Primary Prevention of Colorectal Cancer

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Abstract

Colorectal cancer has been strongly associated with a Western lifestyle. In the past several decades, much has been learned about the dietary, lifestyle, and medication risk factors for this malignancy. Although there is controversy about the role of specific nutritional factors, consideration of the dietary pattern as a whole appears useful for formulating recommendations. For example, several studies have shown that high intake of red and processed meats, highly refined grains and starches, and sugars is related to increased risk of colorectal cancer. Replacing these factors with poultry, fish, and plant sources as the primary source of protein; unsaturated fats as the primary source of fat; and unrefined grains, legumes and fruits as the primary source of carbohydrates is likely to lower risk of colorectal cancer. Although a role for supplements, including vitamin D, folate, and vitamin B6, remains uncertain, calcium supplementation is likely to be at least modestly beneficial. With respect to lifestyle, compelling evidence indicates that avoidance of smoking and heavy alcohol use, prevention of weight gain, and the maintenance of a reasonable level of physical activity are associated with markedly lower risks of colorectal cancer. Medications such as aspirin and non-steroidal anti-inflammatory drugs and post-menopausal hormones for women are associated with significant reductions in colorectal cancer risk, though their utility is affected by associated risks. Taken together, modifications in diet and lifestyle should substantially reduce the risk of colorectal cancer and could complement screening in reducing colorectal cancer incidence.

Introduction

In the United States, colorectal cancer is the third leading cause of cancer death in each sex and second overall in men and women combined. In 2009, an estimated 146,970 men and women will be newly diagnosed with colorectal cancer; 49,920 deaths will be attributable to the disease. At current rates, approximately 5%–6% of individuals will develop a cancer of the colon or rectum within their lifetime. Before the 1900s, colorectal cancer was relatively uncommon in the U.S., but its incidence rose dramatically over the last century in parallel with economic development. Worldwide, the majority of colorectal cancers continue to occur in industrialized countries, although incidence rates are rapidly rising in less-developed nations.
as they increasingly adopt features of a Western lifestyle. Migration studies also demonstrate a higher lifetime incidence of colorectal cancer among immigrants to high-incidence, industrialized countries compared to residents remaining in their native, low-incidence countries. Taken together, these data highlight the importance of environmental influences on colorectal carcinogenesis.

In this review, we provide an overview of the epidemiological evidence supporting the roles of diet, lifestyle, and medication use in colorectal cancer risk. Moreover, we focus on those risk factors that are potentially modifiable, including overall dietary patterns, avoidance of smoking, excessive alcohol, weight gain, maintenance of a reasonable level of physical activity, and use of aspirin. The cornerstones of colorectal cancer prevention are screening and detection of adenomatous polyps. However, improving our understanding of the modifiable risk factors might inform additional primary prevention strategies that can further reduce risk. In addition, because many of the diet and lifestyle characteristics that are related to colorectal carcinogenesis appear to be important for other major chronic diseases, adopting the appropriate changes to these risk factors are likely to improve overall health.

DIET

Fruit, Vegetables, and Fiber

The concept that a diet that is high in fiber, especially from fruits and vegetables, lowers risk of colorectal cancer has been in existence for more than 4 decades, following the observation of the relative rarity of colorectal cancers in African populations that consume a high-fiber diet. Fiber has been proposed to dilute or adsorb fecal carcinogens, modulate colonic transit time, alter bile acid metabolism, reduce colonic pH, or increase the production of short-chain fatty acids. Subsequently, the relation between colorectal cancer and fiber, as well as fruits and vegetables more generally, has been evaluated in case-control and cohort studies. The majority of case-control studies have shown an association between higher intake of fiber, vegetables, and possibly fruits, and lower risk of colon cancer. A meta-analysis of 6 such case-control studies found that a high intake of vegetables or fiber was associated with an approximate 40% to 50% reduction in risk for colon cancer. Similarly, a pooled analysis of 13 case-control studies reported an approximately 50% lower risk of colon cancer associated with higher intake of fiber. However, as case-control evidence for the fiber hypothesis appeared to be consolidating, results from large prospective cohort studies emerged that showed a nonexistent or weak association between dietary fiber intake and colon cancer. In data from a prospective study conducted among the female U.S. nurses enrolled in the Nurses’ Health Study (NHS), we found that a high-fiber diet, measured by a semi-quantitative validated food frequency questionnaire, did not protect against colorectal cancer or adenoma. Furthermore, no associations were observed with specific subtypes of fiber, including cereal, fruit, or vegetable fiber or subtypes of cancer by location or stage. We also found null results in a detailed analysis of fruit and vegetable intake and colorectal cancer risk in this cohort. Similarly, in a Finnish population with a wider range of fiber intakes (16.0 to 34.1 g/day between the lowest and highest quartiles), an inverse association between colorectal cancer and total fiber intake was not seen. Recently, a pooled analysis of 13 prospective cohorts including over 700,000 participants did show a modest, inverse association between fiber intake and colorectal cancer. However, after accounting for other dietary risk factors, this association was no longer significant, suggesting that high fiber intake might simply have been correlated with other protective lifestyle or dietary factors. A pooled analysis of fruit and vegetable intake also failed to detect an association with overall colorectal cancer risk.
The reasons for the apparent inconsistencies between the encouraging results from case-control studies and the largely null findings of cohort studies are not entirely clear. However, case-control studies may be more prone to bias because dietary information was collected after the diagnosis of cancer and individuals with cancer are more likely to recall perceived unhealthy dietary behaviors. Of note, a recent prospective study of over 500,000 individuals from 10 European populations (the EPIC study) did show an approximately 40% reduced risk of colorectal cancer among individuals with the highest intake of fiber.18 Similarly, in this population, high intake of fruit and vegetables was associated with a modest reduction in colorectal cancer risk.19 The reason for the discordance between the inverse association found between fiber and colorectal cancer in the European studies and the lack of association in other cohort studies that were primarily conducted in the U.S. might be related to differences in intake of other nutrients such as folate; folate could have anti-cancer effects (see section on B vitamins). In the U.S., the high prevalence of use of folate-containing multivitamins and the folate fortification of flour and breakfast cereals, (at least since 1998 when fortification became mandatory), might attenuate any additional effects of high-fiber fruits and vegetables, the primary source of these folate in the European populations. So, whereas fruits, vegetables, and fiber might influence colorectal cancer risk, these effects, if present, are likely to be much weaker than previously believed or may only be evident among individuals with extremely low baseline levels of intake.

To specifically address the role of fiber and vegetables in cancer prevention, several randomized, placebo-controlled intervention trials of fiber supplementation on risk of recurrent adenomas among individuals with a prior history of adenoma have been conducted. Diets with large amounts of fruits and vegetables,20 wheat bran fiber supplements,21 or ispaghula fiber supplements,22 were each found to have no effect on the risk of recurrent adenoma. In fact, ispaghula husk was associated with an unexpected increased risk of adenoma. Although it has been proposed that these trials were null due to an inadequate dose of fiber, it is unlikely that larger amounts would be well tolerated. For example, in the wheat bran supplement trial, only 74% of the high-fiber group consumed more than 75% of their supplement compared to 84% of the low-fiber group. Thus, daily, long-term consumption of higher levels of fiber probably would be impractical in the general population.21 These data, when viewed in the context of most prospective epidemiologic studies, raise questions about not only the ability of fiber supplements to reduce risk of colorectal cancer but the feasibility of such an approach.

