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Diet influence on colorectal cancer

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Summary. Colorectal cancer ranks the third highest in cancer incidence and fourth in cancer mortality in both sexes combined worldwide. Dietary factors have been thought to account for about 30% of cancers in Western countries, making diet second only to tobacco as a preventable cause of cancer. With reference to risk factors, considerable attention has focused on diet, and, in particular, red meat, processed meat, fat, carbohydrates, proteins, fibers and alcohol drinking. To address these research gaps and inconsistencies, we therefore reviewed the role of dietary intake of carbohydrates, protein, fats, meat, fish, milk and dairy products, whole grains, fruits and vegetable, fibers, folic acid, calcium and alcohol in colorectal cancer risk.

Key words: colorectal cancer; dietary factors; review

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common of death from cancer (1). It accounts for about 10% of all new cases of cancer and is approximately equal for men and women (2).

Diet is the major source of human exposure to environmental carcinogens and anti-carcinogens which would play a major role in the enhancement as well as the reduction of cancer risk. Internationally, incidence and mortality rates of colorectal cancer show that the significant variations in dietary habits among populations of different cultures and lifestyles could help explain the differences between regions (3).

In the present paper, the role of dietary intake of carbohydrates, protein, fats, meat, fish, milk and dairy products, whole grains, fruits and vegetable, fibers, folic acid, calcium and alcohol in colorectal cancer risk was reviewed.

Diet influence on colorectal cancer

Carbohydrates

With reference to carbohydrate intake, some studies reported positive (4) association whereas other studies found no association between dietary carbohydrate and colon cancer (5-7).

Substantial evidence indicates that hyper-insulinemia may play an important role in colorectal cancer (8, 9). Dietary intake can influence insulin levels, especially among individuals who are insulin resistant and could be associated with increased risk of colorectal cancer. Two case-control studies reported positive associations between intakes of high glycemic load diet and colorectal cancer risk (10, 11). In a recent large prospective study, a slight increase in colorectal risk was observed in men with high dietary glycemic load diet and sugar intakes, but not in women (12).

Proteins

The proof of CRC promotion is much weaker for high-protein diets than for high-fat diets, and epide-

miology studies do not suggest that protein intake is a risk factor (13).

However some mechanisms might explain CRC promotion by high protein diets. A high protein diet, or digestion-resistant proteins, leads to more protein entering the colon and being fermented by the gut microflora (14). Protein fermentation products, like ammonia, phenols and p-cresol, show some promoting properties, possibly because of their toxicity to the mucosa. They disturb cellular metabolism and DNA synthesis, reduce cell life span and enhance cell turnover (15).

The level and the nature of dietary proteins do not seem to be major determinants of carcinogenesis, and proteins from meat do not promote experimental carcinogenesis. In contrast, proteins that are slowly or not digested can promote carcinogenesis, for example; overcooked casein and with potato proteins (16, 17).

Fat

Epidemiological studies indicate a positive association between the dietary intake of saturated fat and/or animal fat and colon cancer risk and an inverse relationship between the intake of fish and fish oil rich in n–3 PUFAs and colon cancer development (18).

High fat intake favors the secretion of bile acids (BA) into the duodenum, and activates bacterial 7-alphadehydroxylase that makes secondary BA. These BA, deoxycholic and lithocholic acids, promote colon carcinogenesis in several animal models, and are elevated in stools from populations at risk for cancer (19). A high fat diet also leads to free fatty acids in the colonic lumen. They may damage the colonic epithelium and increase proliferation, an effect blocked by dietary calcium (20). Bile acids have been known to be tumor promoters for many years, and the addition of cholic acid to rodents' diet enhances colonic epithelial cell proliferation, and increases the number of tumors in animals exposed to carcinogens (19). Blood BA also correlates with tumor incidence in F344 rats (21).

Diets rich in n–3 PUFAs inhibit colon carcinogenesis through the modulation of colonic *ras*-p21, cyclooxygenase-2, and inducible nitric oxide synthase activities and apoptosis. These results suggest that decreasing the intake of n–6 PUFAs and saturated fats and increasing that of n–3 PUFAs, particularly eicosapentaenoic acid and docosahexaenoic acid has the potential to be a major component of colon cancer control (18).

