Review Article

Diet and supplements and their impact on colorectal cancer

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Background: Colorectal cancer is the third commonest cancer and the third leading cause of cancer death among men and women. It has been proposed that dietary factors are responsible for 70-90% of colorectal cancer and diet optimization may prevent most cases.

Aim: To evaluate the role of dietary components and supplements in colorectal cancer.

Methods: Bibliographical searches were performed in Pubmed for the terms "diet and colorectal cancer", "diet and colon cancer", "diet and rectal cancer", "nutrition and colorectal cancer", "probiotics and colorectal cancer", "prebiotics and colorectal cancer", "alcohol and cancer" and "colorectal cancer epidemiology".

Results: Consumption of processed or red meat, especially when cooked at high temperatures may be associated with increased risk of colorectal cancer. The evidence for dietary fibre is unclear but foods that contain high amounts of fibre are usually rich in polyphenols which have been shown to alter molecular processes that can encourage colorectal carcinogenesis. Meta-analyses provide evidence on the benefits of circulating, diet-derived and supplemented, vitamin D and Calcium. We also found that diets rich in Folate may prevent colorectal carcinoma. The evidence on dietary micronutrients such as Zinc and Selenium in association with colorectal cancer is not conclusive. It has been suggested that there may be a direct association between alcohol intake and colorectal cancer. *In vitro* and *in vivo* studies have highlighted a possible protective role of prebiotics and probiotics.

Conclusions: The lack of randomized trials and the presence of confounding factors including smoking, physical activity, obesity and diabetes may often yield inconclusive results. Carefully designed randomized trials are recommended.

Key Words: Colorectal cancer; nutrition; diet; carcinogenesis

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Introduction

Before the twentieth century, colorectal cancer was relatively uncommon however the incidence has risen dramatically especially in the last fifty years. Several risk factors have been proposed including the adoption of westernized diet, obesity and physical inactivity (1,2). The majority of colorectal cancer continues to occur in industrialized countries. It has been estimated that nutrition could account for more than one third of cancer deaths (3), and that dietary factors are responsible for 70% to 90% of all cases. Therefore, diet optimization could potentially help reduce the incidence of this type of malignancy (4,5). Here we review the key evidence for the role of different dietary components and their effect on colorectal cancer prevention and progression.

Methods

Bibliographical searches were performed in Pubmed for the terms "diet and colorectal cancer", "diet and colon cancer", "diet and rectal cancer", "nutrition and colorectal cancer", "probiotics and colorectal cancer", "prebiotics and colorectal cancer", "alcohol and cancer" and "colorectal cancer epidemiology". The search was performed for the period 1980-2012. As expected, the search yielded an overwhelming abundance of evidence on the association between diet and colorectal cancer. For each type of nutrient/chemical compound we excluded most *in vitro* and animal studies and the remaining results were categorized into different levels of evidence (6) focusing on meta-analyses, systematic reviews and randomized controlled trials where available. Information on ongoing clinical trials

was sourced from the URL: *http://clinicaltrials.gov/*.

Results

Red meat

Red meat might be directly linked to the incidence of colorectal cancer or indirectly because diets high in meat may be deficient of other dietary components such as fibre and polyphenols from fruit and vegetables. Cooking meat at high temperatures may lead to the formation of mutagenic and carcinogenic heterocyclic amines through the interaction of muscle creatinine with amino acids (7) as well as the formation of N-nitroso compounds (8). Frying, grilling, broiling or cooking on coal can potentially induce these changes. Haem in meat can act as a nitrosating agent promoting the formation of N-nitroso compounds. Darker meats are more abundant in haem than white meats and therefore, high consumption of red meat (beef, pork, or lamb) could increase the risk of colorectal cancer (9-13). Haem iron has been positively associated in the literature with the development of colonic polyps (14), adenomas (15) and colorectal cancer (16-18). Other studies including the Nurses' Health Study did not show such association (19-21). Furthermore, colorectal carcinogenesis could involve the secretion of insulin as a response to red and processed meats and thus subsequent activation of insulin and insulin growth factor-1 receptors, may lead to increased cell proliferation and reduced apoptosis (22).