Finally, resistant starch has been hypothesized to have specific anti-cancer properties since this form of fiber is preferentially fermented into potentially beneficial short-chain fatty acids in the colon. In preclinical models, animals fed resistant starch have a lower incidence of intestinal tumors.23, 24 In humans, resistant starch reduces cell proliferation in the upper part of the colonic crypts, 25 and some epidemiological studies have supported an inverse association between resistant starch intake and colorectal neoplasia.26 However, a recent multi-center randomized control trial of resistant starch at a dose of 30 g/day conducted among European individuals with Lynch syndrome failed to observe a significant reduction in risk of neoplasia after 4 years of follow-up.27 Although higher amounts of resistant starch could conceivably be required to observe a protective effect, this dose of resistant starch was already more than three times higher than typical intake. Moreover, the overall compliance rate for this level of intake was already limited (77%), again suggesting that higher dosing may not be feasible. Longer term follow-up and further studies of resistant starch among patients without Lynch syndrome are needed.

In summary, increasing intake of fruits, vegetables, or fiber is unlikely to prevent a large proportion of colorectal cancers, particularly among a U.S. population, which has a food supply already fortified with folate and other dietary factors that might protect against colorectal neoplasia. There is also little evidence that concentrated sources of one type of fiber are
efficacious, though fiber-rich diets have health benefits for other gastrointestinal conditions such as diverticular disease and constipation and possibly other chronic diseases.

**Red Meat, Fat, and Carbohydrates**

The effects of red meat (e.g. beef, pork, or lamb) have been examined in many epidemiologic studies; most, though not all, associate an increase in colon cancer or adenoma risk with greater intake of red meat.10–12, 28–44 In a prospective study of a cohort of U.S. male health professionals, the Health Professionals Follow-up Study (HPFS), we found that men who ate beef, pork, or lamb as a main dish more than 5 times a week had a 3-fold increase in risk of colon cancer, compared with men who ate these meats less than once a month.4 Additional studies have also associated processed meats with risk.40 45–47 In the EPIC study population, the absolute risk of developing colorectal cancer within 10 years for a 50 year old participant was 1.71% for the highest category of red and processed meat intake compared with 1.28% for the lowest category of intake.40 The specific mechanisms that underlie the association between red meat and colorectal cancer are unclear. Red meat might stimulate secretion of endogenous insulin, which is a mitogen (see section on body mass index) (Figure 1). Other relevant hypotheses include red meat as a major source of total or saturated fat, heme iron, or carcinogenic heterocyclic amines. In general, neither case-control or prospective studies have supported a specific association between fat and colorectal cancer.4, 10–12 Although some early studies had indicated an association between heme iron and colorectal cancer,48–51 other studies have not produced consistent results.52–54 In the NHS, prospective assessments of dietary iron intake as well as several biochemical measures of iron status indicated that iron levels were not associated with colorectal adenoma.55

Evidence indicates that the association between red meat and colorectal cancer might be related to the cooking process. Several studies have found that risk of colon cancer is specifically increased among meat eaters who consume meat with a heavily browned surface or meat that has been prepared at high temperatures at prolonged durations.34, 38, 56, 57 When meat undergoes prolonged frying, grilling, or broiling at high temperatures, mutagenic heterocyclic amines are formed from creatinine, and these interact with amino acids.58–60 Specific analyses focused on intake of heterocyclic amines, estimated using dietary indices of meat-associated mutagens, have associated the heterocyclic amines with colorectal adenoma or cancer.38, 61–69 In the HPFS, higher consumption of these mutagens was associated with adenoma of the distal colon, independent of total overall meat intake.70 Similarly, heterocyclic amines, measured using urine or leukocyte assays, have been associated with adenoma in other populations.71, 72 Finally, studies examining interactions between meat intake, cooking methods, and genetic polymorphisms that modulate metabolism of heterocyclic amines also provide indirect, yet compelling support for an association between these carcinogens and colorectal neoplasia.64–66, 73–80 For example, in the NHS, women with genotypes associated with rapid acetylation of meat-associated carcinogens had a particularly high risk of colorectal cancer that was associated with red meat intake (multivariate hazard ratio [HR], 3.01; 95% confidence interval [CI], 1.10–8.18). In contrast, women with genotypes associated with slow acetylation did not have a significantly higher risk of cancer with increased red meat intake (multivariate HR, 0.87; 95% CI, 0.35–2.17).81 Alternative sources of animal protein, including low-fat dairy products, fish, and poultry, have been associated with reduced risk of colon cancer or adenoma, compared with that of red meat, in most, but not all studies.4, 10–12, 29, 30, 39, 82, 83 These results do not support an overall adverse effect of protein intake on cancer risk, and even suggest a reduction in risk. The mechanism that underlies this reduction is unknown, but these foods are good sources of methionine, which could improve the regulation of DNA methylation. In addition, some, but not all, studies have associated sources of animal protein, especially fish, that are high in n-3 fatty acids with reduced risk of colorectal cancer.40, 84–88 Recent data from a large prospective U.S. cohort suggested either a weak or non-existent

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association, with a possible differential effect according to sex. Intake of marine n-3 fatty acids was not associated with colorectal cancer risk among men, but was modestly associated with lower risk among women. However, even this benefit was attenuated after adjustment for other risk factors. A similar potential sex difference was also suggested in a meta-analysis of studies examining fish intake and risk of colorectal cancer. Multiple animals and in vitro studies have shown that n-3 fatty acids reduce inflammation, disrupt activity of the nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX-2), competitively inhibit arachidonic acid metabolism, and induce 15-prostaglandin dehydrogenase (15-PGDH), a physiological COX-2 antagonist. Each of these mechanisms could retard carcinogenesis (see section on aspirin and NSAIDs) (Figure 2). In summary, limiting intake of processed meat and red meat, especially after high-temperature cooking, and replacing these foods with poultry or fish as alternative protein sources could be a reasonable approach to reducing risk of colorectal cancer.

Beyond fats and proteins, there is some evidence associating intake of highly refined carbohydrates with colorectal cancer. Intake of highly refined carbohydrates stimulates short-term surges of insulin secretion, which might stimulate colonic carcinogenesis (see section on body mass index) (Figure 1). Some studies have associated diets with a high glycemic load or glycemic index with risk of colorectal adenoma or cancer. However, many other studies have failed to confirm these associations.

**Calcium and Vitamin D**

Calcium has been proposed to reduce risk of colorectal cancer by binding to toxic secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon, or by directly reducing proliferation, stimulating differentiation, and inducing apoptosis in the colonic mucosa. Large prospective studies have consistently shown a modest and significant inverse association between calcium intake and colorectal cancer risk. In an analysis of cases from the NHS and HPFS, total, dietary and supplemental calcium reduced the risk of distal colon cancer but not of proximal colon cancer. Notably, most of the risk reduction was achieved by attaining intakes of 700 to 800 mg/day, which suggests a threshold level above which further calcium would not be beneficial. In a recent analysis that pooled the results of 10 large, prospective cohort studies, those in the highest quintile of calcium intake had a 22% reduction in risk of colorectal cancer, compared to those in the lowest quintile.