Meat

Meat is a primary source of water, fat and protein, providing all essential amino acids as well as good amounts of various micronutrients (22). However, since 2007 considerable alarms rose about the cancer risks associated with red and processed meat specially colorectal cancer (CRC) (23, 24). Several studies concluded that a 12–17% increased risk of CRC was associated with a daily increase of 100 g of all meat or red meat, and a 49% increased risk associated with a daily increase of 25 g of processed meat (25, 26).

In a study conducted over 10 years on 478,040 men and women from 10 European countries, a statistically significant increase in CRC risk was positively associated with the high intake of red and processed meat (more than 160 g/day) (27).

The most convincing evidence on meat association with cancer is from processed meat such as ham, bacon, smoked chicken, pastrami, hot dogs, and salami which can promote carcinogenesis, or yield promoters in vivo (28). Processed meats often differ from red meat by three major points: (i) they often contain more fat than red meat; (ii) they contain specific additives, notably salt and sodium nitrite; (iii) their long-time storage yields cholesterol oxidation products. Processing and cooking can generate heterocyclic amines (HCAs), polycyclic aromatic hydrocarbon (PAHs), and N-nitroso compounds (NOCs) which are mutagens and animal carcinogens (29).

Fish

Fish intake was not associated with colorectal cancer risk in many recently published prospective studies (30, 31). However, some results suggest that the risk increase associated with low versus high fish consumption of fish (<14 g/day versus >50 g/day) was approximately 40%, independent of the levels of red and processed meat intake (32). In another research, it was reported that fish consumption decreased the risk of colorectal cancer by 12% (33).This could be due to the potential benefits of fish to human health linked with anti-inflammatory and anticarcinogenic effects of

its long-chain n-3 fatty acids content (34). In mice or rat colorectal cancer models, omega-3 fatty acids protect against colorectal cancer by inhibiting cyclooxygenase-2, which suppress eicosanoid biosynthesis from arachidonic acid (35, 36). In conclusion, the World Cancer Research Fund concluded that "diets high in fish consumption possibly have no relationship with risk of colorectal cancer" (37).

It should be noted that smoked or salted fish might increase the risk, probably due to an increased intake of N-nitroso compounds (38).

Milk and dairy products

Studies have reached mixed conclusions concerning the effect of dairy products as colorectal cancer risk factors (39).

Dairy products are usually high in saturated fat associated with increased colorectal cancer risk, but also high in calcium associated with reduced colorectal cancer risk (40).

In the European Prospective Investigation into Cancer and Nutrition (EPIC), the associations between intakes of whole-fat, semi-skimmed and skimmed milk with colorectal cancer risk were studied. The role of non-dairy calcium sources was also investigated. During the mean 11 years of follow-up and after multivariable adjustments, all types of milk were inversely associated with colorectal cancer risk regardless of the fat content of the dairy products considered. This association was limited to dairy sources of calcium only, with no association observed for non-dairy calcium sources, cheese or yoghurt (41).

A nonlinear association between milk and total dairy products and colorectal cancer risk was reported, and the inverse associations appeared to be the strongest at the higher range of intake (42).

Whole grains, vegetables and fruits

According to the World Cancer Research Fund/ American Institute for Cancer Research, there is convincing evidence that intake of foods containing dietary fiber decreases the risk of CRC (43), and studies have suggested that dietary fiber from cereal sources is especially associated with this lower risk (44, 45). Fiber increase stool size and increase the speed of food transit through the colon, also diluting the gut contents will reduce the absorption of carcinogens by the colon mucosa (46).

Whole grains are an important source of dietary fiber and are found to be associated with a decrease risk of colorectal cancer (47).

Greater consumption of fruits and vegetables, particularly, dark-green leafy, cruciferous, a deep-yellow on tones, is associated with a lower risk of colorectal cancer. In a quantitative overview of the published results of nine cases control studies (48) fruits and vegetables are excellent sources of fiber, vitamins, minerals, and phytochemicals. It was found that the consumption of 100g/day of vegetables was associated with a decreased risk in colorectal cancer and colon cancer risk. Most studies included in analysis observed a null association between vegetable consumption and colorectal cancer.

