epithelial cells via the intracellular action of calcium (55); Vitamin D's protective effect against colorectal neoplasia is by reducing epithelial cell proliferation (56). There have been numerous epidemiological studies on calcium and CRC risk, as well as studies on vitamin D and CRC risk. However, there remains a lack of clarity of the effects on CRC of both these dietary components, due to inconsistent findings among numerous epidemiological studies and multiple pooled analyses. Overall, results from observational studies found calcium intake to be not associated with a substantially lower CRC risk (57,58) particularly for the more reliable large prospective studies (57). A meta-analysis of summarizing a large number of observational studies mostly supported an inverse association for both calcium and milk/dairy products (a rich source of both calcium and vitamin D) (59,60). The evidence from randomized trials only shows a protective effect of calcium on adenoma recurrence among individuals with a history of adenomas (RR=0.80, 95% CI, 0.69-0.94) for

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those receiving calcium 1,200 to 2,000 mg/d, but no effect in general populations (RR=0.62, 95% CI, 0.11-3.40) (59). It should be noted that the statistical power in the two clinical trials conducted in general populations is limited (59).

In 1980, Garland hypothesized that lower levels of vitamin D resulting from weaker UV-B radiation at higher latitudes may account for the striking geographical pattern of CRC mortality (60). The evidence from epidemiologic studies are limited to small sample sizes, yet in general found vitamin D inversely associated with CRC risk (57,61-64). Meta-analyses of longitudinal studies reported a 50% lower CRC risk associated with a serum 25(OH)D level ≥33 ng/mL, compared to ≤12 ng/mL (65), or an OR of 0.57 (95% CI, 0.43-0.76) for an increase of 25(OH)D by 20 ng/mL (66).

Selenium

As an essential trace element involved in different physiological functions in the human body, selenium has received increasing attention as a possible cancer prevention substance, through several possible mechanisms for the potential anticarcinogenic effects including apoptosis (67), protection from oxidative DNA damage (68), and increased immune function (69). However, the epidemiologic evidence on associations between selenium and CRC risk has been mixed, inconclusive and limited to small studies. Many observational studies support a protective effect of selenium on CRC risk (70-72) but not consistently (73,74). A meta-analysis of 12 observational studies and 2 clinical trials reported no association between selenium and CRC risk in women, but an inverse association in men (OR=0.68, 95% CI, 0.57-0.82) (75). There was a large randomized trial on selenium supplementation for skin cancer prevention, and the secondary analysis showed a 58% reduction (95% CI, 0.18-0.95) in CRC incidence among participants randomly assigned to take selenium (200 μg daily) (76), although the results were attenuated and no longer statistically significant after additional years of follow-up (77). A pooled analysis of 3 randomized trials on various nutritional interventions for CRC prevention reported a pooled OR of 0.66 (95% CI, 0.50-0.87), contrasting participants of highest *vs.* lowest blood selenium values (78). Yet, none of these trials were designed to test selenium as an intervention, and all participants were at high adenoma risk after recent colonoscopic adenoma resection (79).

Magnesium

Magnesium is abundant in many foods, and particularly rich in spices, nuts, cereals, coffee, cocoa, tea and green-leafy vegetables. Magnesium is involved in a wide variety of biochemical reactions that modulate key cell functions, and has a crucial role in genomic stability and DNA synthesis (80). Epidemiologic studies suggested that magnesium may be associated with a decreased CRC risk but the findings are inconsistent. A meta-analysis of 8 prospective studies containing 338,979 participants and 8,000 CRC cases reported a summary RR of 0.89 (95% CI, 0.79-1.00) for the highest *vs.* lowest category of magnesium intake, with evidence of a dose-response (81).