The findings from observational studies have been confirmed in randomized, placebo-controlled trials conducted among patients with a history of adenoma. Results of an intervention trial of calcium supplementation (1200 mg of elemental calcium vs. placebo) among 913 participants found a moderate but statistically significant reduction in risk of recurrent adenoma at 4 years; the rate of new adenomas was 31% among those assigned calcium and 38% among those assigned placebo. In subsequent analyses, the benefit was most pronounced for advanced adenoma, with a risk ratio of 0.65 (95% CI, 0.46–0.93) compared to placebo, and the effect of calcium persisted for at least 5 years after cessation of treatment. Moreover, the protective effect of calcium appeared entirely limited to those with higher 25-hydroxy-[25-(OH)] vitamin D levels. Similar results were observed for 2 g elemental calcium daily versus placebo in a European trial, although the result was not statistically significant in this relatively small study.

In 1980, Garland and Garland proposed that lower levels of vitamin D, resulting from reduced solar ultraviolet-B radiation exposure, could account for the increase in mortality from colon cancer among populations at higher latitudes. Vitamin D could reduce risk of colorectal cancer through various mechanisms, including reducing cell proliferation, inhibiting angiogenesis, promoting cell differentiation, and stimulating apoptosis. Increasing data also indicate an anti-inflammatory mechanism (Figure 2). In animal models of colitis, deficiency of the vitamin D receptor resulted in severe inflammation, whereas vitamin
Vitamin D supplements inhibited colitis and COX-2 expression.\textsuperscript{124–126} In humans, polymorphisms in the vitamin D receptor and vitamin D deficiency have been associated with inflammatory bowel disease,\textsuperscript{127–131} gingival inflammation,\textsuperscript{132} and periodontal disease, a marker for chronic inflammation.\textsuperscript{133} Vitamin D supplements were also associated with a dose-dependent decrease in the inflammatory marker C-reactive protein (CRP) in an intervention study.\textsuperscript{134} It is not clear whether the actions of vitamin D require calcium; calcium-dependent and calcium-independent mechanisms have been proposed.\textsuperscript{110, 111, 119} Several prospective studies have examined circulating levels of 25(OH)-D and found an inverse association with rectal cancer,\textsuperscript{135} colorectal cancer, or adenoma.\textsuperscript{119, 136–143} In a meta-analysis of these studies, based on 535 colorectal cancer cases, individuals with serum levels of 25(OH) \( \geq 33 \) ng/mL (82 nmol/L) had 50\% lower incidence of colorectal cancer (\( p<0.01 \)) than individuals with levels less than 12 ng/mL (30 nmol/L).\textsuperscript{144} The 2 largest studies included in the meta-analysis were from the NHS and the Women’s Health Initiative (WHI), a randomized placebo-controlled trial of 400 IU vitamin D plus 1000 mg/day of calcium in 36,282 post-menopausal women. The NHS study showed, based on 193 incident cases of colorectal cancer, that the relative risk of colorectal cancer decreased linearly across quintiles of plasma 25-(OH) vitamin D concentration, with a 47\% risk reduction for the highest compared to the lowest quintile.\textsuperscript{137} Similarly, in the WHI study, an inverse association was observed between baseline levels of 25-(OH) vitamin D and colorectal cancer risk.\textsuperscript{143}

However, the results of the WHI study did not support a protective role of the calcium and vitamin D intervention on colorectal cancer risk over a follow-up period of 7 years. Nonetheless, this trial had some important limitations. First, the vitamin D dose of 400 IU/day was probably inadequate to yield a substantial contrast between the group given vitamin D and the group given placebo. Specifically, the expected increase in serum levels of 25-(OH) vitamin D following an increment of 400 IU/day would be approximately 3 ng/ml. In comparison, in the epidemiologic studies of 25-(OH) vitamin D, the difference between the highest and lowest quintiles was at least 20 ng/mL. Second, for the calcium intervention, most of the women also had baseline calcium intakes of more than 1000 mg/day, exceeding the threshold for a benefit based on the observational studies. Third, 7 years of follow-up might have been insufficient to show an effect on cancer incidence. The epidemiologic data on duration, although limited, indicate that any influence of calcium and vitamin D intake on colorectal cancer risk could require at least 10 years to emerge.\textsuperscript{145} Finally, the WHI study had a factorial design and also examined a hormone replacement intervention. In a post-hoc analysis, we found that women that were randomly assigned to the group that was given hormones did not have a lower risk of colorectal cancer from vitamin D and calcium, whereas women who did not take hormones did benefit.\textsuperscript{146}

In summary, data support a significant, yet modest ability of calcium intake to prevent colorectal cancer. The precise mechanism by which vitamin D prevents colorectal cancer is not clear, but future randomized control trials of higher doses of vitamin D might provide more information. Although an association between colorectal cancer and vitamin D has not been definitively proven, it is important to achieve a level of at least 30 ng/mL, since this dose has been shown to be optimal for other health conditions.

**B Vitamins**

B vitamins are integral components of one-carbon metabolism, which affects processes that influence cancer risk such as DNA synthesis, repair, and methylation. Based on this premise, B vitamins, particularly folate and vitamin B6, have been studied in relation to risk of colorectal cancer. Folate has received most attention. Studies that have examined folate intake in relation to risk of colorectal cancer or adenoma have largely shown that higher intakes are typically associated with reduced risk.\textsuperscript{147} Specifically, a meta-analysis found an association with
dietary folate but not with folate from supplements. This finding suggests either that correlated factors other than, or in combination with folate are the truly protective factors, or that the form of folate administration could influence its effectiveness. Consistent with experimental data that folate deficiency may induce p53 mutations, low dietary folate has also been specifically associated with increased risk of colorectal cancers with p53 mutations but not wild-type tumors. Also relevant to the folate hypothesis is the role of methylenetetrahydrofolate reductase (MTHFR), an enzyme at a critical metabolic branch point that directs the folate pool towards remethylation of homocysteine to methionine at the expense of thymidylate synthesis. A functionally variant form of MTHFR has been consistently associated with risk of colorectal cancer, especially when considered in conjunction with intakes of folate or alcohol. The finding with MTHFR tends to add further credence of a biologic role for folate in colorectal carcinogenesis (Figure 3).

