Chapter

Nutrition: A Natural and Promising Option in Colorectal Cancer Intervention

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Abstract

Nutrition: a natural and promising option in colorectal cancer intervention Nutrition plays a significant role in the intervention of colorectal cancer (CRC) by decreasing the risks of colorectal carcinogenesis. Products from both plant and animal origins have been involved in the prevention and/or treatment of CRC. Intake of dietary products including fibre-rich foods, nutraceuticals, wholegrains, dairy products, and limited consumption or avoidance of red/processed meat and alcohol could reduce the risk of CRC. These nutritional compounds, in CRC intervention, could be in form of folklore/alternative medicine or isolated compounds used in the production of many chemotherapeutic agents. Monitoring of individual's nutritional status could serve as a possible preventive or therapeutic measure against CRC, majorly by interaction with intestinal microbiota, thereby potentiating host anti-cancer immune response and/or interfering with mechanisms of carcinogenesis.

Keywords: colorectal cancer, diet, intestinal microbiome, nutrition, phytochemicals

1. Introduction

The incidence of colorectal cancer (CRC), the fourth commonly diagnosed cancer and third leading cause of cancer-related deaths worldwide, is a global burden. Factors that increase the risk of CRC development include medical, hereditary, and behavioural factors. Of this, behavioural factors including dietary habits such as consumption of red/processed meat and alcohol, which can be linked to adoption of westernized way of life by developing countries, lack of physical exercise, smoking, ageing and obesity [1], as well as consumption of carbonated drinks with high sugar level and fast-foods [2]. On the contrary, the beneficial effect of nutrition is implicated in reducing the risk of CRC upon consumption of wholegrains, fibre-rich diets, dairy products, micronutrients, vegetables, fruits, and nutraceuticals [3, 4]. Also, avoidance or limited consumption of red/processed meat, alcohol and smoking could reduce the incidence or prevent CRC [3]. In other words, nutrition, either directly or indirectly, from plant or animal origin, plays a significant role in colorectal carcinogenesis.

2. Detrimental effect of nutrition
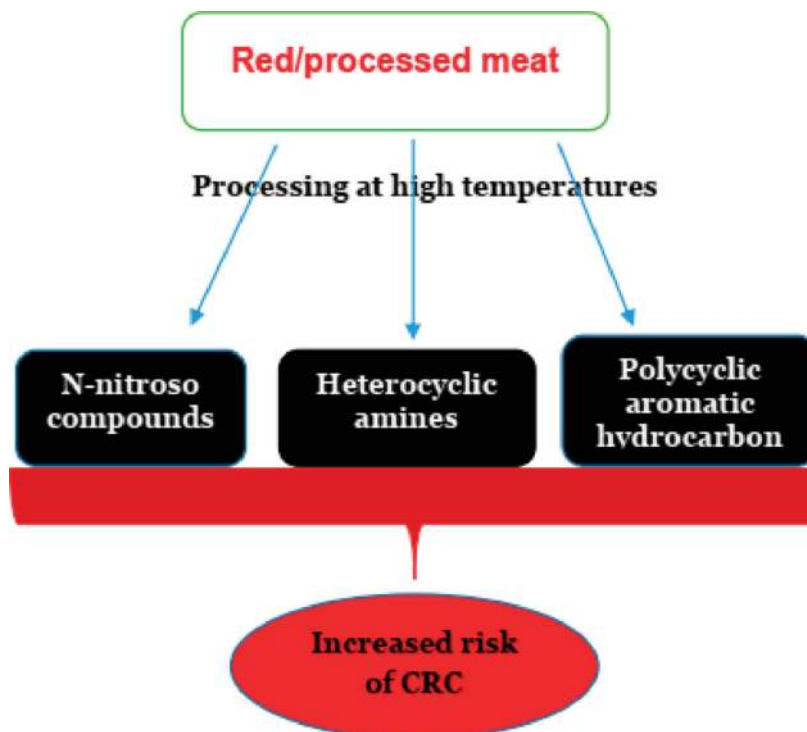
2.1 Red and processed meat

High intake of red/processed meat is linked to high risk of CRC. Red meat such as beef, pork, veal, and lamb, and preserved red meat by smoking, grilling, cooking, frying, salting, and curing are called processed meat.