Dietary pattern, obesity and related mechanisms

Dietary pattern summarizes the total diet or the key dietary components including food items, food groups, and nutrients (82), and may provide additional insights with the combined effects of many food components. Summarized epidemiologic evidence suggest that healthier pattern consisting of greater intakes of fruits and vegetables, and lower intakes of red and processed meat, appeared protective against colorectal adenoma and cancer incidence, while a less healthy pattern characterized by higher intakes of red and processed meat, as well as potatoes and refined carbohydrates, may increase risk (83). There has also been great interest in total dietary consumption and its consequences, specifically obesity, in relation to colorectal and other cancers (84). Because these risks are modifiable, these pathways are seen as key in cancer control efforts (85). Colon cancer is among those specifically identified as linked to obesity; for example, two large prospective cohort studies have demonstrated that being obese [body mass index (BMI) >30 kg/m^2] confers a 1.5-fold greater risk of developing colon cancer relative to individuals of normal weight (BMI 18.5-24.9 kg/m^2) (86,87). With respect to mortality, the Cancer Prevention Study II, which prospectively followed more than 900,000 US adults, similarly found a 1.5- to 1.8-fold increased risk of colon cancer related death for obese individuals, reflecting the increased incidence of and perhaps the increased mortality from colon cancer once diagnosed (88). A meta-analysis of 31 observational studies reported that for a 2 kg/m^2 increase in BMI, the CRC risk increased by 7% (95% CI, 4-10%), and for a 2-cm increase in waist circumference, the risk increased by 4% (95% CI, 2-5%) (89). Another meta-

analysis showed that the inverse association between BMI and CRC risk was stronger for colon than rectal cancer, and for men than women (90). Some recent research probing obesity pathways concern the issue of 'secondary prevention' after diagnosis and treatment of early stage disease. Following earlier studies by Meyerhardt *et al.* (91) and Dignam *et al.* (92), which found excess risk of both cancer recurrence and overall mortality among obese patients utilizing large participant cohorts from multicenter clinical trials for stage II and III colon cancer, subsequent studies turned to elucidating the role of dietary constituents among colon cancer patients. The first of these studies examined the 'Western' diet pattern characterized by relatively high red and processed meats, refined grain, and sugar content, and indicated that those with higher consumption of these components experienced significantly elevated recurrence and mortality risk (93). A more recent study more closely examined the Western diet and the role of dietary glycemic measures (94). This study found that high carbohydrate intake and glycemic load significantly increased recurrence and mortality. These effects were present among all body types but strongest among those who were overweight or obese. In relation to CRC risk, the Western dietary pattern has previously been reported to be associated with an elevated CRC incidence (95). However, the Women's Health Initiative Dietary Modification Trial, a large randomized trial conducted in postmenopausal women, suggested that a low-fat dietary pattern intervention did not reduce CRC risk during 8 years of follow-up (96).

This work relates to a large body of research focused on potential mechanisms by which obesity leads to higher colon cancer incidence. One prominent theme involves metabolic and insulin related pathways (97-104). Insulin, insulin-like growth factors (IGF), and IGF binding proteins have all been causatively implicated for colon cancer via mitogenic effects on the colonic mucosa and other mechanisms. In a prospective nested case-control study within the Physicians' Health Study, Ma *et al.* (101) found that men in the highest quintile for IGF-1 had a 2.5 increased risk of colorectal cancer compared to the lowest quintile. Among women, an analysis of the Nurse's Health Study cohort found a comparable >2-fold for those in the highest quartile of IGF-1 compared with those in the lowest (102). That study, as well as investigations by Kaaks *et al.* (103) and a more recent study by Ma *et al.* (104) also observed that colorectal cancer risk increased with increasing levels of C-peptide (a marker of insulin production). Interestingly, reduction in IGF exposure via increased presence of its binding protein

was found to significantly reduce colon cancer mortality among affected individuals in a large cohort study (105). This particular pathway represents but one of numerous putative links linking cancer and obesity (84).

