ANNALS OF GASTROENTEROLOGY 2009, 22(3):143-149

*Current View*

# The role of diet in the prevention of colorectal cancer: Current aspects

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Colorectal cancer is mainly a disease of high-income countries, where overall rates are nearly four times higher than in middle- to low-income countries. This cancer accounts for somewhat over 9 per cent of all cancer incidence, but around 8 per cent of all cancer deaths.[1]

## *Etiology*

Colon cancer is the second leading cause of cancer related death in American adults. The incidence and mortality are highest in African Americans (AAs) (incidence: 52 per 100 000) and lowest in American Hispanics (37 per 100 000). Comparative studies with Native Africans (<5 per 100 000) suggest that genetic susceptibility is an unlikely explanation and that environmental influences are to blame. Studies have suggested that risk is high because of excessive intakes of animal meat and fat products and differences in colonic bacterial metabolism.[2]

In general it has been hypothesized that the higher risk of colon cancer in AAs results from differences in the colonic milieu, which consists of substances derived from the environment, such as nutrients, and the bacterial flora, which are also influenced by the environment. In conclusion, there is evidence suggesting that environmental colonic carcinogenesis is far more complex than commonly appreciated and that risk is determined by the overall lifetime balance between environmental factors that promote and those that aggravate mucosal health.[3]

**Keywords:** Colorectal cancer, diet, etiology, prevention

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## *Established causes*

**Diseases:** Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increase the risk and may be seen as a cause of, colon cancer.1 Epidemiologic data suggest that a history of diabetes mellitus, and, in particular, type 2 diabetes, and impaired glucose tolerance are risk factors for colorectal cancer. Individuals with type 2 diabetes have peripheral resistance to insulin and develop hyperinsulinemia as a compensatory response, and this hyperinsulinemic state is believed to be the mechanism that underlies the association between diabetes and colorectal carcinogenesis.[4]

**Medication:** Non-steroidal anti-inflammatory drugs such as aspirin and hormone replacement therapy in postmenopausal women have been shown to decrease colon cancer risk.1 There is considerable evidence from most observational studies that persons who took aspirin regularly had a lower risk of colorectal cancer than those who did not. A proposed mechanism that may account for this association includes the established role of aspirin as an inhibitor of cyclooxygenase pathways for formation of inflammatory mediators in the bowel, such as prostaglandin E2 and prostaglandin F.6 Furthermore, multiple studies have investigated the association between statins, the most commonly used type of cholesterol lowering drug, and colorectal cancer incidence, but these studies have produced mixed results.[6-8]

## *Lifestyle factors*

**Physical activity:** There is abundant epidemiological evidence from prospective studies showing lower risk of colorectal cancer with higher overall levels of physical activity, as well as with greater frequency and intensity, and there is evidence of a dose-response effect. There is little heterogeneity, except that the effect is not as clear

for rectal cancer as it is for colon cancer. Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity, as well as reducing blood pressure and insulin resistance. In addition, physical activity increases gut motility.[1]

A related hypothesis is that exercise increases water intake, which has been associated with reduced risk of colorectal adenoma and cancer. Physical activity also has been proposed to reduce colon cancer risk by reducing body weight or through mechanisms independent of body composition. It is also possible that physical activity may play an anti-inflammatory role by acting directly on the immune system or through its effect on obesity, which is considered by some to cause low-grade systemic inflammation and is associated with elevated serum levels of several inflammatory markers. Increased physical activity is associated with lower concentrations of C-reactive protein and fibrinogen and can induce several cytokine inhibitors and anti-inflammatory cytokines.[9]

**Occupational exposure to chemical carcinogens:** In contrast to the findings for lung cancer, the relation between asbestos exposure and the risk of colorectal cancer remains controversial.[10]

### *Anthropometric characteristics*

**Obesity:** There is abundant and consistent epidemiological evidence with a clear dose-response relationship suggesting that greater body fatness is a cause of colorectal cancer. Data suggest a larger increased risk for colon cancer than for rectal cancer. Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis. It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers.[1]

Recently, a few investigations suggest that the association between obesity and colorectal cancer risk among women is limited to certain subgroups, perhaps based on their oestrogen status. Indeed, there seems to be an overall increased risk of colorectal cancer among younger women (e.g., <50 years) but not in older women. This shift in colorectal cancer risk among women seems to correspond with the timing of menopause, which suggests possible effect modification by factors related to oestrogen status. This observation, along with studies that showing that the use of postmenopausal hormones decreases the risk of colorectal cancer among postmenopausal women who have low endogenous oestrogen levels, has led some investigators to consider oestrogen as a potential effect modifier of the association between obesity and colorectal cancer.[11]