The association of total or red meat cooked at high temperatures and increased risk of colorectal cancer has been shown in some case-control studies (23-25) but not in others (26). High consumption of red meat such as beef, pork, or lamb was associated with increased risk of colorectal cancer in both men and women in cohort studies (27,28). Data from the Health Professionals Follow-up study (HPFS) cohort showed a three-fold increase risk of colon cancer in subjects who consumed red meat more than five times in a week (29). Furthermore, it showed an increased risk of developing distal colon adenoma.

A meta-analysis from 2002 by Norat *et al*. showed a 33% increased risk of colorectal cancer in people consuming higher levels of red and processed meat (30). A systematic review of prospective studies by Sandhu *et al*. determined that an increase of 100 g in daily consumption of all meat or red meat was associated with a 12-17% increase in risk of colorectal cancer (31). However contrary to this, a prospective cohort study of 45,496 women by the National Cancer Institute (32), showed no association between consumption of red meat, processed meat, or well-cooked meat and colorectal cancer risk. Other studies have also been unable to support a role of fresh meat and dietary fat in the etiology of colon cancer (28,33).

In 2007, the research 'Expert Report' of the second world cancer research fund/American research concluded that intake of red and processed meat increases the risk of colorectal cancer (34), however, more recent reviews of prospective epidemiological studies found that there is not enough epidemiological evidence to link red and processed meat with colorectal cancer (35,36). A recent meta-analysis of prospective studies by Chan *et al*. concluded that processed and red meat is associated with increased risk of colorectal cancer, and a linear increase in risk was reported for intake of red and processed meats up to 140 g/day.

Fish and poultry are alternative sources of protein and have been shown to reduce the risk of colon cancer and adenoma (27,28,37-45). Possible mechanisms may involve more efficient methylation due to high methionine content in these foods or the presence of n-3 polyunsaturated fatty acids (PUFA), especially from oily fish.

In summary, performing studies on diet is complex with so many variables and confounding factors. Overall, there is evidence from both case-control and cohort studies that consumption of processed or red meat, especially when cooked at high temperatures by methods such as frying, grilling or broiling, is associated with increased risk of colorectal cancer. The dose-response relationship as well as the gender differences need to be investigated further. A determined diet might suggest limitation or avoidance of red or processed meats and support the consumption of white meat and fish.

Fat

Several case- control studies have demonstrated an increase in the risk of colorectal cancer with increased total energy intake (46-48). Dietary lipids provide a rich source of energy and diets high in lipids, especially animal fat, may increase the risk of colorectal cancer (49,50). In contrast to this, there are large cohort studies that do not support an effect of dietary fat on colon cancer (51,52). Different types of fats may play different roles in colorectal carcinogenesis via different mechanisms such as upregulation of apoptosis, inhibition of interleukin 1 and tumour necrosis factor -α synthesis, COX-2 inhibition and modulation of the redox enviroment in the colonocytes (53,54).

Saturated fat

Saturated fats are principally found in animal products including red meat and dairy products, such as cheese and butter. Coconut oil, coconut milk, palm oil, and cocoa butter are all sources of plant-derived saturated fats. Case-control (55) and prospective cohort (27) studies demonstrated an increase in risk of colorectal cancer

in people with higher consumption of saturated fat but confounding factors in the food matrix such as red meat and reduced intake of dietary fibre always pose a challenge for researchers.

A prospective study of 88,751 women confirmed that high intake of animal fat increases the risk of colon cancer and supports substitution of red meat as a source of protein with fish or chicken (27). The results of the Dietary Approaches to Stop Hyrtension Diet (DASH) study of 130,000 participants found a 20% relative risk reduction in patients who consumed lower levels of animal fat (56). In a meta-analysis, Alexander *et al*. found no independent association between animal fat intake and the risk for colorectal cancer (33). The Women's Health Initiative Dietary Modification Trial was a randomized controlled trial, which showed that low-fat dietary pattern did not reduce the incidence of invasive colorectal cancer (57).

The advice to reduce intake of saturated fat in order to reduce the risk of colorectal cancer remains only suggestive due to the lack of consistency from clinical studies.

Omega-3 (n-3) PUFA

Epidemiological studies and populations consuming large numbers of polyunsaturated fish oils have been found to have lower rates of colon cancer (58). This has led to the hypothesis that diets high in n-3 fatty acids may reduce the risk of colorectal cancer. An inverse association between n-3 PUFA (omega-3) and colorectal cancer has been shown in case-control (45,59,60) and prospective studies (61,62). On the contrary, Daniel *et al*. reported that one of the major dietary sources of omega-3 fatty acids, alpha-linolenic acid, was associated with increased risk of colorectal cancer in women and that omega-6 intake was inversely related to colorectal cancer risk in men (63). In their cohort, Sasazuki *et al*. found no evidence that omega-6 acids increased the risk.