Folic acid

Folic acid, a water-soluble vitamin, is found naturally in a variety of foods such as green leafy vegetables, asparagus, broccoli, Brussels sprouts, citrus fruit, legumes, dry cereals, whole grain, yeast, lima beans, liver and other organ meats. Both the natural form and the synthetic one are widely used in supplements and for food fortification. Folic acid deficiency causes an imbalance in the one-carbon metabolic pathway, which is vital to hemoglobin synthesis as well as DNA synthesis, repair and methylation (49).

Dietary intake and blood measurements of folate have been shown to be inversely related to the risk of colorectal cancer or its precursor adenomas in most of the published observational epidemiologic studies (50). According to recent a study, a diet low in folate and methionine and high in alcohol (methyl-deplete diet) is associated with an increased risk of colorectal cancer (51). Similarly, a diet low in folate and protein and high in alcohol is inversely related to colon cancer in men but not to rectal cancer with no relationship found between serum folate as a biomarker and colon or rectal cancer (52).

Small human intervention trials have also reported that folic acid supplementation (400 μg to 10 mg/ day for 3 months to 2 years) improves or reverses several functional biomarkers of folate metabolism and colorectal cancer (50). Giovannucci *et al.* also revealed

that the consumption of folic acid containing multiple vitamin supplements is related with lower risk of colon cancer (53).

One recent study reported that folic acid supplementation at 5 mg/day for 3 years significantly reduced the number of recurrent adenomas (54). Inversely, two folic acid chemoprevention trials (500 μg to 1 mg/day for 2–3 years) in subjects with previously resected colorectal adenomas did not demonstrate a protective effect of folic acid supplementation on the incidence of recurrent colorectal adenomas (55, 56).

Recently, an emerging body of evidence has raised concern that high levels of folate or folic acid may in fact promote colorectal carcinogenesis. A Swedish population-based case–control study has found that high plasma folate concentrations are associated with an increased risk of colorectal cancer (57). Furthermore, folic acid supplementation at 1 mg/day for 6 years was found to significantly increase the recurrence of advanced colorectal adenomas in subjects with a history of colorectal adenomas (58).

Although, several data suggest that there is sufficient cause for concern about the potentially deleterious effect of folic acid supplementation on colorectal cancer development and progression. Furthermore studies are needed to provide definitive evidence to address the potential benefits and risks of folate on colorectal cancer incidence rates and mortality. In particular, long term researches should be performed to identify the dose–response relationship between total folate intake and colorectal cancer risk.

Calcium

The role of calcium in colorectal neoplasia has been investigated in a lot of studies such as animal studies, correlation studies, and cohort studies. Additional settings include human intervention studies on the effect of calcium supplementation on cell proliferation (59) and in vitro studies on human epithelial cells (60).
It is hypothesized (61) that calcium might reduce colon cancer risk by binding secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon, thus reducing the proliferative stimulus of these compounds on colon mucosa. Calcium can also directly influence the proliferative activity of the colon mucosa (59).

Alcohol

A strong association between intake of alcohol and risk of colon cancer has been observed in ecological (62), cohort (63) and population-base case-control (64).

Alcohol has been shown to be related to higher risk of colorectal adenoma (65), 3 of 4 cohort studies that investigated the association of alcohol and colon cancer among non-alcoholics showed significant results. The mechanism that alcohol makes to increase the risk for colorectal cancer is unknown. One possibility is alcohol's role as an antagonist of folate and methionine metabolism (66). The alcohol breakdown product acetaldehyde may inactivate methyltetrahydrofolate, the form of folate required for methionine synthesis (67). It was also proved that the carcinogenicity of methyl-deficient diets is enhanced by ethanol in rodents (68).

Conclusion

This review demonstrates that a variety of modifiable dietary factors are associated with differences in colorectal cancer incidence rates. This suggests the potential for colorectal cancer risk reduction by reducing high dietary glycemic load diet, slowly digested proteins, animal fat, red meat and alcohol consumption and by increasing fruits, vegetables, whole grains, fiber, dairy sources of calcium, fish and calcium intake. Furthermore studies are needed to provide definitive evidence to address the potential benefits and risks of folate on colorectal cancer incidence rates and mortality.

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