2.1.1 Mechanisms

High risk of CRC with diet rich in red/processed meat (associated with low fruits, vegetables and fibre) could result from the production of heterocyclic amines and polycyclic aromatic hydrocarbons during processing at high temperatures (**Figure 1**) [5]. Haem, present in high intake of processed/red meat, could stimulate endogenous formation of potent carcinogens, N-nitroso compounds, and cytotoxic alkenals from lipid peroxidation, thereby promoting colorectal carcinogenesis [6].

2.2 High sugar/fat diet, fast foods, and sugar-sweetened drinks

Consumption of diet rich in sugar, fat, and fast foods, as well as sugar-sweetened drinks can be linked to increased risk of CRC. Fast foods and other processed foods including snacks, bakery foods and candies, are energy dense and are frequently consumed in large quantities as they are readily available. Addition of free sugars including high fructose corn syrup, sucrose to drinks and sugars present naturally in fruit juices, syrups and honey to ensure sweet taste can increase CRC risks.

Figure 1.
Mechanisms of high intake of red and processed meat in colorectal carcinogenesis.

Therefore, drinks such as sweetened water, sodas, energy drinks, barley water, sports drinks, as well as tea-based beverages sweetened with sugars or syrups should be reduced, avoided, or replaced with sugar free drinks or drinks sweetened with artificial sweeteners [7].

2.3 Alcohol consumption

Several studies including meta-analysis, many cohort, and experimental studies, have reported the association between chronic intake of alcohol and increase in the risk of colon cancer [8, 9]. High or moderate intake of alcohol (> 12.5 grams/day) is associated with increased incidence of CRC and its mortality [10]. Although, there are discrepancies among various populations based on differences in genetic factors, body composition and other dietary factors including folate intake [8].

2.3.1 Mechanisms

The colon is one of the major organs for the distribution of orally ingested alcohol, making intracolonic level of ethanol to be equal to that of the blood level [11, 12]. At elevated level, ethanol it is converted to acetaldehyde (a known carcinogen) by colorectum cytochrome P450 2E1 (CYP 2E1), as its activity is also expressed in the colon and rectum alongside other tissues (**Figure 2**) [13]. This carcinogen, classified as group 1 carcinogen to humans by the International Agency for Research on Cancer (IARC), induces oxidative stress through an increase in the production of reactive oxygen species (ROS), as against cellular antioxidant defense system [9]. Reactive oxygen species can lead to lipid peroxidation, protein modification or bind to DNA to form carcinogenic adducts; hence, inhibition of DNA synthesis and repair mechanism, alteration in structure and function of glutathione. These could therefore, increase the proliferation of colonic mucosal [8].
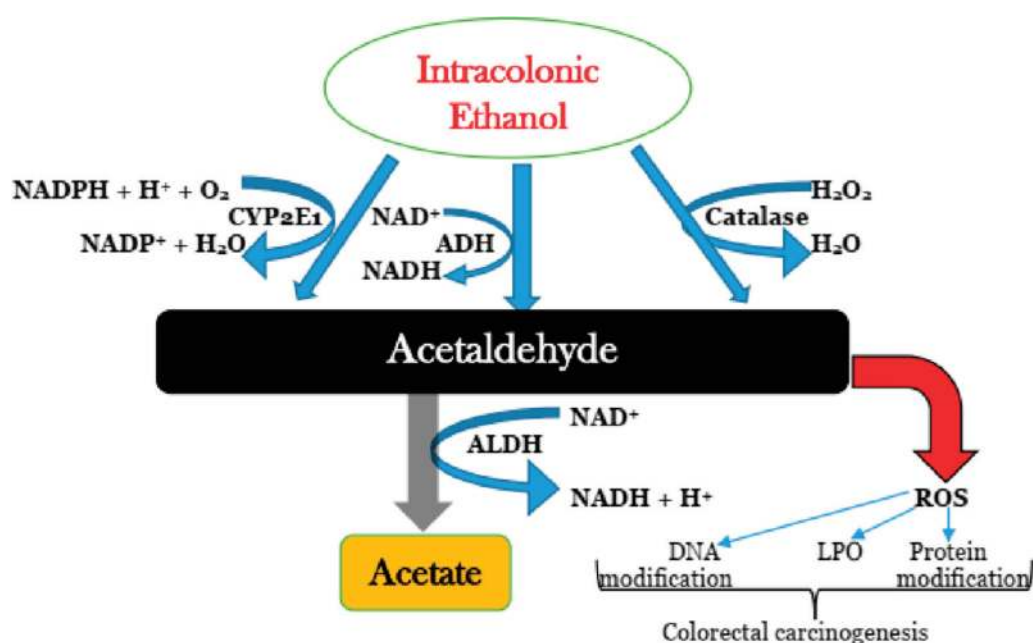