This observational data and the supporting mechanistic evidence provided the impetus to conduct several randomized controlled trials of folic acid (the synthetic form of folate) in relation to risk of subsequent adenomas in individuals with a history of adenoma. In contrast with the observational studies, these trials tended not to support a benefit of folic acid given at 0.5 mg or 1 mg daily. In fact, one trial suggested a possible increased risk of recurrent advanced adenoma or multiple adenomas related to excessive folate. These studies indicate that an additional supplement of folic acid is unlikely to be beneficial, and even harmful, for those who already have had a colonic neoplasm. However, the effect of folic acid may differ among individuals with baseline folate deficiency. In our recent randomized trial, although folic acid supplementation was not associated with overall reduction in risk of recurrent adenoma, participants with low plasma folate concentrations at baseline did experience a significant decrease in adenoma recurrence (RR, 0.61; 95% CI: 0.42, 0.90). It is also possible that future studies may suggest a role for measuring baseline plasma folate levels prior to use of folate supplementation. The timing of supplementation may also be a key determinant of its effect on neoplasia. Studies from animal models have shown that adequate dietary folate can suppress initial tumor formation, but excess folate during later stages of carcinogenesis could promote carcinogenesis. Taken together with observations that methylation patterns can be altered even in the apparently normal mucosa of patients with tumors, there could be a preexisting “field defect” in the colonic mucosa of patients with prior adenoma that folic acid is unable to reverse. Finally, there is evidence that more than a decade would be required to observe any preventative effects of folate on colorectal carcinogenesis—this time period exceeds that of short-term randomized trials to monitor development of adenoma. In summary, most individuals should receive the recommended 400 µg/day of folate, but it is not clear whether higher doses are beneficial or harmful with respect to colorectal cancer prevention. Due to food fortification in the U.S., few in the U.S. are folate deficient; however, folate-deficient populations, particularly those without a prior history of neoplasia, could benefit from supplements to prevent colorectal cancer.

Only in the past several years has the association between vitamin B6 and risk of colorectal cancer received adequate study. Vitamin B6 is involved in many cellular functions, so it could have anti-cancer mechanisms beyond its role in one-carbon metabolism. Remarkably, most studies have associated higher intake of vitamin B6 or higher levels of pyridoxal 5'-phosphate (PLP), the main circulating form of B6, with a 30%–40% decrease in risk of colorectal cancer. In many of the studies, the inverse association between vitamin B6 and colorectal cancer was even stronger than that observed for folate; the decrease in risk might be greatest among individuals with heavy intake of alcohol. Dietary B6 intake may also be preferentially associated with risk of colorectal cancers with p53 mutations. Of note, there is some data which suggest that vitamin B6 increases risk for rectal cancer. Clearly, interventional studies are required to clarify whether vitamin B6 does reduce the incidence of colorectal cancer.
cancer. In summary, based on current evidence, it is not recommended that intake of vitamin B6 be increased to prevent colorectal cancer.

Antioxidants and Other Micronutrients

Several other dietary micronutrients, including selenium, beta carotene, and vitamins A, C, and E are believed to have anti-carcinogenic effects, based on their anti-oxidant or anti-inflammatory properties and findings from observational studies. Perhaps the strongest relationships have been observed with selenium. With a few exceptions, most studies have demonstrated an inverse association between colorectal adenoma and selenium levels, measured from toenail or plasma samples. Moreover, a remarkable, statistically significant, 50% reduction in colorectal cancer incidence and a non-significant reduction in adenoma incidence were observed in study participants given selenium in the form of brewer’s yeast; skin cancer incidence was reduced in another study of selenium. However, randomized trials specifically designed to examine antioxidant supplements have not supported these observational results. A recent randomized, placebo-controlled trial of oral selenium (200 microgram/d) and vitamin E (400 IU/d), given alone or in combination to men, did not find any reduction in risk prespecified cancer endpoints, including colorectal cancer. A randomized, placebo-controlled trial of vitamin E (50 mg/d), beta carotene (20 mg/day), or the combination in male smokers in Finland did not find that these micronutrients reduced colorectal cancer incidence, yet raised concerns about increased risk for lung cancer and ischemic heart disease related to beta carotene intake. Randomized, placebo controlled-trials of patients with prior adenoma did not demonstrate reduced risk of recurrent adenoma in patients given beta carotene supplements, a combination of vitamin C, vitamin E, and beta carotene supplements, or a diet high in anti-oxidant rich fruits and vegetables. A meta-analysis of randomized trials of antioxidant supplements, including beta-carotene and vitamins A, C, and E, did not find that these nutrients reduced incidence of gastrointestinal cancers. In summary, antioxidant vitamin supplements do not appear to prevent colorectal cancer.

Dietary Patterns

Recognizing the potential for interactive and synergistic effects between various dietary components, researchers have examined the relationship between colorectal cancer and dietary patterns, rather than specific macronutrients or micronutrients. The NHS associated a “Western diet”, consisting of large amounts of red meat and highly refined carbohydrates, with increased risk of colorectal cancer, compared to a “prudent diet” that includes only small amounts of red meat and refined carbohydrates. These results have been largely supported by analyses of dietary patterns in other populations. Mechanistically, the potential anti-cancer benefit of such dietary patterns might be related to hyperinsulinemia (Figure 1) or inflammation (Figure 2). In summary, although the relative importance of and mechanisms associated with specific macronutrient components or micronutrients are uncertain, consideration of the overall dietary pattern might be more important in modifying colorectal cancer risk.

LIFESTYLE

Alcohol

The relationship between alcohol and cancer has been controversial, but most evidence indicates that high intake of alcohol increases risk of colorectal cancer. The association between alcohol intake and colon adenoma and cancer risk has been observed in most, but not all, prospective cohort and case-control studies. The HPFS indicated that men who drink more than 2 drinks of alcohol per day had a 2-fold higher risk of colon cancer compared to men who drank less than 0.25 drinks per day. In NHS and HPFS, we have also demonstrated an increased risk of colorectal adenoma with heavy alcohol use. A pooled analysis of 8 prospective cohort studies (including the NHS and HPFS), which
included nearly 500,000 participants, yielded a multivariate risk of colorectal cancer of 1.24 (95% CI 1.07–1.42) for consumption of ≥30 g/day of alcohol compared to low intake. Similar associations were observed in the EPIC cohort that also included nearly 500,000 participants. This association is not confounded by other risk factors for colorectal cancer and is generally observed for both rectal and colon cancers, as well as for specific types of beverage (beer vs. wine). A meta-analysis corroborated these findings. Of note, a recent study did suggest that alcohol was particularly associated with rectal cancers compared with colon cancers as well as with microsatellite instability low (MSI-L) compared with microsatellite instability high (MSI-H) tumors. Because most studies have associated colorectal cancer risk with the highest levels of intake, it is not clear whether intake of less than 30 g/day (about 2 drinks/day) alcohol affects risk. The mechanisms by which alcohol promote cancer are unknown, but the ability of alcohol to reduce folate levels is of interest (see section on folate) (Figure 3). In addition, alcohol might antagonize metabolism of methyl groups, contributing to abnormal DNA methylation. Finally, alcohol could suppress tumor immune surveillance, delay DNA repair, alter composition of bile acids, or induce cytochrome p450 enzymes to activate hepatic carcinogens. In summary, it appears prudent to recommend minimizing alcohol intake as a means of preventing colorectal cancer, especially among individuals with high levels of intake.