Fatty fish are an excellent source of omega-3 fatty acids and vitamin D. Butler *et al*. showed that dietary marine n-3 PUFAs were positively associated with advanced colorectal cancer (64) while other studies suggested the opposite (39-42,62,65). A Chinese meta-analysis of prospective studies of nearly half a million individuals did not show any protective properties effect of n-3 fatty acids on colorectal cancer risk (66). A recent meta-analysis of case-control and prospective cohort studies suggested that fish consumption decreased the risk of colorectal cancer by 12%. However, the results showed a less profound effect on colonic as opposed to rectal cancers and highlighted differences between case-control and cohort studies (67). Omega-3 fatty acids may be taken as food supplements however there is very limited data available in association to colorectal cancer. Skeie *et al*. showed that cod-liver oil consumption lowers risk of death in patients with solid tumours without significant results on colorectal cancer risk (68). In fact, a systematic review of 20 prospective cohort studies found that dietary supplementation with omega-3 fatty acids is unlikely to prevent cancer (69).

The evidence to suggest that consumption of diets high in omega-3 PUFAs may prevent colorectal cancer is limited and in many cases contradictory. This includes not only n-3 fatty acids derived from fish but also from other sources such as α-Linolenic acid from food sources including rapeseed, soybeans, walnuts, flaxseed and olive oil. The evidence to suggest supplementation of omega-3 PUFAs with cod-liver oil is non-conclusive.

Dietary fibre, fruit and vegetable

The hypothesis that high fibre consumption may be reducing the risk of colorectal cancer has been postulated following the observation of the low incidence of colorectal cancer in African populations that consume a high-fiber diet (70). Fibre is defined as heterogeneous plant material composed of cellulose, hemicellulose and pectin. It has been proposed to work by reducing faecal transit times, diluting and binding carcinogens, altering the proliferation of gastrointestinal epithelium, maintaining colorectal epithelial cell integrity (71), adsorbing heterocyclic amines (72) affecting bile acid metabolism, and stimulating bacterial anaerobic fermentation to increase the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. SCFAs have been shown to decrease colonic pH and inhibit carcinogenesis (73).

Colorectal adenomas are the precursors of most colorectal cancers. The effect of diet in relation to colorectal adenomas and adenoma recurrence was explored in several studies. Diets high in wheat bran (74), fruit and vegetables (49,75), citrus fruits (19), cruciferous vegetables (76), dark-green vegetables and onions and garlic (77) and tomatoes (23) may confer protection against colorectal adenomas and subsequently colorectal carcinoma. Some prospective studies did not show this association (74,75).

Early meta-analyses of case-control studies have generally shown a protective association between fibre and colorectal cancer (78,79). In one study, high fibre diet was associated with decreased survival (80). Cohort studies yielded mixed results often showing none or a weak inverse association between dietary fiber and risk of colorectal cancer (19,28,37,38). Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the Swedish mammography cohort study showed reduced risk of colorectal cancer and

colorectal adenomas among people who consumed the highest amounts of fibre particularly from grains fruits and vegetable (81-85). However, in a meta-analysis of prospective studies, Park *et al.* suggested that high dietary fiber intake was actually not associated with a reduced risk of colorectal cancer (86). In a recent meta-analysis of prospective cohort and nested case-control studies of dietary fibre the authors suggest a 10% reduction in risk of colorectal cancer for each 10 g/day intake of total dietary fibre and cereal fibre (87). Whole grain was also associated inversely (87). Other studies, did not suggest a protective association with specific subtypes of fibre such as fruit, vegetable or cereal (27,88,89).

One can conclude that the evidence for fibre is unclear in terms of benefit in reducing colonic adenoma pathway and colorectal cancer formation. There are discrepancices between case-control and prospective cohort studies for reasons such as recall bias, selection bias and sample size. The general health benefits of fibre which may pertain to a variety of cancers as well as the other benefits to the colon such as diverticulosis and constipation suggests that a high fibre diet including wheat bran, cereal, whole grain, citrus fruits, cruciferous vegetables, dark-green vegetables, onions, garlic and tomatoes may be recommended.