Figure 2.
Metabolism of ethanol by intracolonic bacteria and role in colorectal carcinogenesis.

Ethanol is also oxidized by bacterial alcohol dehydrogenase and catalase (expressed in the colon by colonic microbiota) to produce acetaldehyde in the colorectum [14, 15].

Acetaldehyde is therefore, accumulated in the colon (due to low activity of bacterial aldehyde dehydrogenase, which converts acetaldehyde to acetate in the colonic mucosa), and colorectal carcinogenesis is enhanced by binding to DNA and form carcinogenic DNA adducts [9, 11].

Alcohol can also act as a solvent for other dietary or environmental carcinogens into the mucosal cells, thereby inhibiting the metabolism of hormones, production of prostaglandins and lipid peroxidation [6].

Intracolonic ethanol is converted to acetaldehyde by colorectum cytochrome P450 2E1 (CYP2E1), alcohol dehydrogenase (ADH) and catalase, and the acetaldehyde is converted to acetate by aldehyde dehydrogenase (ALDH), while its accumulation results in carcinogenic DNA adducts, lipid peroxidation (LPO) or protein modification, and stimulates colorectal carcinogenesis.

2.4 Cigarette/tobacco smoking

Compounds such as acetaldehyde, aromatic amines, benzo[a]pyrene, N-nitrosamines, aromatic amines, and polycyclic aromatic hydrocarbons are carcinogens found in cigarette smoke. Nicotine and nicotine-derived nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, are known compounds present in tobacco smoke that enhance CRC metastasis by promoting cell migration and transformation of epithelial–mesenchyma [16]. These compounds could also form DNA adducts and bind to DNA, thereby causing gene mutation [17] or induce gut microbiota dysbiosis leading to colorectal carcinogenesis.

2.4.1 Mechanisms

Cigarette smoking could promote colorectal carcinogenesis due to alteration, imbalance, or disruption in gut microbiota composition (gut microbiota dysbiosis), leading to increase in stool and colonic levels of taurodeoxycholic acid (TDCA), a secondary bile acid. These changes could lead to activation of signaling pathways such as mitogen-activated protein kinase/extracellular signal-regulated protein kinase 1/2 (MAPK/ERK), interleukin 17 (IL-17) and tumour necrosis factor (TNF) in colonic epithelium, thereby promoting colonocyte proliferation [18]. Epigenetic modifications such as high microsatellite instability (MSI-H), the CpG island methylator phenotype, and the BRAF V600E mutation may reduce survival rate of CRC patient, as these have been reported to be functionally involved in colorectal carcinogenesis related to tobacco smoking. These modifications may result from (1) mutation of the glutathione S-transferase Mu 1 (GSTM1) gene, which results in impairment in the detoxification of tobacco carcinogens, thereby enhancing of carcinogenesis; (2) induction of aberrant promoter DNA methylation and silencing regulatory genes involved in tumor progression [16].

2.5 Animal fats

Studies, although limited, have linked intake of animal fats to CRC risk. A diet high in animal fats affects colonic microbiome leading to intestinal inflammation, thereby increasing the risk of CRC.