**Abdominal obesity:** The evidence that abdominal obesity is a cause of colorectal cancer is convincing.1 From a large prospective cohort study held at the Participants of the European Prospective Investigation into Cancer and Nutrition, it has been found that body weight and BMI were statistically significantly related to colon cancer risk in men, but only weakly related to risk in women. In contrast, both waist circumference and waist-to-hip ratio were strongly related to colon cancer risk in both sexes. These data support the hypothesis that abdominal obesity is a risk factor for colon cancer in both sexes and suggest that fat distribution is more important than body weight or Body Mass Index (BMI) for disease risk in women. One potential reason for the discrepancy is that men and women have different body compositions. Fat makes up a lower percentage of the body mass of men (approximately 20%) than of women (approximately 30%). The relationship of body weight to fat distribution also differs between men and women. Higher body weight is more closely related to abdominal obesity than lower body obesity in men and more closely related to gluteofemoral obesity than to abdominal obesity in women. Furthermore, upper-body fat has been shown to be more strongly associated with metabolic abnormalities than lower-body obesity.[12]

**Adult attained height:** The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of colorectal cancer is convincing.1 It has also been reported that the magnitude of this association seems to be similar in men and women.12 The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.[1]

### *Dietary factors*

Colorectal cancer aetiology is complex, involving both genetic and environmental factors. However, 50–80 percent of cases of colorectal cancer are considered due to environmental factors, such as dietary habits.[13] To the writers' knowledge, there is only one, recent, review suggesting that evidence that diet has an effect on the incidence of CRC is only moderate and might be affected by the multifactorial nature of colorectal cancer.[14] The evidence presented below do not seem to support this thesis.

**Animal fat:** There is a limited amount of fairly consistent evidence suggesting that consumption of animal fat is a cause of colorectal cancer. Diets high in fat lead to

increased levels of bile acids in the colon. Bile acids are metabolised by the bacterial flora to secondary bile acids, which can promote cancer in rodents. The conversion of bile acids to secondary bile acids is decreased by the lower pH induced by short-chain fatty acids produced in diets high in non-starch polysaccharides.[1]

Results from ecologic studies indicate that diets high in animal fat (rich in saturated fatty acids) are associated with increased risk of colorectal cancer in contrast to diets high in fish and fish products (rich in omega-3 PUFAs), which are associated with reduced risk.15 A large body of literature spanning numerous cohorts from many countries and with different demographic characteristics does not provide evidence to suggest a significant association between omega-3 fatty acids and cancer incidence.[16]

**Carbohydrates:** There is limited evidence suggesting that foods containing sugars are a cause of colorectal cancer.[1]

*Dietary fibre:* Dietary fibre has been hypothesized to reduce the risk of colorectal cancer. Potential mechanisms for a protective effect include dilution of faecal carcinogens and procarcinogens, reduction of transit time of faeces through the bowel, production of short chain fatty acids, which promote anticarcinogenic action, and binding of carcinogenic bile acids. However, the results of numerous epidemiological studies have been inconsistent. Ecological correlation studies and many case-control studies have found an inverse association between dietary fibre intake and risk of colorectal cancer. On the other hand, most prospective cohort studies have found no association between dietary fibre intake and risk of colorectal cancer or adenomas, and randomized clinical trials of dietary fibre supplementation have failed to show reductions in the recurrence of colorectal adenomas.17 It has been proposed that when examining the association between dietary fibre consumption and colorectal caner risk, it should seriously be taken into consideration that there is considerable confounding by other dietary and lifestyle factors.[18]

**Folate:** Folate, a water-soluble B vitamin and important cofactor in 1-carbon transfer, is an important nutritional factor that may modulate the development of colorectal cancer. The mechanisms by which dietary folate can modulate colorectal carcinogenesis are related to the sole biochemical function known for folate: mediating the transfer of 1-carbon moieties. In this role, folate is an important factor in DNA synthesis, stability and integrity, and repair, aberrations of which have been implicated in colorectal carcinogenesis. Folate may also modulate DNA methylation, which is an important epigenetic determinant in gene expression (an inverse relationship), in the maintenance of DNA integrity and stability, in chromosomal modifications, and in the development of mutations.19 Evidence from cohort studies is plentiful, with a dose-response relationship, but there is unexplained inconsistency. Residual confounding from dietary fibre is possible. There is limited evidence suggesting that foods containing folate protect against colorectal cancer.[1]