Folic acid/folate (vitamin B9)

These are water-soluble vitamins found in fruits, dark green vegetables and dried beans. Humans are not able to synthesize this vitamin, which has to come from dietary sources. The bioavailability of folic acid is higher than folate because it is non-conjugated and hence more stable. Several mechanisms have been suggested for its role as a preventer of carcinogenesis through molecular mechanisms such as DNA synthesis, repair and methylation (90,91).

The observation that folic acid supplementation was associated with a substantial decrease in colon cancer among patients with ulcerative colitis led researchers to examine the role of folic acid in the prevention of colorectal cancer (92). Observational studies highlighted that deficiency of dietary folate correlates with increased occurrence of colorectal neoplasia (93) but may protect against cancer risk or adenoma formation only in those patients with low folate baseline (94). Examination of the data from the Nurses' Health Study (NHS) and the HPFS, showed that high intake of dietary folate was inversely associated with risk of colorectal adenomas (95). A few years later, using data from the NHS cohort, the same group were able to show a considerably lower risk of colon cancer among women who used multivitamins containing 400 μg of folate (96). This was also confirmed in other populations such as the Cancer Prevention Study II cohort (97). A large scale meta-analysis of prospective studies supported the hypothesis that folate has a small protective effect against colorectal cancer (98). Manson *et al.* showed how dietary folate supplementation maybe responsible for reduction of incidence of colorectal cancer in the US and Canada (99), however, Giovanucci *et al.* showed how dietary folate reduced risk of colorectal cancer or adenoma but not when folate came from supplements (100). Giovanucci suggested that folate supplementation could be associated with higher risk of adenoma recurrence and may even be harmful to patients with a previous history of colon cancer (100). A randomized secondary prevention trial reported that folate supplements increased the risk of recurrent advanced adenomas or recurrent adenomas (93).

In conclusion, diets rich in folate may prevent colorectal carcinoma. Further studies are required in order to assess the role of supplemented folate and the reported risks of adenoma recurrence.

Alcohol

The mechanism by which alcohol might be linked to carcinogenesis is unknown but proposed pathways include its ability to reduce folate (101), promote abnormal DNA methylation (102), delay DNA repair, alter the composition of bile salts or induce Cytochrome p450 to activate carcinogens (103).

A large number studies have suggested an association between alcohol intake and colonic adenoma as well as colorectal cancer risk (104-106). Intake of 30 grams of alcohol per day is associated with increased risk of colorectal cancer compared to low intake. Giovannucci *et al.* showed that men in HPFS cohort who drank more than two drinks of alcohol per day had a 2-fold higher risk of colon cancer (107) compared to men who drank fewer than 0.25 drinks per day. Heavy drinkers were found to have a higher risk of colorectal adenoma. Data from the NHS and EPIC cohorts (95,104) showed similar findings. A meta-analysis of five large cohort studies showed similar results for both men and women (108). This risk may be directly related to alcohol or to the effects of alcohol on folate levels. In fact, women with low serum folate levels who consumed large amounts of alcohol, had a greater risk of colorectal cancer (109). Two other studies found no association of total alcohol consumption with all-cause mortality in colorectal (110) and colon cancer (111) and Zell *et al.* reported a lower risk of all-cause mortality when subjects consumed wine regularly as opposed to infrequently (112). Consumption of red wine can be beneficial but the protective role could be allocated to polyphenols rather than its alcohol content (113).

In conclusion, currently the literature would suggest minimizing alcohol intake as a means to reduce the risk of developing colorectal cancer or colorectal adenoma. A consumption of less than 30 g per day as well as folate supplementation is recommended in people who consume alcohol regularly.