2.5.1 Mechanisms

High consumption of animal fats could increase colonic production of primary bile acids, which undergo degradation by anaerobic bacteria in the large bowel, and result in the formation of carcinogenic secondary bile acids including deoxycholic and lithocholic acids. High concentrations of these compounds could lead to increased colonocytes proliferation, through the production of ROS, thereby increasing the risk of mutation and malignant transformation [17].

Low intake or avoidance of red/processed meat, sugar/fat diet, fast foods, and sugar-sweetened drinks, alcohol, smoking, and animal fats is encouraged, as these could reduce the risk of CRC.

3. Beneficial effect of nutrition

3.1 Wholegrains

Wholegrains, including brown rice, whole-wheat bread, whole grain cornmeal, cracked wheat, and oatmeal, play a major role against CRC. Polysaccharides composition, and quantity and variety of dietary fibers present in wholegrains make them differ in their physicochemical and structural properties, as well as physiological effects [19]. Wholegrains are sources of energy, proteins, some other primary and secondary metabolites such as vitamins (especially B vitamins including folate), minerals, phytochemicals (phenolic compounds), phyto-oestrogens, and other bioactive compounds which can protect or prevent CRC [19–21]. Wholegrains are also rich source of dietary fibre, oligosaccharides and resistant starch that can influence gut environment (more explanation under dietary fibre).

3.1.1 Mechanisms

Wholegrains reduce the incidence of CRC through four mechanisms [22] by (1) the action of intestinal microbiota on dietary fibres from wholegrains in the synthesis of short-chain fatty acids, and prevents insulin resistance and serves as major source of energy (butyrate) for the colon [20], (2) phytochemicals (phenolic compounds), minerals/micronutrients, and vitamins from wholegrains have antioxidant potential capable of oxidative damage in the colon and prevents carcinogenesis [19, 20]; (3) insoluble fibre in wholegrains increases bulk of luminal contents, and dilutes potential carcinogens in the colonic epithelium to prevent colorectal carcinogenesis [23]; (4) Phytoestrogens (similar to the activities of estrogen) from wholegrains reduce risk of CRC by binding to estrogen receptors through the hormonal mechanisms [20, 21].

3.2 Dietary fibre

Dietary fibres are classified under complex carbohydrates found in plants, and are undigested in the small intestine but undergo fermentation by colonic flora [24]. This fibre is made up of non-starchy polysaccharides which are found in fruits, vegetables, wholegrains or cereals, legumes (such as beans and lentils), plantains and tubers. Dietary fibres from pectin, guar, and oat bran are highly fermentable, while those from wheat bran and cellulose are poorly fermentable.
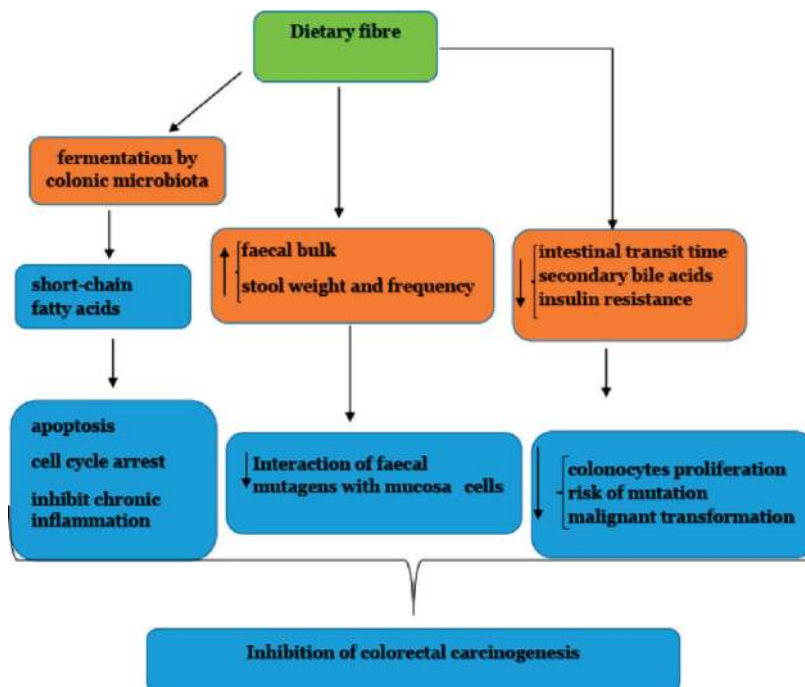
3.2.1 Mechanisms