Obviously, a critical component of obesity is physical activity. The association between physical activity and CRC risk is well established, with the majority of relevant studies finding physically active individuals benefit from substantial risk reduction (approximately 20%) comparing to the sedentary ones, confirmed by two meta-analyses (106,107). The evidence is strong and consistent for both proximal colon and distal colon cancers with a similar magnitude (107). The main challenge is disentangling the direct effects of physical activity from strongly related factors such as obesity and comorbidities that may influence outcomes. Randomized intervention trials have been completed with positive findings, and others are underway; these studies have been mostly focused on colorectal cancer survivors (clinical event reduction) or biomarkers (prevention studies) for practical reasons (108-110).

Other common lifestyle exposures

Alcohol

Alcohol consumption is one of the most important known causes of human cancer, possibly through genotoxic effect of acetaldehyde (111) and interference of folate absorption by alcohol (112). The most recent meta-analysis pooled data from 27 cohort and 34 case-control studies, and reported significantly increased CRC risk with a dose-response relationship (113): comparing to never drinkers, moderate drinkers who consume 2-3 drinks per day have 21% increased CRC risk and heavy drinkers who have 4 or more drinks per day have 52% increased CRC risk. These results are consistent with other pooled analyses, with increased risk observed for both colon and rectal cancers (114-116).

Smoking

Cigarette smoking has been shown to cause many nonpulmonary cancers with no direct tobacco-related carcinogens, yet the association between smoking and CRC remains controversial. A meta-analysis of 106 observational studies estimated that cigarette smokers are 1.18 times (95% CI, 1.11-1.25 times) more likely to develop CRC compared to those who never smoke, with evidence of a dose-response (117). Another meta-analysis of 36 studies

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reported that duration and age of initiation were also significantly associated with CRC incidence (118). A recent study reported that the excess CRC risk due to smoking decreased immediately after quitting for proximal colon and rectal cancer, but not until about 20 years post-quitting for distal colon cancer (119).

Hormone replacement therapy (HRT)

Estrogen/progestin replacement therapy is prescribed to control postmenopausal symptom or to prevent hormone deficiency-related diseases such as osteoporosis. Existing evidence shows that HRT is associated with lower CRC risk, yet the mechanism remained unclear. Case control studies have shown significant reduction in CRC risk among ever users (120,121). Large cohort studies suggested a modest risk reduction among ever users (122), but there was a lack of dose-response relationship (123). Also, the association was found stronger among women aged 65+, with a body mass index <30 and who regularly use aspirin or ibuprofen (124). A meta-analysis concluded that recent HRT users had a 33% reduction in CRC risk (pooled RR=0.67, 95% CI, 0.59-0.77) but no association was observed with ever use of HRT and duration of use did not matter (125). Other studies also supported that the protective effect of HRT is short-lived and disappears following cessation of use (124). The Women's Health Initiative trial found that women who took estrogen plus progestin had 44% reduced risk (95% CI, 19-62%) of colorectal cancer compared to women who took placebo but colorectal cancers in the estrogen plus progestin group were at a more advanced stage (126). The Women's Health Initiative trial later reported that there was no significant difference in colorectal cancer incidence between the estrogen-only and placebo arms (127).

Chemoprevention of colorectal cancer

Prevention of colorectal cancer and its precursor conditions via some substance or compound, or chemoprevention, offers great potential if the intervention is safe and cost-effective. The main focus of these has not been nutritional, but rather medicinal agents with reasonably safe adverse event profiles. For more than two decades, accumulating evidence from observational studies (128-133) and large randomized trials (134-137) suggests that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) protect against the development of colonic adenomas and CRC, and reduces disease recurrence (136-139). Meta-