**Tobacco**

The classic studies that linked smoking to cancer incidence and mortality did not associate cigarette smoking with an increased risk of colorectal cancer; most likely because of the long time lag between exposure and colorectal tumor formation, which is approximately 30 to 40 years. Tobacco releases a range of carcinogenic compounds, including polynuclear aromatic hydrocarbons, heterocyclic amines, nitrosamines, and aromatic amines, that can reach the colorectal mucosa through the circulatory system or direct ingestion. Tobacco use has been consistently associated with an increased risk of colorectal adenoma; the time required for this association is shorter than for colorectal cancer. Many of the findings on tobacco and colorectal neoplasia risk were summarized in a recent meta-analysis of adenoma studies, and meta-analyses of cancer studies, which generally reached similar conclusions. One of the meta-analyses examined 4 dose-response variables, each of which yielded statistically significant results: daily cigarette consumption (38% risk increase for an increment of 40 cigarettes/day), duration (20% risk increase for an increment of 40 years of duration), pack-years (51% risk increase for an increment of 60 pack-years), and age of initiation (4% decrease in risk for a delay of 10 years in smoking initiation). Interestingly, the incidence of colorectal cancer also appeared to be stronger in past smokers than in current smokers, consistent with the initiation of an irreversible early event, such as genetic damage. However, a more recent prospective study suggests that past smokers who quit for at least 31 years no longer had an increased risk. The association appeared to be stronger for rectal cancer than for colon cancer, and possibly for the proximal colon compared to the distal colon, as well as for MSI-H compared with MSI-L tumors. Studies of population-attributable risks in the U.S. have estimated that approximately 15%–20% of colorectal cancers can be attributed to smoking; the proportion might be higher for rectal than for colon cancers. In summary, because cessation of smoking late in life does not necessarily eliminate the increased risk for colorectal cancer, it is critical to prevent smoking in adolescents and young adults and to convince smokers to quit as early in life as possible. Although not presently recommended, more intensive screening of smokers for colorectal neoplasia may be justified given the approximately 2-fold increase in risk of being diagnosed with an adenoma and a higher risk of colorectal cancer mortality associated with current smoking.
Body Mass and Fat Distribution

Case-control and prospective studies have consistently associated excess body weight (or body mass index [BMI]; kg/m²) with an increased risk of colon cancer. The HPFS showed that BMI is directly associated with risk, with men in the highest quintile of BMI having nearly a 2-fold higher risk of colon cancer compared with men in the lowest quintile. In NHS, women with a BMI >29 kg/m² had a 1.5-fold increased risk of colon cancer and 2-fold increased risk of large (≥1 cm) adenoma. We recently completed a meta-analysis of 56 case-control and cohort studies, conducted among 7,213,335 individuals including 93,812 cases of colorectal cancer. In that analysis, compared with those with a BMI < 23.0 kg/m², the increased risk of colorectal cancer were 14% for individuals with a BMI of 23.0–24.9; 19% for a BMI of 25.0–27.4; 24% for BMI of 27.5–29.9; and 41% for BMI of ≥30.0 kg/m². The association was stronger for men than for women, and for the colon than for the rectum. For rectal cancer, a weak association was observed only for men but not for women. In a separate meta-analysis of prospective studies, colon cancer risk increased with increasing waist circumference (33% increased risk in men and 16% increase in women per 10-cm increment in waist circumference). Increasing waist-hip-ratio (WHR) was also associated with an increased risk in both men and women. Controls for various other lifestyle factors did not appreciably alter the findings for BMI or body circumference measures.

The mechanisms whereby obesity increases risk for colon cancer are not well established. However, the mitogenic properties of insulin, obesity-related insulin resistance, and associated hyperinsulinemia might be involved in colon cancer pathogenesis (Figure 1). Insulin could also promote colorectal carcinogenesis by increasing levels of bioactive insulin-like growth factor (IGF)-1, either directly or through decreasing levels of IGF binding proteins levels, which leads to increased free IGF-1. In the Physicians’ Health Study (PHS) of male physicians, there was 2.5-fold increased risk of colorectal cancer with increasing levels of plasma C-peptide (a marker of insulin secretion) when extreme quintiles (highest vs. lowest) were compared. With a few notable exceptions, most other studies have supported this association. The largest prospective study, which included 1078 cases of colorectal cancer, found that increased levels of C-peptide were associated with a 37% increase in colorectal cancer risk among men and women. Levels of adiponectin, an insulin-sensitizing adipokine, have been inversely associated with the risk of colorectal cancer; men in the HPFS in the highest quintile of adiponectin had a relative risk (RR) of 0.40 (95% CI, 0.22–0.74) for colorectal cancer compared with men in the lowest quintile. Another study has also associated adiponectin with adenoma.

Individuals with diabetes mellitus have also been shown to have an increased risk of colorectal cancer. This may be related not only the previously reviewed metabolic consequences of obesity, physical inactivity, and insulin resistance, but also hyperglycemia associated with the disease. However, the evidence supporting a link between hyperglycemia and colorectal cancer data is inconsistent. Glycosylated hemoglobin (HbA1c), a widely used measure of blood glucose control in patients with diabetes, has been shown to be a more stable indicator of glycemia over a prior 6 to 8 week period than direct measures of plasma glucose. In a large, prospective case-control study nested in the EPIC cohort, increasing HbA1c was associated with a modestly increased risk of colorectal cancer in women, but not men. HbA1c was also associated with risk of colorectal cancer in three other small studies. However, several other studies have suggested no association of HbA1c with risk of colorectal cancer or adenoma. Based on these findings, obesity, particularly central adiposity, appears to affect risk of colorectal cancer. As shown in Figure 1, factors that increase insulin resistance, such as abdominal obesity and a sedentary lifestyle, combined with dietary factors (see section on red meat and carbohydrates) that stimulate insulin secretion, might induce hyperinsulinemia,
which increases risk for colorectal cancer. Obesity may also be a pro-inflammatory state, which has also been linked to cancer. (Figure 2). For example, a recent study demonstrated an increase in expression of the pro-inflammatory enzyme cyclooxygenase-2 (COX-2) in normal mucosa adjacent to colorectal tumors that were overweight, compared to patients with a healthy body mass index (BMI). In addition, in a placebo-controlled trial, patients with higher BMIs that were given an aspirin daily (325-mg) had a greater reduction in risk of recurrent adenoma (RR=0.44) than those with normal weight (RR=1.23) (see section on aspirin and NSAIDs).

Physical Activity

An association between greater levels of physical activity and decreased risk of colon cancer has been one of the most consistently observed. The inverse association for colon cancer has been observed both in prospective cohort and case-control studies. In the HPFS, we showed that physical activity was inversely associated with risk for colon cancer, with a RR of 0.53 (95% CI, 0.32–0.88) for men in the highest quintile of activity, compared to men in the lowest quintile. Similarly, in the NHS, women who expended >21 metabolic equivalent task-hours (MET-hours)/week had a RR of colon cancer of 0.54 (CI, 0.33–0.90), compared with women who expended < 2 MET-hours/week. Moreover, higher levels of physical activity have been associated with a reduced risk of colon adenoma and particularly large or advanced lesions. Although a physically active lifestyle might be associated with other healthful behaviors, a number of characteristics of the findings indicate that higher levels of physical activity level directly prevent lower colon cancer. The association has been consistently reported in many studies of various designs, in diverse populations, for men and women, and after statistical control for a variety of other lifestyle factors.

A compelling finding is that the inverse association has been observed for both leisure-time and occupational activities, for which patterns of potential confounding lifestyle characteristics are likely to differ.