**Iron:** The evidence is sparse, of poor quality, and inconsistent. There is limited evidence suggesting that foods containing iron are, in general, a cause of colorectal cancer.[1]

**Selenium:** It has been hypothesized that selenium intake could prevent colorectal cancer. Possible biological mechanisms for this association, hypothesized from laboratory studies, include repair and prevention of oxidative damage, intracellular signalling, activation of thyroid hormone, regulation of immune response, and enhanced apoptosis.20 However, evidence is sparse. There is limited evidence to suggest that selenium protects against colorectal cancer.[1]

**Calcium and Vitamin D:** Calcium can reduce risk of colorectal tumours by binding bile and fatty acids in the bowel, thus reducing exposure of colonic epithelium to these potentially carcinogenic compounds or by acting directly on colonic epithelium, influencing cellular differentiation, apoptosis, and associated proliferative activity, probably mediated by the calcium-sensing receptor.21 There is generally consistent evidence from several cohort studies, and evidence from trials for colorectal adenomas suggesting that calcium probably protects against colorectal cancer. The effects of vitamin D and calcium are strongly interrelated because both are growth restraining, both induce differentiation and apoptosis in intestinal cells, and calcium-mediated effects are strongly dependent on vitamin D levels. However, the evidence on vitamin D is inconsistent. There is limited evidence suggesting that foods containing vitamin D or vitamin D status protect against colorectal cancer.[1]

**Other dietary factors:** Magnesium is an essential ion that has an important role in regulating cell cycles and maintaining genomic stability. Administration of supplemental magnesium in animals with experimentally induced colon cancer resulted in fewer colon tumours and smaller cryptal cells of the colon, suggesting an inhibitory role of magnesium in colon cancer cell proliferation. The mechanism by which magnesium prevents the growth of colon tumours was later found to be due to the inhibition of c-myc oncogene expression in the colon cancer cells and

the potentially reduced toxic effects of bile acids on colonic epithelial cells. At the intracellular level, magnesium also effectively modulates insulin activity. Magnesium deficiency is often seen among patients with insulin resistance and type 2 diabetes, which have also been linked to an increase in colorectal cancer incidence. Observational studies of the association between magnesium intake and colorectal cancer incidence are very sparse.[22]

Folate, methionine, vitamin $B_6$, and vitamin $B_{12}$ play important roles in one-carbon metabolism, which is critical for nucleotide synthesis and DNA methylation. Aberrations in either nucleotide synthesis or DNA methylation can contribute to carcinogenesis in general and colorectal cancer in particular. Despite its importance in one-carbon metabolism and several animal studies that have shown a protective role for vitamin $B_6$ against colorectal carcinogenesis, few epidemiologic studies have evaluated the association between vitamin $B_6$ and risk of colorectal neoplasia.[23]

Choline and betaine are involved in methyl-group metabolism as methyl-group donors; thus, like folate, another methyl-group donor, they may be associated with a reduced risk of colorectal adenomas. To the writers' knowledge only one recent epidemiologic study has examined the association of intake of these nutrients and colorectal adenoma risk. The findings of this study do not support an inverse association between choline or betaine intake and the risk of colorectal adenoma.[24]

Antioxidant vitamins such as vitamin E and vitamin C have been suggested as potential anticancer agents because they fight free radicals, which may cause oxidative damage to DNA, possibly leading to development of cancer. This hypothesis was central to several cancer chemoprevention trials of vitamin C, vitamin E, and β-carotene in the late 1980s and early 1990s. Furthermore, several trials have tested the efficacy of antioxidants to prevent adenomatous polyps. Most of these trials, unexpectedly, did not see a reduction in cancer incidence or polyp recurrence in the antioxidant-supplemented group.[25]