Dietary fibres are fermented in the bowel by colonic microbiota to form short-chain fatty acids, such as butyrate and propionate (**Figure 3**), which have been reported to have anti-proliferative potential by inducing apoptosis and arresting of cell cycle and differentiation, and chronic inflammatory process inhibition [6, 24]. Dietary fibres can also increase faecal bulk or stool weight and frequency [24, 25], which could reduce the ability of faecal mutagens to interact with mucosa cells [24]. Examples of these are the insoluble fibres such as nuts, wheat bran, whole-wheat flour, beans, and vegetables including cauliflower, green beans and potatoes. Dietary fibres could also reduce intestinal transit time, decrease production of secondary bile acids, and reduce insulin resistance.

3.3 Dairy products and calcium supplements

High consumption of dairy products such as milk, yogurt and cheese have been linked to reduction in the incidence of CRC (Barrubés et al., 2019).

3.3.1 Mechanism

This reduction has been attributed to the presence of calcium, and other compounds such as casein, lactose, lactoferrin and butyrate present in these products, which can also increase calcium bioavailability. The role of yogurt in reducing the risk of CRC can be attributed to the presence of calcium and gut microbiome, most especially the bacteria that produces lactic acid (*Streptococcus thermophiles* and

Figure 3.
Mechanisms of dietary fiber consumption and risk of colorectal cancer.

Lactobacillus bulgaricus) which bring about the reduction of soluble fecal bile acids, fecal-activated bacterial enzymes, and nitoreductase [3].

Calcium has the ability to bind free fatty acids and unconjugated bile acids, thereby reducing the toxic effects of these compounds on the colon and rectum [3]. Calcium exerts its effect by promoting cell differentiation and apoptosis, inhibiting cell proliferation, preventing colonic K-ras mutations, and inhibiting colorectal carcinogenesis induced by haem. The major limitation to this is the association of diet rich in calcium to prostate cancer [6]. In view of this, care should be taken in consumption of dairy foods, most especially those high in calcium, although there are many other bioactive constituents present in dairy foods which might contribute to its role in reducing CRC risk.

3.4 Fish and fish products

Several meta-analysis studies have reported that high fish intake (majorly fresh fish such as freshwater fish and sea fish) could reduce the risk of CRC [26–29]. Fish is known to contain long chain polyunsaturated fatty acids (PUFAs), majorly the n-3 fatty acids, including eicosapentaenoic and docosahexaenoic acids and are known to inhibit colorectal carcinogenesis [27, 30]. However, care should be taken in the consumption of processed fish such as salted, dried, smoked, and barbequed fish, as there could be an association with increased risk of CRC. This is because, dried/salted fish contains N-nitrosamines [26, 31], and fish processing at high temperatures, produce heterocyclic amines, which are carcinogenic [30].

3.4.1 Mechanism

Fish is known to be a good source of vitamin D, and vitamin D alters gene expression directly through the vitamin D receptor and induces cell differentiation and apoptosis, thereby inhibiting the initiation and progression of CRC. Fish also contains selenium, which can prevent or repair oxidative DNA damage, alter metabolism of carcinogens and regulate immune response. High intake of n-3 fatty acids reduces both the synthesis of arachidonic acid metabolites (prostaglandin E_2 and leukotriene B_4) and the expression of nuclear transcription factor κB (NF-Kb) and inducible nitric oxide synthetase (iNOS). All these processes can inhibit colorectal carcinogenesis [26, 29, 31].