Overall, the results from these studies indicate a dose-response relation, with risk reduction present across a wide range of physical activity frequency and intensity. In a recent meta-analysis of 52 studies, physically active individuals had a 20%–30% lower risk of colon cancer compared to less active individuals. Whereas risk might be further reduced with even higher levels of activity, even moderate levels of physical activity (e.g., brisk walking for 3–4 hours/week) are associated with substantial benefits. The mechanisms by which physical activity reduces cancer risk is not known, but could involve, in part, reductions in insulin levels and systemic inflammation. Physical activity could also increase colonic motility, though colonic motility has not been definitely linked to colon cancer risk. The cancer-preventing effects of physical activity might also be partially mediated by reducing abdominal adiposity. Nonetheless, evidence supports maintaining a high level of physical activity, even in the absence of significant weight loss, to lower risk of colorectal cancer. In summary, routine physical activity in addition to maintenance of a healthy body weight is associated with significantly lower risk of colorectal cancer.

MEDICATIONS

Aspirin, NSAIDs, and COX-2 Selective Inhibitors

Beginning in the 1980s and 1990s, several case-control studies, followed by prospective cohort studies, consistently associated aspirin use with a lower risk of colorectal cancer and adenoma. Clinical observations and case series studies, later corroborated by the results of randomized control trials, also demonstrated that NSAIDs such as sulindac and the COX-2 selective inhibitor celecoxib reduced the adenomatous polyp burden among patients with familial adenomatous polyposis. Subsequently, 4 randomized, placebo-controlled...
trials of aspirin provided compelling evidence that aspirin directly inhibits sporadic carcinogenesis; each trial demonstrated that short-term aspirin use reduces the risk of adenoma recurrence in patients with a prior history of colorectal neoplasia.\textsuperscript{151–310} A recent meta-analysis of these trials found that aspirin users had pooled risk ratio of 0.83 (95% CI, 0.72–0.96) for any adenoma and 0.72 (95% CI, 0.57–0.90) for advanced adenomas.\textsuperscript{311} Although 2 large trials, the PHS and the Women’s Health Study, failed to confirm that aspirin protects against colorectal cancer,\textsuperscript{312–313} these findings could reflect the low doses of aspirin used or insufficient duration of treatment or follow-up. In support of this explanation, the NHS and HPFS,\textsuperscript{314–315} as well as a secondary analysis of data from 2 other randomized trials, found that long-term use of higher doses of aspirin protect against colorectal cancer.\textsuperscript{316} A dose-dependent relationship is also apparent based on findings from a separate analyses of NHS participants which showed that higher doses of aspirin, especially among women with \textit{UGT1A6} polymorphisms that impair aspirin metabolism, were inversely associated with adenoma formation.\textsuperscript{317, 318} This finding was also observed in other cohorts.\textsuperscript{319}

Three recent randomized trials showed that the COX-2 selective inhibitors celecoxib and rofecoxib prevented adenoma recurrence among patients with a prior history of adenoma.\textsuperscript{320–322} In the Adenoma Prevention with Celecoxib (APC) trial, adenoma recurrence was reduced by 33%–45% in patients that received 3 years of treatment with celecoxib.\textsuperscript{322} Unfortunately, the APC trial identified a dose-dependent, 3-fold higher risk of cardiovascular events, which was also observed in a study of rofecoxib.\textsuperscript{323–326} This subsequently led to the withdrawal of rofecoxib from the market. However, a recent pooled analysis of 6 randomized control trials of celecoxib in patients with non-arthritis indications found that celecoxib (400 mg twice each day) was not associated with increased cardiovascular risk among patients with low baseline risk of cardiovascular disease.\textsuperscript{327} Moreover, in the APC trial, a planned 5-year efficacy analysis found that a previous history of atherosclerotic heart disease was the only risk factor that significantly interacted with celecoxib use in the association with cardiovascular events.\textsuperscript{328} Taken together, this data indicate that celecoxib is relatively safe for individuals that are at low risk for cardiovascular disorders. Unfortunately, many risk factors for colorectal cancer (e.g. body mass index, physical inactivity) overlap with those of cardiovascular disease.\textsuperscript{329}

Although there have been many observational studies supporting a role for non-aspirin, non-COX-2 selective, NSAIDs in colorectal cancer prevention,\textsuperscript{271, 284–287, 289–291, 296–299} randomized trial data are limited. The NSAID sulindac has been shown to reduce polyp burden in patients with FAP.\textsuperscript{301–303} For sporadic adenoma, data are limited to a trial of patients with a history of adenoma that examined the effects of a combination of sulindac and the ornithine decarboxylase inhibitor difluoromethylornitine (DFMO), compared with those of placebo. This combination was selected because of the ability of these reagents to synergistically reduce levels of colonic polynoamines (e.g., putrescine, spermidine, and spermine), which are believed to be pro-carcinogenic. DFMO inhibits polyamine synthesis,\textsuperscript{347} whereas sulindac is believed to increase polyamine acetylation and export. In this small trial, the combination of DFMO and sulindac reduced the risk of recurrent adenoma by 70%. Although there were concerns about potential adverse effects of DFMO on hearing, there was no significant difference reported in hearing changes or audiogram results from patients given DFMO compared to those given placebo.\textsuperscript{348} However, as observed in patients given COX-2–selective NSAIDs, there appeared to be a higher incidence of cardiovascular toxicity among patients with a high baseline risk of cardiovascular events that were given sulindac.\textsuperscript{349} Because the trial was not designed to examine sulindac and DFMO separately, it is uncertain if either agent used alone is an effective chemopreventive.

There have been many proposed mechanisms by which aspirin, NSAIDs, and COX-2 selective inhibitors reduce risk of colorectal neoplasia (Figure 2). However, perhaps the most compelling
hypothesis is related to the ability of these agents to inhibit COX-2. A specific role for COX-2 in colorectal neoplasia is supported by several lines of evidence: 1) disruption of COX-2 inhibits development of polyps in mice with a mutation in APC; 2) host expression of COX-2, but not COX-1, is required for survival of mouse tumor xenografts; 3) COX-2, but not COX-1, is progressively overexpressed in human colorectal adenomas and cancers; 4) COX-2 expression is highly upregulated, even in morphologically normal mucosa of APC min mice and humans with colorectal cancer. We recently showed in a large cohort of men and women that regular aspirin use reduced the risk of colorectal cancers that overexpress COX-2 but not the risk of colorectal cancers with weak or absent expression of COX-2. These data indicate that aspirin likely affects the formation of adenomas and cancer by inhibiting COX-2. Similarly, a secondary analysis of data from a randomized, placebo-controlled trial of aspirin found that genetic variations in COX-2 can modify the effect of aspirin treatment on risk of recurrent adenoma. Nonetheless, aspirin and NSAIDs have other potential anti-cancer mechanisms that are unrelated to cyclooxygenase, including inhibition of nuclear factor-κB, induction of apoptosis by activation of p38 kinase, and catabolism of polyamines, as previously discussed.

The preceding body of evidence was considered by the United States Preventive Services Task Force (USPSTF) in reaching a consensus statement regarding aspirin and NSAIDs for the prevention of colorectal cancer. The USPSTF concluded that overall, harms outweighed the benefits of aspirin and NSAID use for the prevention of colorectal cancer in asymptomatic adults who are at average risk for colorectal cancer. For COX-2-selective agents and NSAIDs, concerns about potential cardiovascular events are particularly limiting, as well as the risk of gastrointestinal ulceration and bleeding. Although aspirin appears to have a more favorable cardiovascular profile, hemorrhagic stroke and gastrointestinal bleeding remain a concern, especially with long-term use. The USPSTF did advocate further investigation into optimizing the risk-benefit profile of aspirin for the purpose of cancer prevention. A recent international consensus panel reached a similar conclusion, advocating that additional research be conducted into the use of aspirin in high-risk populations for which benefits might outweigh the harms.