Phytoestrogens, contained in plant foods, have nonsteroidal estrogen-like activities. There is epidemiologic evidence that phytoestrogens may protect against the development of hormone-dependent cancers (e.g. breast and prostate) and it has been suggested that this may extend to colorectal cancer. The development of colorectal cancer is thought to be influenced by oestrogen exposure; for example, hormone-replacement therapy halves the risk of colorectal cancer among women. Phytoestrogens may act through hormonal mechanisms to reduce cancer risk by binding to oestrogen receptors or interacting with enzymes involved in sex steroid biosynthesis and metabolism. However, epidemiologic findings are inconsistent.[26]

Flavonoids are biologically active polyphenolic compounds widely distributed in plants. Colon-specific in vitro cell line and in vivo animal studies have reported anticarcinogenic properties associated with flavonoids, including free radical scavenging, modifying or inactivating enzymes that activate or detoxify carcinogens, inhibiting the induction of transcription factors (such as activator protein-1 activity), and inducing apoptosis. However, epidemiologic evidence is sparse.[27]

Carotenoids are red and yellow fat-soluble pigments found in many fruits and vegetables. In case-control studies, the risks of colon and rectal cancer have generally been lower with increasing total carotenoid intake. Data on associations between intakes of specific carotenoids and colon or rectal cancer risk have been conflicting, while epidemiologic evidence is sparse.[28]

### *Food consumption*

*Foods containing dietary fibre:* Fibre exerts several effects in the gastrointestinal tract, but the precise mechanisms for its probable protective role are still not clearly understood. Fibre dilutes faecal content, decreases transit time, and increases stool weight. Fermentation products, especially short-chain fatty acids, are produced by the gut flora from a wide range of dietary carbohydrates and mucins that reach the colon. Short-chain fatty acids, such as butyrate, induce apoptosis, cell cycle arrest, and differentiation in experimental studies. Fibre intake is also strongly correlated with intake of folate, though adjusting for this often does not affect the risk reduction attributed to fibre. In conclusion, a clear dose-response relationship is apparent from generally consistent cohort studies, supported by evidence for plausible mechanisms, but residual confounding could not be excluded. Foods containing dietary fibre probably protect against colorectal cancer.[1]

**Non-starchy vegetables:** A review of the medical literature from 1994 to 2003 summarized the relationship between raw and cooked vegetables and cancer risk and examined whether they may affect cancer risk differently. Twenty-eight studies examined the relationship between raw and cooked vegetables and the risk of various cancers. Twenty-one studies assessed raw, but not cooked, vegetables and cancer risk. The majority of these assessed risk of oral, pharyngeal, laryngeal, oesophageal, lung, gastric, and colorectal cancers. Most showed that vegetables, raw or cooked, were inversely related to most of these cancers. However, the results concerning colorectal cancer were not

consistent.29 In conclusion, a substantial amount of evidence is available but it is inconsistent. There is limited evidence suggesting that non-starchy vegetables protect against colorectal cancer.[1]

**Garlic:** A published meta-analysis of seven case-control/cohort studies that have examined the association of garlic consumption with colorectal cancer confirmed an inverse association, with a 30% reduction in relative risk.30 The evidence, though not copious and mostly from case-control studies, is consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Garlic probably protects against colorectal cancer.[1]

**Fruits:** There is a substantial amount of evidence but it is inconsistent. There is limited evidence suggesting that fruits protect against colorectal cancer.[1]

**Red meat:** There are several potential underlying mechanisms for a positive association of red meat consumption with colorectal cancer, including the generation of potentially carcinogenic N-nitroso compounds. Some meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons. Red meat contains haem iron. Free iron can lead to the production of free radicals. In conclusion, red meat is a convincing cause of colorectal cancer.1 Furthermore, the results of a recent study provide strong evidence for a modifying effect of metabolizing genes on the association of meat intake and heterocyclic amines exposure with colorectal polyp risk.31 Finally, it has recently been suggested that the exposure to the meat mutagens could be involved in the recurrence of clinically significant adenomatous polyps.[32]

**Processed meat:** Processed meat is a convincing cause of colorectal cancer. Nitrates are both produced endogenously in gastric acid and added as preservatives to processed meats. They may contribute to N-nitroso compound production and exposure. These compounds are suspected mutagens and carcinogens. Many processed meats also contain high levels of salt and nitrite. Meats cooked at high temperatures can contain heterocyclic amines and polycyclic aromatic hydrocarbons. Haem promotes the formation of N-nitroso compounds and also contains iron. Free iron can lead to the production of free radicals.[1]