3.5 Fruits and non-starch vegetables

High consumption of fruits and non-starchy vegetables have been associated with reduced risk of CRC [4]. This is due to the presence of several phytochemicals with antioxidant, anti-inflammatory, and anti-cancer properties which include vitamins, carotenoids, tocopherols, ascorbic acid, alkaloids, phenolic compounds, and intake of several other nutrients and compounds such as folate. These compounds counteract the effect of ROS by their antioxidant properties, and inhibit cellular damage and carcinogenic insults [32, 33].

3.6 Nutraceuticals and phytochemicals

Nutraceuticals, also known as functional foods, are bioactive compounds that originated from natural sources such as secondary metabolites in plant, dietary

supplements, herbal products from fruits, vegetables and plants, and microorganisms or marine organisms, that are capable of preventing, treating and managing several diseases including CRC prevention and therapy [34, 35]. Phytochemicals, mainly from fruits and vegetables, possess strong antioxidant and anti-proliferative activities, and a combination of these compounds brings about their synergistic effect against several cancers [33].

3.6.1 Secondary metabolites in plants (phytochemicals)

Carotenoids such as α- and β-carotene from carrots; lycopene from grapes, papaya, and tomatoes; halocynthiaxanthin from a marine organism, *Halocynthia roretzi*, and other phytochemicals which include astaxanthin, cryoptoxanthin, xanthophyll, and zeaxanthin metabolites, have significant role as free radical scavengers and ability to induce apoptosis in CRC cells [34, 36, 37].

Polyphenols, classified into flavonoids and non-flavonoids, are group of phytochemicals which are converted by intestinal microbiota to simple phenolic acids, and are absorbed in the small intestine, thereby reducing the risk of CRC [32, 38]. Polyphenols (resveratrol, catechins, epicatechins, epigallocatechin-3 gallate (EGCG), flavanols, flavones, and isoflavones) from various sources including plants (such as green tea, grapes, turmeric, ginger), marine algae, seaweeds, and microorganisms serve as chemopreventive agents and play significant role against colorectal carcinogenesis [34, 39].

Flavonoids are dietary polyphenols that occur naturally in plant and beverages, such as fruits and vegetables, and juices, and have been associated with reduction in CRC risks [40]. Flavonoids are sub-classified into six based on their chemical structure. These include flavonols (including quercetin, myricetin, kaempferol, and isorhamnetin from sources such as tea, onions, apples, citrus, berries, and broccoli), flavones (including apigenin and luteolin from sources such as celery, perilla, lettuce, and peppers), flavanones (including hesperetin and naringenin), flavan-3-ols (including catechin, epicatechin, epigallocatechin, epicatechin-3-gallate, epigallocatechin-3-gallate from sources such as apples, cocoa, grapes, green tea, and red wine,), anthocyanins (including cyanidin, delphinidin, malvidin, pelargonidin, petunidin, peonidin from sources such as grapes, black currants, eggplant and radishes), and isoflavones (including genistein and daidzein from soy products). These compounds could prevent and reduce the risk of CRC [34, 38].

Apart from the chemopreventive role of these compounds against CRC, there are little or no side effects as compared to other CRC treatment options such as surgery, chemotherapy, and radiation.

3.6.2 Dietary supplements

Dietary supplements such as omega-3 fatty acids, vitamins (vitamin D, folate, and vitamin B complex), eugenol from honey, balm, cinnamon, clove oil, citrus, and Flos, have been reported to reduce the risk of CRC [34, 41].

3.6.3 Herbal products

Herbs and herb products have been used as a single or combination preventive or therapeutic measures for CRC. Several medicinal plants (either as extracts, juices, or diet fortified) have been studied using different experimental models. These include

the use of *Crassocephalum rubens* fortified diet [42], Indian spice saffron (*Crocus sativus*), *Triticum aestivum* [43], *Camellia sinensis* [44], Chinese herbal medicines [45], and their effect against initiation and progression of CRC. These products have been reported not only to have the potential to reduce the risk of CRC but also capable of reducing the adverse reactions associated with the use of chemotherapy [45]. The preventive and therapeutic potential of these herbs, and their mechanisms of reduction in the risk of CRC could be linked to the several active compounds inherent in them [46].