Such a subgroup would likely include individuals with established colorectal cancer that have undergone a resection for curative intent. Although such patients generally enjoy a favorable prognosis compared to patients diagnosed with unresectable disease, they remain at high risk of recurrence and death from the disease. Thus, we recently examined, among 1,279 patients with established Stage I, II, III colorectal cancers enrolled in the NHS and HPFS, whether aspirin use can influence prognosis. We found that use of aspirin after diagnosis of colorectal cancer is associated with improved survival from the disease. Compared with non-users, participants who regularly used aspirin after diagnosis had a 29% reduction in colorectal-cancer specific mortality and a 21% reduction of overall mortality. Regular aspirin use after diagnosis was associated with a particularly low risk of colorectal-cancer specific mortality among participants in whom primary tumors overexpressed COX-2. Therefore, aspirin might influence the biology of established colorectal tumors, in addition to preventing their occurrence. Moreover, COX-2 or related markers might be used to determine which patients with newly diagnosed colorectal cancer are most likely to respond to anti-COX-2 directed therapies. A study performed in women with colorectal cancer also supports an effect of NSAIDs on survival. Nonetheless, randomized trials are needed to confirm these results before routine clinical recommendations can be implemented.

In summary, aspirin and COX-2 selective inhibitors reduce the risk of colorectal neoplasia. Presently, their routine use is not recommended for prevention of colorectal cancer in the general population due to concern about their associated toxicities. However, there are specific populations in which the potential benefit associated with their use may outweigh the risks.
Post-Menopausal Hormones

Differences in sex hormones might account for the fact that the ratio of women to men with colorectal cancer is lower before age 50–54 years (i.e. for premenopausal women) than after (i.e. for postmenopausal women). This observation stimulated research into whether postmenopausal hormones reduce risk of colorectal cancer. Estrogens have been proposed to alter bile acid composition, modulate colonic transit, and decrease production of mitogenic insulin-like growth factor. Colorectal epithelium expresses estrogen receptors, which might be modulated by age-related promoter hypermethylation. Colon cancers also express estrogen receptor-β, which might modulate the effect of exogenous estrogens on tumor growth. With a few exceptions, most prospective studies show an inverse association between use of postmenopausal hormones and risk of colorectal cancer. Similarly, most studies have also shown an inverse association between postmenopausal hormone use and risk of colorectal adenoma. Based on data from the NHS, postmenopausal hormone use was associated with a decreased risk of colorectal cancer (multivariate RR, 0.65; 95% CI, 0.50–0.83) and large colorectal adenoma (≥1cm in diameter) (multivariate RR, 0.74; 95% CI, 0.55–0.99). These results were confirmed in a 2 separate meta-analyses of epidemiological studies.

These observational results were subsequently confirmed in the WHI estrogen plus progestin randomized, placebo-controlled trial conducted among nearly 17,000 post-menopausal women. In that trial, after a mean of 5.2 years of follow-up, estrogen and progestin were associated with a 37% reduction in colorectal cancer risk, comparable with the results from prospective, observational studies. However, these results were tempered by a finding that colorectal cancers in women who were given estrogen plus progestin were diagnosed at a more advanced stage than those of patients that received placebo. In contrast, the WHI estrogen-alone trial did not show any benefit for colorectal cancer. This is in agreement with most observational studies that have also shown an inverse association between colorectal cancer and the combination of estrogen plus progestin, but not for estrogen-alone. Of note, one recent study did observe that long duration estrogen-alone therapy but not estrogen plus progestin is associated with lower risk of colorectal cancer.

In summary, although postmenopausal hormone therapy appears to be associated with a lower risk of colorectal cancer, it remains unclear which preparations of estrogen-alone or estrogen plus progestin are optimal. Moreover, because postmenopausal hormones increase the risk of breast cancer and cardiovascular events, the associated balance of risks and benefits do not support a recommendation of use of postmenopausal hormones as a means of preventing colorectal cancer.

The Overall Potential of Primary Prevention

Based on the dietary, lifestyle, and medication risk factors we have outlined, there is substantial potential for primary prevention of colorectal cancer through modification of several environmental influences. For dietary factors, although controversy exists regarding the role of specific nutritional elements, consideration of the dietary pattern as a whole might be useful for formulating recommendations. For example, several studies have shown that high intake of red and processed meats, high-fat dairy products, highly refined grains and starches, and sugars are related to a higher risk of colon cancer. Thus, replacing these factors with poultry, fish and plant sources as the primary source of protein; mono-unsaturated, and poly-unsaturated fats as the primary source of fat; and unrefined grains, legumes and fruits as the primary source of carbohydrates is likely to lower risk of colorectal cancer. This benefit is likely to be sustained irrespective of whether the independent benefit of each component or their precise anti-cancer mechanisms is established. Although the role for many supplements, including vitamin D, folate, and B6, remains largely uncertain, calcium supplementation is likely at least modestly...
beneficial, particularly in those with low intake of dietary calcium. Vitamin D intakes of 1000–
2000 IU/day might improve overall health status and possibly lower risk of colorectal cancer.

For lifestyle factors, there is compelling evidence that avoidance of smoking and heavy alcohol
use, prevention of weight gain, and the maintenance of a reasonable level of physical activity
can each have a positive influence on risk of colorectal cancer. In addition, there is strong
evidence that medications such as aspirin and NSAIDs are effective chemopreventive drugs.
Certain preparations of postmenopausal hormones might also be associated with lower risk of
colorectal cancer. Although none of these agents are recommended for widespread primary
prevention due to their side effect profile, they provide proof-of-principle of the potential to
translate epidemiological findings into clinically efficacious chemopreventive drug
interventions.

Taken together, modification of multiple diet and lifestyle factors is likely to have a substantial
overall impact on risk of colorectal cancer. In a previous study of the HPFS, as many as 70%
of the overall burden of colon cancers in the U.S. population could be prevented through
moderate changes in diet and lifestyle. Using population-based projections, a separate study
reached similar conclusions, albeit with more modest estimates of benefit. To further
integrate the combined effect of modifiable risk factors, we recently developed a
comprehensive model of colon cancer incidence that accounted for changes in the influence
of risk factors throughout the lifespan. We found that women with profiles of modifiable
lifestyle factors that were “high risk” had a nearly 4-fold higher risk of colon cancer compared
with women with “low-risk” profiles (Figure 4). Although endoscopic screening could
reduce cancer incidence among these high-risk women, their risk remained significantly higher
than women whose lifestyle behaviors placed them in the moderate- or low-risk categories
(Figure 5). Thus, primary prevention of colorectal cancer through lifestyle changes is an
important complement to colorectal cancer screening in reducing colon cancer incidence.
Moreover, because many diet and lifestyle risk factors for colorectal cancer overlap with other
chronic illnesses, including cardiovascular disease, further research into these risk factors
would have benefits beyond prevention of colorectal cancer.