**Fish:** It is biologically plausible that long-chain fish omega-3 polyunsaturated fatty acids (PUFAs) protect against cancer. Fish oils reduce tumours in animal studies. Likely mechanisms are thought to include their role in reduction of omega-6 PUFA-derived eicosanoid biosynthesis (eicosanoids influence inflammation) and direct inhibition of cyclo-oxygenase-2, also implicated in the cancer process. This mechanism, though plausible, is not well supported. Alternative suggestions include the relatively high selenium or vitamin D content of fish. In conclusion, there is limited evidence suggesting that eating fish protects against colorectal cancer.[1]

**Milk:** Milk probably protects against colorectal cancer. Any effect of milk in reducing colorectal cancer risk is likely to be mediated, at least in part, by calcium, which has direct growth-restraining and differentiation- and apoptosis-inducing actions on normal and tumour colorectal cells. Milk includes many bioactive constituents, which may also play a role.[1]

**Cheese:** The evidence is inconsistent. There is limited evidence suggesting that cheese is a cause of colorectal cancer. The potential mechanisms for the association of cheese with cancers of the colon and rectum are unclear. Saturated fatty acids can induce expression of inflammatory mediators and stimulate increased insulin production.[1]

**Alcoholic drinks:** The evidence that consumption of more than about 30g per day of ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing; and it is probably a cause in women.1 This association is evident for cancer of the proximal colon, distal colon, and rectum. No clear difference in relative risks is found among specific alcoholic beverages.33 Reactive metabolites of alcohol such as acetaldehyde can be carcinogenic. There is also an interaction with smoking. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Lastly, high consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis.[1]

**Nut and seed intake:** Nuts and seeds may be considered as an important component of a healthy diet. In general, they are nutrient dense and provide protein, fat (mostly unsaturated fatty acids), dietary fibre, and many bioactive constituents, such as vitamins (e.g., folic acid, niacin, vitamin E, and vitamin B6), minerals (e.g., copper, magnesium, potassium, and zinc), antioxidants, phytoestrogens, and other phytochemicals. From one recent epidemiological study that investigated the association between nut and seed consumption and the risk of colorectal cancer in participants of the European Investigation into Cancer and Nutrition, no association was found between higher

intake of nuts and seeds and risk of colorectal, colon, and rectal cancers in men and women combined, but a significant inverse association was observed in subgroup analyses for colon cancer in women at the highest versus the lowest category of intake. It is not evident from this data why there may be a stronger association in women or why it may be limited to the colon, suggesting that much further research is necessary.[34]

**Coffee:** Results of epidemiologic studies have not resolved whether coffee consumption is related to colorectal cancer risk. The constituents of coffee might have genotoxic, mutagenic, or antimutagenic properties, any of which could influence colorectal cancer risk. For example, caffeine has been reported to inhibit chemical carcinogenesis and UVB light-induced carcinogenesis in animal models. Conversely, caffeine has also been found to be mutagenic. Coffee consumption has also been speculated to decrease the risk for colorectal cancer because it increases large bowel motility in the rectosigmoid region, which might decrease contact between bowel contents and colon epithelia and thus decrease mucosal damage. Coffee may also prevent mucosal damage by reducing the excretion of bile acid and sterols into the bowel. Furthermore, caffeine has been reported to lower insulin sensitivity, and hyperinsulinemia has been hypothesized to increase risk of colon cancer.[35]

**Tea:** The hypothesis of tea as a chemopreventive agent for colorectal cancer development has been extensively studied using in vitro and non-human in vivo experiments. From mutagenicity to tumor development, the majority of experimental studies supported this hypothesis. Over the last three decades, a number of epidemiologic studies were conducted to investigate the association between tea consumption and colorectal cancer risk in humans. Recent narrative reviews concluded that epidemiologic studies did not provide consistent evidence to support tea as chemopreventive agent for colorectal cancer development.[36]

### *Food patterns*

The 2005 Dietary Guidelines for Americans include quantitative recommendations for two eating patterns, the USDA Food Guide and the Dietary Approaches to Stop Hypertension (DASH) Eating Plan, to promote optimal health and reduce disease risk. A Mediterranean dietary pattern has also been promoted for health benefits. From a relatively recent study with objective to determine whether adherence to the USDA Food Guide recommendations, the DASH Eating Plan, or a Mediterranean dietary pattern is associated with reduced risk of distal colorectal adenoma, it has been shown that following the current U.S. dietary recommendations or a Mediterranean dietary pattern is associated with reduced risk of colorectal adenoma, especially in men.[37]

### *Conclusions*

The evidence that physical activity protects against colorectal cancer is convincing, although the evidence is stronger for colon than for rectum.