Calcium and vitamin D

Vitamin D is one of the fat-soluble vitamins and more than 90% is synthesized endogenously from skin exposure to UV sunlight (114). The remaining comes from the diet as pro-vitamin cholecalciferol (D3), which is found naturally in oily saltwater fish, egg yolks and livers and from the plant-derived pro-vitamin ergocalciferol (D2) found in foods such as mushrooms. Food fortification may provide an extra source of vitamin D. The active form of vitamin D is 1,25-dihydroxyvitamin D_3 (Calcitriol) which is formed by hydroxylating the pro-vitamins in the liver and kidneys. The use of Calcitriol in experimental studies has been shown to induce differentiation and inhibition of tumour cell proliferation of various types of cancer cells, however, its use is limited due to development of toxic hypercalcaemia. For this reasons, calcitriol analogues are usually used (115,116). Vitamin D and calcium are thought to exert their protective effects by decreasing cell proliferation, inhibiting angiogenesis, stimulating apoptosis and promoting cell differentiation (117). Other proposed mechanisms may involve binding of calcium to bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon (118,119).

Garland *et al*. proposed that lower levels of vitamin D could account for the increase in mortality from colon cancer in higher latitudes (120) and epidemiological studies showed that deaths from colorectal cancer have been found to be higher in areas with less sunlight (121). Populations consuming higher amounts of fresh fish, shellfish, calcium and vitamin D have lower incidence of colorectal cancer (122) and may even have the lowest incidence of both colon and rectal cancer in Europe and North America (123).

Data from case-control studies are inconsistent. The protective effects of calcium alone were demonstrated in some case-control studies (124) but not in others (125). Case-control studies involving only women showed reduced risk of colorectal cancer (126,127). This was not demonstrated in studies involving both men and women (128). No significant inverse association was observed between calcium and vitamin D levels and the risk of colorectal cancer (125,128). The Women's health initiative study was a randomized controlled trial, which showed that daily supplementation of calcium with vitamin D for seven years, had no effect on the incidence of colorectal cancer among postmenopausal women (129). In terms of Vitamin D levels, a meta-analysis by Garland *et al*. found an inverse association between circulating levels of 25- hydroxyvitamin D_3 and the risk of colorectal cancer (130).

Calcium was found to have protective effect on colorectal cancer risk in some prospective studies (131-133) but not in others (134,135). Data from the HPFS and NHS cohorts showed that total, dietary and supplemented calcium reduced the risk of distal colon but not proximal cancer. Most of the risk reduction was achieved by calcium intake of 700-800 mg/day. A meta analysis of 10 cohort studies showed 22% reduction in the risk of colorectal cancer in those with higher intake of calcium (136).

Regarding colorectal polyps, a three-year intervention study with calcium and antioxidants, found no effect on polyp growth but possibly a protective role against adenoma formation (137). Higher intake of calcium alone (138) or when combined with Vitamin D (139) was found to be protective against adenoma recurrence.

In conclusion, data from case-control studies are inconsistent but cohort studies and meta-analyses provide evidence on the benefits of circulating, diet-derived and supplemented vitamin D and calcium. Further studies are needed to ascertain whether there is any sex predilection. On the basis of current evidence one could suggest intake of vitamin D at a dose of 1,000 IU per day which is regarded as safe, and attaining calcium intakes of 700-800 mg per day. Modest duration of sunlight exposure should be sought to raise levels of 25-hydroxyvitamin D_3. Diets rich in oily fish, shellfish, milk and dairy products contain high amounts of calcium and vitamin D.

Polyphenols

Polyphenols are a class of chemicals known for their numerous benefits especially their antioxidant effects (113,140,141), inhibition of cellular proliferation (142), induction of cell cycle arrest (143), interaction with apoptotic pathways and antiangiogenic and antimetastatic properties (144). They are divided in five classes; flavonoids, phenolic acids, ligans, stillbenes and others. The most important dietary sources of polyphenols are fruits, vegetables, seeds, and beverages such as fruit juice, green tea, coffee, cocoa drinks, red wine, and beer. The chemoprotective role of polyphenols against cancer has been extensively studied. Evidence from case-control studies (145), cell culture and animal studies have shown a protective role against colorectal malignancy (145,146).

Curcumin

This polyphenol is a curcuminoid found in turmeric

spice that has antioxidant, anti-inflammatory and anti-tumour properties (147,148). Curcumin has been shown to work by inhibiting cell invasion (149) and by having anti-inflammatory properties (150). It has been shown to reduce the number and size of ileal and rectal adenomas in patients with familial adenomatous polyposis (151).