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REFERENCES

2. Curado, MP.; Edwards, B.; Shin, HR.; Storm, H.; Ferlay, J.; Heanue, M.; Boyle, P. IARC Scientific
108. [PubMed: 15761078]
[PubMed: 7695871]
8. Trock B, Lanza E, Greenwald P. Dietary fiber, vegetables, and colon cancer: critical review and meta-


Gastroenterology. Author manuscript; available in PMC 2011 June 1.


76. Lang NP, Butler MA, Massengill J, Lawson M, Stotts RC, Hauer-Jensen M, Kadlubar FF. Rapid metabolic phenotypes for acetyltransferase and cytochrome P4501A2 and putative exposure to food-


146. Ding EL, Mehta S, Fawzi WW, Giovannucci EL. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: Reanalysis of Women’s Health Initiative randomized trial. Int J Cancer. 2007


Gastroenterology. Author manuscript; available in PMC 2011 June 1.


Gastroenterology. Author manuscript; available in PMC 2011 June 1.


Gastroenterology. Author manuscript; available in PMC 2011 June 1.


406. Hildebrand JS, Jacobs EJ, Campbell PT, McCullough ML, Teras LR, Thun MJ, Gapstur SM. Colorectal Cancer Incidence and Postmenopausal Hormone Use by Type, Recency, and Duration in Cancer Prevention Study II. Cancer Epidemiol Biomarkers Prev. 2009


**Biographies**
Abdominal obesity, physical inactivity, and some aspects of a Western diet that stimulate insulin secretion could increase risk of colorectal cancer by causing repeated bouts of hyperinsulinemia. High levels of insulin might have direct effects on susceptible cells through insulin receptors or through IGF-1 receptors by decreasing IGF binding proteins thereby increasing free levels of IGF-1. Activation of insulin and IGF-1 receptors might lead to increased cell proliferation and reduced apoptosis, which could increase the risk tumorigenesis.
Figure 2. Proposed inflammatory mechanisms relating diet, lifestyle, and medication use to colorectal cancer
Dietary components (e.g. vitamin D and n-3 fatty acids), lifestyle factors (e.g. physical activity), and medications (e.g. aspirin, COX-2 inhibitors, NSAIDs), might have anticancer effects (red lines) whereas lifestyle factors such as obesity could promote cancer (black lines) through anti-inflammatory mechanisms that are largely mediated through inhibition of the COX-2 enzyme. COX-2 could be upregulated by inflammatory or oncogenic stimuli via inflammatory cytokines such as or interleukin-6 (IL-6) or others that induce nuclear factor κB (NF-κB). COX-2 converts membrane-associated arachidonic acid to prostaglandins, including PGH₂, PGD₂, PGF₂α, PGI₂ (prostacyclin), and thromboxane A2, as well as PGE₂. In turn,
PGE$_2$ stimulates EP2, which upregulates transcriptional activity of β-catenin and activates the oncogene products phosphatidylinositol-3-kinase (PI3K) and the kinase AKT. PGE$_2$ also stimulates EP4, which triggers phosphorylation of the epidermal growth factor receptor (EGFR), thereby activating PI3K, AKT, and the oncogenic RAS-mitogen-activated protein kinase (MAPK) cascade. PGE$_2$ stimulation of PI3K signaling also activates the transcriptional activity of the peroxisome-proliferator-activated receptor δ (PPAR δ). These PGE$_2$-induced signaling pathways induce expression of a number of genes, including the angiogenic factor vascular endothelial growth factor (VEGF), the anti-apoptotic factor Bcl-2, and the proliferation-promoting factor cyclin D1. Many of the downstream targets of PGE$_2$ act in positive feedback loops to induce greater expression of COX-2 (green arrows). Aspirin and NSAIDs might also directly stimulate PPARs and block phosphorylation of AKT. 15-prostaglandin dehydrogenase (15-PGDH) inhibits PGE$_2$ and thereby functions as a prostaglandin-degrading enzyme. Upregulation of prostaglandin synthesis increases urinary 11 α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid (PGE-M), the major metabolite of PGE$_2$. 
Figure 3. Proposed mechanism relating folate, alcohol, MTHFR genotype, and colorectal cancer (THIS FIGURE IS BEING PREPARED BY ILLUSTRATOR) The TT genotype of MTHFR is associated with impaired function of the MTHFR enzyme in converting 5,10-methylene tetrahydrofolate (THF) into 5-methyl THF. For individuals with CC or CT genotypes, only modest associations are observed between folate, alcohol, and risk of colorectal neoplasia. However, individuals with the TT genotype might be particularly sensitive to the anti-cancer effects of high folate intake and low alcohol consumption. Specifically, with high stores of folate, the higher levels of 5,10-methyl THR might prevent imbalances of nucleotide pools during DNA synthesis (e.g. reduced uracil misincorporation) and a sufficient amount of 5,10-methylene THF is converted to 5-methyl THF for DNA methylation. In contrast, when the...
methyl content in the diet is low or depleted by alcohol consumption, individuals with TT genotypes might be less able to compensate for the impairment in MTHFR function; therefore, these individuals are less able to produce sufficient amounts of 5-methyl THF for DNA methylation. Impairment of DNA methylation processes results in dysregulation of gene expression.419
Figure 4. Age-specific incidence of colon cancer per 100,000 person-years according to modifiable risk factors

Women were enrolled in the Nurses’ Health Study and were followed between 1980 and 2004. Women were assumed to have no postmenopausal hormone use, no aspirin use, average height, no family history of colorectal cancer, and have never been screened for colorectal cancer. 1) a “high-risk” participant (one who accrued 10 pack-years of smoking before age 30 years, had a consistently high relative body weight, had physical activity of 2 metabolic equivalent (MET)-hours/week, consumed 1 serving of red or processed meat per day, and had a folate intake of 150 µg/day); 2) a "moderate-risk" participant (one who was a nonsmoker, had an average body mass index, had physical activity of 13.5 MET-hours/week, did not consume red or processed meat, and had a folate intake of 300 µg/day); and 3) a "low-risk" participant (one who was a nonsmoker, had a consistently low relative body weight, had physical activity of 21 MET-hours/week, did not consume red or processed meat, and had a folate intake of 400 µg/day). Taken from Wei et al.410

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Figure 5. Age-specific incidence of colon cancer per 100,000 person-years according to modifiable risk factors and screening behavior

Women were enrolled in the Nurses’ Health Study and were followed between 1980 and 2004. Women were assumed to have no postmenopausal hormone use, no aspirin use, average height, no family history of colorectal cancer, and have never been screened for colorectal cancer. 1) a high-risk” participant (one who accrued 10 pack-years of smoking before age 30 years, had a consistently high relative body weight, had physical activity of 2 metabolicMET)-hours/week, consumed 1 serving of red or processed meat per day, was never screened for colon cancer, and had a folate intake of 150 µg/day); 2) a high-risk participant who was screened from age 50 years to age 70 years; 3) a “moderate-risk” participant (one who was a nonsmoker, had an average body mass index, had physical activity of 13.5 MET-hours/week, did not consume red or processed meat, was never screened, and had a folate intake of 300 µg/day); and 4) a “low-risk” participant (one who was a nonsmoker, had a consistently low relative body
weight, had physical activity of 21 MET-hours/week, did not consume red or processed meat, was never screened, and had a folate intake of 400 µg/day). Taken from Wei et al.410