The evidence that red meat, processed meat, substantial consumption (more than about 30g per day ethanol) of alcoholic drinks (by men, and probably by women), body fatness and abdominal fatness, and the factors that lead to greater adult attained height, or its consequences, are causes of colorectal cancer is convincing.

Foods containing dietary fibre, as well as garlic, milk, and calcium, probably protect against this cancer.

There is limited evidence suggesting that non-starchy vegetables, fruits, foods containing folate, as well as fish, foods containing vitamin D, and also selenium and foods containing it, protect against colorectal cancer, and that foods containing iron, and also cheese, foods containing animal fats, and foods containing sugars are causes of this cancer.[1]

## REFERENCES

1. World Cancer Research Fund/American Institute for Cancer Research: Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007.
2. Sharma S, O' Keefe SJD. Environmental influences on the high mortality from colorectal cancer in African Americans. Postgrad Med J 2007; 83:583-589.
3. O' Keefe SJD, Chung D, Mahmoud N, et al. Why Do African Americans Get More Colon Cancer than Native Africans? J Nutrition 2007; 137:175S-182S.
4. Seow A, Yuan JM, Koh WP, Lee HP, Yu MC. Diabetes Mellitus and Risk of Colorectal Cancer in the Singapore Chinese Health Study. J Nat Cancer Inst 2006; 98:135-138.
5. Alison M, Garland C, Chlebowski R, et al. The Association between Aspirin Use and the Incidence of Colorectal Cancer in Women. Am J Epidemiol 2006; 164:567-575.
6. Whitworth A. Cholesterol Lowering Drugs Not Associated with Reduced Colorectal Cancer Risk. Journal of the National Cancer Institute 2006; 98:1
7. Poynter JN, Gruber SB, Higgins PDR, Almog R, Bonner JD, Rennert HS, Low M, Greenson JK, Rennert G. Statins and the Risk of Colorectal Cancer. The NEJM 2005; 352:2184-2192.
8. Jacobs EJ, Rodriguez C, Brady KA, Connell CJ, Thun MJ, Calle EE. Cholesterol-Lowering Drugs and Colorectal Cancer Incidence in a Large United States Cohort. J Nat Cancer Inst 2006; 98:69-72.