3.6.4 Marine nutraceuticals

Bioactive compounds from marine organisms including acetylapoaranotin (isolated from marine *Aspergillus sp*), astaxanthin (from crab, marine animals, and *Haematococcus pluvialis*), and siphonaxanthin (from a marine green algae *Codium fragile*) have been of interest as therapeutic intervention for CRC [34], via different mechanisms.

3.7 Effect of diet on colorectal cancer patients

A hospital-based case–control study among Chinese populations, conducted in Hong Kong, revealed that current, regular, and heavy alcohol drinkers, and cigarette smokers increased risk of CRC, and avoidance of these for a long time reversed the risk [47]. A large prospective cohort study where patients were screened showed a reduction in the risk of adenoma in patients taking dietary fiber (most especially from cereal and fruit [48]. Also, in a theory-driven behavioral dietary intervention program conducted on Chinese CRC patients, improvement in diet rich in refined grain and high fibre intake, and reduction in red and processed meat was noted with no dietary deficiency and/or dietary-related anemia, which could be as a result of other sources of protein (poultry, seafood and tofu). This improvement in dietary intervention was linked to awareness on the role of diet in CRC prevention and treatment, thereby resulting in increased chances of patients' survival [49].

In a large British cohort (UK Biobank study), there was a lower risk of CRC among low meat-eaters (those that consumed processed/red meat or poultry in less than 5 times a week) when compared with the regular meat-eaters (those that consumed processed/red meat or poultry more than 5 times a week) [50]. This confirms that high risk of CRC is associated with high and regular diet of processed/red meat. In another large-scale cohort studies (UK Biobank), there was an association between high consumption of processed meat and increased risk of mortality in patients with inflammatory bowel disease, leading to high CRC risk [51, 52].

Among CRC patients in China, it was reported that low intake of poultry, seafood, processed/unprocessed red meat, could prevent high risk of CRC. However, no general agreement on high intake of white meat (fish and poultry) in reducing the risk of CRC, as contrasting results have been reported [53]. In a UK Biobank study, consumption of red/processed meat, below the UK recommended daily intake (not more than 90 g of red and processed meat a day) is suggested, as participants consuming an average of 76 g per day was associated with increased risk of CRC [54].

In the European prospective investigation into cancer and nutrition (EPIC) cohort study, no association was noted between pre-diagnostic intake of red meat or fibre and CRC survival after diagnosis, However, it was suggested that poultry intake can reduce mortality among female CRC survivors, and increased CRC-specific mortality

risk with intake of processed meat. This is because dietary intake before diagnosis is assumed to predict post-diagnostic data, therefore, post-diagnostic dietary research was suggested to confirm the association [55].

There are limited clinical trials evaluating the post-surgery role of diet in CRC patients. Although, studies have shown that diet rich in red/processed meat, refined grains, sweets, and high alcohol consumption were associated with increased recurrence rates of CRC, while increased coffee consumption, dietary fiber, and vegetables, mainly light and low-fat foods, were associated with decreased CRC mortality rate [8, 56]. Also, the alternate healthy eating index-2010 (high intake of whole grains, fruits, vegetables, legumes, nuts, and long chain omega-3 fatty acids, and low intake of salt, saturated fat and red/processed meat) and moderate consumption of alcohol and lower consumption of sugar sweetened beverages and juices were associated with reduced risk of CRC mortality among women [57].

In general, more studies are suggested to investigate the role of nutrition on CRC survival (post-diagnosis), as most dietary data is currently centered on CRC prevention.

4. Conclusion

Plant-based diet, including high intake of dietary fibre, wholegrains, fruits, and vegetables, as well as animal-based diet such as fish, dairy products should be considered. Also, diets including low or avoidance of red and processed meat/fish, animal fats, cigarette smoking, alcohol, diet rich in sugar/fat, fast foods and sugar-sweetened drinks are encouraged. These are suggested to generally play significant roles in preventing CRC and as follow-up nutritional requirements for CRC patients (pre- and post-diagnosis/therapy), thereby reducing the overall risk of CRC and associated mortality.

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Conflict of interest

The author declares no conflict of interest.

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