Flavonoids

Apigenin is a flavonoid found in parsley and celery and it has been shown to inhibit colonic carcinogenesis by inducing apoptosis in animal models (152). Cyanidin, a flavonoid in strawberries and cherries has been studied *in vitro* and in animal models and has also been shown to inhibit colonic carcninogenesis (153). Other flavonoids with similar properties include Delphinidin which is found in dark fruit (154) and Genistein which is abundant in Soy beans (155). Quercetin from onions, broccoli and apples has been shown to decrease cell growth by interacting with β-catenin (156) and by induction of apoptosis (157). Citrus fruits contain high levels 5-hydroxy-6,7,8,4'-tetramethoxyflavone and Naringenin which has been shown to induce apoptosis and cell-cycle arrest of luminal surface colonocytes (158,159).

Green tea

Green tea is rich in a type of Flavonoids, the Flavonols. Examples include Catechin and Epicatechin. Epigallocatechin-3-gallate (EGCG) is the most abundant Catechin in green tea. The benefits have not only been shown *in vitro* and animal models (113,160-163) but also in large population studies. Consumption of green tea has been associated with a 40% reduction in colorectal cancer risk in a cohort of 69,710 Chinese women (163).

Coffee

Coffee is a complex blend of hundred of chemicals including anti-oxidants, mutagenic, and anti-mutagenic compounds (164). Additionally, it has been shown to affect gastrointestinal physiology such as stimulating a motor response of the distal colon, reducing faecal transit times and reducing the gut's exposure to potentially carcinogenic faecal load (165). Over the last few decades the relationship between coffee and colorectal cancer has been extensively explored (166,167). Outcomes from clinical studies have been inconsistent and no firm guidance has been suggested. Several meta-analyses of cohort and case-control studies found that substantial consumption of coffee is associated with lower risk of colorectal cancer (168-170). Other meta-analyses failed to reconfirm this inverse association (171). Li *et al*. examined the results of 25 case-control studies and 16 cohort studies in the most recent meta-analysis of the literature. Subgroup analysis of case-control results found a significant decrease in cancer risk, especially in Europe and for females. A subgroup analysis of cohort studies, showed a lower risk of colon cancer in Asian women only (172).

There are inconsistencies between case-control and prospective studies as well as noted differences between sex and race. Consumption of coffee maybe protective against colorectal cancer but further studies are required to establish a dose-risk relationship and further clarify whether there is any sex predilection in the risk.

Other phytochemicals

Natural phenols

These molecules are smaller in size than polyphenols. Examples include Resveratol which is found in the skin of grapes and red wine and has been shown to inhibit metastasis by reducing hypoxia inducible factor-1α and MMP-9 expression in colonocytes (173) as well as inhibiting Wnt signalling and β-catenin localisation (174).

Carotenoids

Carotenoids are naturally occuring pigments some of which can be converted by the body into vitamin A. Examples include β-carotene which is found in carrots, red palm oil and pumkin. Lycopene is another example of pigmented phytochemical found in tomatoes, watermelons, papaya, apricots and citrus fruit. They have been found to exhibit anti-oxidant, anti-proliferative and anti-inflammatory properties (175-177).

Isothiocyanates

These are Sulphur-containing phytochemicals found in abundance in cabbage, turnips, broccoli, kale, cauliflower, watercress, brussel sprouts, mustard seeds and horseradish. They have been found to possess chemopreventative activity (178-180) against colonic cancer.

Overall, diets high in polyphenols and other phytochemicals such as carotenoids, isothiocyanates and natural phenols have been shown to be protective against colorectal cancer. Foods rich in these compounds includes spices such as mustard seeds and tumeric, fruits including strawberries, cherries, apples, citrus fruit, grapes, watermelons, papaya, apricot and vegetables such as onions, brocolli, carrots, red palm oil, pumkin, leafy green vegetables and tomatoes. Consumption of green tea may also be beneficial.

Zinc

Animal models have shown that low zinc levels may

be associated with preneoplastic lesions and colonic carcinogenesis (181). *In vitro* studies suggested that Zinc supplementation may positively influence tumour cell response to anticancer drugs by altering colonic cancer cell gene expression (182). In the Iowa Women's Health Study, intake of dietary zinc was associated with a decreased risk of both proximal and distal colon cancer (18). A more recent prospective study by Zhang *et al*. did not find a role for Zinc intake with colorectal cancer risk but the authors highlighted a possible inverse association between dietary zinc and rectal cancer in women (183). Therefore, no substantive evidence is available for dietary Zinc intake however the putative inverse association in women needs to be explored further.