9. Chao A, Connell CJ, Jacobs EJ, et al. Amount, Type, and Timing of Recreational Physical Activity in Relation to Colon and Rectal Cancer in Older Adults: the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers & Prevention 2004; 13:2187-2195.
10. Aliyu OA, Cullen MR, Barnett MJ, Cartmel B. Evidence for Excess Colorectal Cancer Incidence among Asbestos-exposed Men in the Beta-Carotene and Retinol Efficacy Trial. Am J Epidemiol 2005; 162:868-878.
11. Wolf LA, Terry PD, Potter JD, Bostick RM. Do Factors Related to Endogenous and Exogenous Estrogens Modify the Relationship between Obesity and Risk of Colorectal Adenomas in Women? Cancer Epidemiol Biomarkers & Prevention 2007; 16:676-683.
12. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, et al. Body Size and Risk of Colon and Rectal Cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC) J Nat Cancer Instit 2006; 98:920-931.
13. Theodoratou E, McNeill G, Cetnarskyj R, Farrington SM, Tenesa A, et al. Dietary Fatty Acids and Colorectal Cancer: A Case-Control Study American J Epidemiol 2007; 166:181-195.
14. Ryan-Harshman M. Diet and colorectal cancer: Review of the evidence. Can Fam Physician 2007; 53:1913-1920.
15. Theodoratou E, Mcneil G, Cetnarskyj R, Farrington SM, Tenesa A, et al. Diettary Fatty Acids and Colorectal Cancer: A Case-Control Study American J Epidemiol 2007; 166:181-195.
16. MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM et al. Effects of Omega-3 Fatty Acids on Cancer Risk. JAMA 2006; 295:403-415.
17. Park Y, Hunter DJ, Spiegelman D, Bergkivst L, Berrino F, et al. Dietary Fiber Intake and Risk of Colorectal Cancer: A Pooled Analysis of Prospective Cohort Studies. JAMA 2005; 294:2849-2857.
18. Michels KB, Fuchs CS, Giovannucci E, Colditz GA, Hunter DJ, et al. Fiber Intake and Incidence of Colorectal Cancer among 76,947 Women and 47,279 Men. Cancer Epidemiology Biomarkers & Prevention 2005; 14:842-849.
19. Kim YI. Role of Folate in Colon Cancer Development and Progression. J Nutrition 2003; 133:3731S-3739S.
20. Connelly-Frost A, Poole C, Satia JA, et al. Selenium, Apoptosis, and Colorectal Adenomas. Cancer Epidemiol Biomarkers & Prevention 2006; 15:486-493.
21. Petres U, Chatterjee N, McGlynn KA, et al. Calcium intake and colorectal adenoma in a US colorectal cancer early detection program. Am J Clinical Nutrit 2004; 80:1358-1365
22. Lin J, Cook NR, Lee IM, et al. Total Magnesium Intake and Colorectal Cancer Incidence in Women. Cancer Epidemiol Biomarkers & Prevention 2006; 15:2006-2009.
23. Wei EK, Giovannucci E, Selhub J, et al. Plasma Vitamin B6 and the Risk of Colorectal Cancer and Adenoma in Women. J Nat Cancer Instit 2005; 97:684-692.
24. Cho E, Willett WC, Colditz GA, et al. Dietary Choline and Betaine and the Risk of Distal Colorectal Adenoma in Women. J Nat Cancer Instit 2007; 99:1224-1231.
25. Connelly AE, Satia-Abouta J, Martin CE, et al. Vitamin C Intake and Apoptosis in Normal Rectal Epithelium. Cancer Epidemiol Biomark & Prevention 2003; 12:559-565.
26. Cotterchio M, Boucher BA, Manno M, et al. Dietary Phytoestrogen Intake Is Associated with Reduced Colorectal Cancer Risk. J Nutrition 2006; 136:3046-3053.
27. Theodoratou E, Kyle J, Cetnarskyj R, et al. Dietary Flavonoids and the Risk of Colorectal Cancer. Cancer Epidemiol Biomarkers & Prevention 2007; 16:684-693.
28. Männistö S, Yuan SS, Hunter DJ, et al. Dietary Carotenoids and Risk of Colorectal Cancer in a Pooled Analysis of 11 Cohort Studies. Am J Epidemiol 2007; 165:246-255
29. Link LB, Potter JD. Raw versus Cooked Vegetables and Cancer Risk. Cancer Epidemiol Biomarkers & Prevention 2004; 13:1422-1435.
30. Ngo SNT, Williams DB, Cobiac L, Head RJ. Does Garlic Reduce Risk of Colorectal Cancer? A Systematic Review. J Nutrition 2007; 137:2264-2269.
31. Shin A, Shrubsole MJ, Rice JM, et al. Meat Intake, Heterocyclic Amine Exposure, and Metabolizing Enzyme Polymorphisms in Relation to Colorectal Polyp Risk. Cancer Epidemiol Biomarkers & Prevention 2008; 17:320-329
32. Martinez ME, Jacobs ET, Ashbeck EL. Meat intake, preparation methods, mutagens and colorectal adenoma recurrence. Carcinogenesis 2007; 28:2019-2027.
33. Cho E, Smith-Warner SA, Ritz J. Alcohol Intake and Colorectal Cancer: A Pooled Analysis of 8 Cohort Studies. Annals 2004; 140:603-613.
34. Jenab M, Ferrari P, Slimani N, et al. Association of nut and Seed Intake with Colorectal Cancer Risk in the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers & Prevention 2004; 13:1595-1603.
35. Michels KB, Willett WC, Fuchs CS, Giovannucci E. Coffee, Tea, and Caffeine Consumption and Incidence of Colon and Rectal Cancer. Journal of the National Cancer Institute 2005; 97:282-292
36. Sun CL, Yuan JM, Koh WP, Yu MC. Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. Carcinogenesis 2006; 27:1301-1309
37. Dixon LB, Subar AF, Peters U, et al. Adherence to the USDA Food Guide, DASH Eating Plan, and Mediterranean Dietary Pattern Reduces Risk of Colorectal Adenoma. J Nutrit 2007; 137:2443-2450.