analysis of 17 case-control studies showed an inverse association between regular use of aspirin and reduced CRC risk (pooled OR=0.62, 95% CI, 0.58-0.67), while the association was weaker in cohort studies presumably due to substantial variation between studies in measuring aspirin exposure (140). Evidence from randomized trials has not been consistent. Two trials conducted among patients with a history of CRC or adenomas showed that low-dose aspirin has a chemopreventive effect on new adenomas (136,137). Yet among healthy individuals, two earlier large trials of low-dose aspirin (the Physicians' Health Study and the Women's Health Study) showed no effect on CRC incidence during 10-year follow-up, possibly due to an insufficient dose (134,141,142). Recent long-term follow-up of four aspirin trials (Primary: Thrombosis Prevention Trial, British Doctors Aspirin Trial; Secondary: Swedish Aspirin Low Dose Trial, UK-TIA Aspirin Trial) showed a reduction of 50% in CRC risk after five or more years of regular consumption with a dosage of at least 75 mg daily (75-300 mg) (143). Aspirin has emerged as the most likely NSAID for use in chemoprevention because of its known cardiovascular benefit and available safety and efficacy data (144). Other traditional NSAIDs, particularly selective COX-2 inhibitors such as celecoxib, have been shown to cause regression of adenomas in familial adenomatous polyposis, and are now given to patients at high risk of CRC (138,139), and yet cannot be routinely recommended concerning potential cardiovascular events. The Colorectal Adenoma/carcinoma Prevention Programme (CAPP) was launched in 1990, with CAPP1 investigating familial adenomatous polyposis in 200 young adults and CAPP2 being the first large-scale genetically targeted chemoprevention trial in 1,000 adults with HNPCC (also known as Lynch syndrome). The CAPP2 randomized trial reported that 600 mg aspirin per day for a mean of 25 months substantially reduced CRC incidence among carriers of hereditary CRC (145). However, the minimum dose of aspirin to achieve the protective effect is still uncertain and will be the objective of a new CAPP trial in Lynch Syndrome. The underlying mechanism of NSAIDs inhibiting carcinogenesis remains inconclusive, with proposed explanations as increased apoptosis and impairment of tumor cell growth by inhibition of cyclooxygenase-2 (COX-2) (146).

The side-effects of NSAIDs are well documented and mainly attributed to inhibition of COX activity. The most frequently reported serious adverse events associated with aspirin use are related to gastrointestinal bleeding, even

with low-dose aspirin (147). Comparing to other NSAIDs, aspirin has lower risk of occlusive cardiovascular events, yet the dose-dependent risk of bleeding complications with aspirin intake may limit its potential for primary prevention of CRC (148). In additional to optimal dose, optimum treatment duration and age of initiation also remained uncertain (144). Concerning risk and benefit, the United States Preventive Services Task Force recommended against the routine use of aspirin for CRC prevention in 2007 (149). However, the 2011 pooled analysis with 8 randomized controlled trials showed that daily aspirin for 5-10 years reduced 5-year cancer mortality by 34% (P=0.03) and a 20-year cancer mortality by 20% (P<0.001) (150). Considering the bleeding complications are not life-threatening, the risk-benefit of aspirin use in CRC prevention requires a formal re-evaluation. As toxicity of aspirin largely depends on dosage, the minimal effective dose required for CRC prevention is critical (151).

Conclusions

It has been estimated that dietary factors account for nearly half of all colorectal cancer cases, and therefore diet and lifestyle are key intervention points in primary prevention. This review summarized and updated the relevant epidemiologic evidence for dietary constituents and other modifiable factors, some of which are likely correlated with diet behavior. There is convincing, or moderately convincing and rather consistent, evidence that intakes of garlic, vitamin B6 and magnesium, maintaining a healthy weight and waist via both diet and exercise, and avoiding or reducing red meat, alcohol, and smoking, may significantly protect against developing colorectal cancer. There is high quality yet less consistent evidence for the following dietary components: fruit and vegetable intake (fiber and folate), fish and Omega-3 fatty acids, selenium, dairy, calcium and vitamin D. For high risk populations for whom dietary and lifestyle interventions may not be sufficient for primary prevention, aspirin and other chemoprevention agents may be considered, although the minimal effective dose remains unclear. Ongoing studies may shed light on additional safe interventions that can reduce colorectal cancer and will likely have other health benefits.

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