Selenium

An inverse association between Selenium supplementation and the risk of colorectal cancer was observed in several studies (184-189). Selenium supplementation by way of brewer's yeast supplementation was associated with up to 50% reduction in the incidence of colorectal cancer (188,190). Other studies contradict these findings and show no significant associations (191-192). Therefore, studies do not currently provide evidence for Selenium supplementation.

Gut microbiota

The colon contains more bioactive cells than the rest of the body (193). Inulin-type fructants are oligosaccharides obtained through diet and 90% of them are effectively metabolized by endogenous colonic microbiota into gases and organic acids including short chain fatty acids (SCFAs) (194). Animal-model experiments showed that these oligofructants can reduce the numbers of aberrant crypt foci (195) and influence the activity of natural killer cells and production of IL-10 (196). Naturally-occurring oligofructants can be found in foods such as onions, Jerusalem artichokes, garlic, asparagus and chicory. Examples of SCFAs include acetic and butyric acid. SCFAs have been shown to reduce tumourgenesis (197) and proposed mechanisms include promotion of the growth of probiotic *Lactobacilli* species which maintain epithelial health and downregulate the inflammatory response (198). As *Bifidobacteria* and *Lactobacilli* are selectively stimulated to grow, this may happen at the expense of pathogenic bacteria (199). Other benefits of microbiota include synthesis of vitamins such as folate (200). In human trials synbiotics were found to decrease DNA damage in colonic mucosa and lower the level of colonic proliferation (201). Low proliferation is a recognized marker of low colonic cancer risk (202).

Other components in our diet may affect the gut microbiota and influence colorectal oncogenesis. Gut microbiota hydrolyse polyphenols to a great extend affecting the amount of these chemicals being absorbed, thus, ameliorating their protective properties. Excess fat in the diet means that more bile will be produced and more bile acids will escape the enterohepatic circulation. In the colon, these can be metabolized to mutagenic components (203). High butyrate levels are known to protect against the mutagenic effects of bile acids (204). Moreover, *Lactobacilli* have been shown to directly reduce the mutagenic properties in bile acids (205). As mentioned above, meat cooked at high temperatures contains high levels of heterocyclic amines which have been found to be fermented by gut microbiota. The byproducts of this process can damage DNA and increase the risk of colorectal cancer (206).

There is a completed Phase 2 trial assessing the role of probiotics on gut microbiotca and colorectal cancer but the results have not been published yet (207). The role of VSL#3 probiotics in rectal cancer is investigated in a phase 3 clinical trial but results are also awaited (208). Currently there is no strong evidence regarding prebiotics and colorectal cancer risk.

Overall, the role of probiotics and prebiotics is not completely clear but *in vitro* and *in vivo* studies have highlighted a possible protective role of gut microbiota in colorectal carcinogenesis. There appears to be benefit from a diet high in oligofructant-containing foods including onions, jerusalem artichokes, garlic, asparagus and chicory.

Lifestyle

Apart from alcohol and smoking (38), other lifestyle factors have also been associated with the risk of developing colorectal cancer. Higher levels of physical activity have been reported to reduce risk by up to 40% and several studies have reported adverse outcomes in patients who are obese (209-211), suffer from diabetes (209,212) or use the oral contraceptive pill (213). Non-modifiable factors which may increase the risk include higher body height (38,214), post-menopausal status (213,215) and endogenous oestrogen exposure (215).

Discussion/conclusions

There is an abundance of evidence in the literature on the role of nutrition on colorectal carcinogenesis. Often the evidence may be inconclusive due to the lack of randomized trials and because many studies have been overwhelmed

by confounding factors such as smoking status, physical activity, obesity and diabetes. Many studies were influenced by possible recall and selection biases, which make it difficult to draw solid conclusions. In this review, we set out to identify nutritional factors that could play a role in the development of colorectal cancer. Red or processed meats especially when cooked at high temperatures should be limited and can be replaced by the consumption of white meat and fish. Diets high in n-3 fatty acids, dietary fibre, folate, vitamin D, calcium and polyphenols may protect against colorectal cancer and colorectal adenoma formation. The consumption of alcohol is not advocated. The role of probiotics and prebiotics is not completely clear but *in vitro* and *in vivo* studies have highlighted a possible protective role of gut microbiota in colorectal carcinogenesis.

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