Modifiable and Non-modifiable Risk Factors for Colon and Rectal Cancer

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1 Introduction

Colorectal cancer (CRC) is the world's third most common cancer. Before the twentieth century, CRC was relatively uncommon; however, the incidence has risen dramatically especially in the last 50 years. Several risk factors have been proposed, including the adoption of westernized diet, obesity, and physical inactivity. The majority of colorectal cancer continues to occur in industrialized countries. According to the recent studies, CRC is associated with several modifiable and non-modifiable risk factors. These risk factors involve CRC history in first-degree relative, inflammatory bowel disease, consumption of red meat, fruit, and vegetables, cigarette smoking, body mass index to overall population, race, gender, personal habit of alcohol consumption and smoking, ethnicity diabetes, and physical activity. Here we review the key evidence for the role of different risk factors and their effect on CRC prevention and progression.

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2 Modifiable Risk Factors and Their Prevention

Most risk factors associated with CRC are modifiable, and they involve obesity and the consumption of food rich in saturated fats. They also involve low physical activity, increased body mass index, cigarette smoking, low fruit consumption, low vegetable consumption, low folate intake, high alcohol intake, disturbance in energy balance, and red meat intake, which are associated with moderately higher risk of CRC. As a result of these lifestyle risk factors, there is a significant differences in incidence and mortality rate from colorectal cancer across the world.

There is a strong association between colorectal cancer risk and alcohol: people drinking a lot of alcohol had 60% higher risk of colorectal cancer in comparison with none or light consumers. Obesity, smoking, high meat intakes, and diabetes all are associated with a 20% higher risk of colorectal cancer in comparison with people in the lowest categories for each. Protection against colorectal cancer is associated with physical activity. Public health strategies that enhance increased physical activity, moderate consumption of red and processed meat, modest alcohol consumption, smoking cessation, and weight loss in most of the times cause significant benefits at the population range for decreasing the chance of colorectal cancer.

2.1 Red Meat and Processed Meat Consumption

Several epidemiologic studies have shown that meat intake is significantly associated with an increased risk of colon cancer [1–3]. In 2007, the World Cancer Research Fund released a report stating that there was convincing evidence of a causal role for red and processed meat in CRC [4]. Also, a quantitative evaluation of 26 cohort studies reports with information about 15,057 people with CRC, examined the association between meat (red meat, processed meat, fish, and poultry) and CRC [5]. The evaluation concluded that compared with people having the lowest intake of processed meat, those having the highest intake experienced a 20% increased risk for developing CRC [5]. The authors did not observe any apparent association between risk of CRC and consumption of either fish or poultry [5]. Another meta-analysis published in 2013 also observed an elevated risk of colorectal adenoma with intake of red and processed meat [6]. Red meat might be related to the incidence of CRC either directly or indirectly. Frying, grilling, broiling, or cooking meat over coal at high temperatures can lead to the formation of mutagenic and carcinogenic heterocyclic amines through the interaction of muscle creatine with amino acids and to the formation of N-nitroso compounds [7]. Those substances can induce genetic alterations and form DNA adducts characteristic of colorectal tumors [7].

The heme iron content of meats might contribute to colorectal neoplasia by inducing oxidative DNA damage and by increasing endogenous formation of

N-nitroso compounds, which are known to be powerful multisite carcinogens [8]. Thus, the greater abundance of heme in darker meats than in white meats could increase the risk of CRC. Many studies have observed a positive association between heme and the development of colonic polyps, adenomas, and CRC [9]. Fish and poultry are alternative sources of protein and have been shown to reduce the risk of colon cancer and adenoma. Mechanisms such as the presence of n-3 polyunsaturated fatty acids, especially in oily fish, and more efficient methylation because of the high methionine content in those foods have been proposed for the protective effect of white meats [10]. In this regard, a preventive diet might involve limitation or avoidance of red or processed meats and consumption of white meat and fish [11]. Although epidemiologic studies have observed a strong association between meat intake and an increased risk of CRC, it is important to mention that some components of meat are anticancer substances and essential for optimal human health (selenium; zinc; omega-3 fatty acids; vitamins B6, B12, D, and folic acid) [12].

2.2 Protective Role of Fruit and Vegetables

Dietary fiber varies significantly in physical properties and chemical composition, but can be classified according to water solubility, which affects its function in the body and might be relevant to the risk of CRC. Bran fiber is insoluble; fruit and vegetable fiber tends to be more soluble [13]. After observing the low incidence of CRC in African nations whose populations consume a high-fiber diet, the hypothesis that high fiber consumption might reduce the risk of CRC was proposed by Burkitt and colleagues in the 1970s [14]. Cellulose, hemicellulose, and pectin are plant materials that are defined as fiber [15]. Their protective effect against CRC could be explained by the fact that their presence in meals contributes to lower transit time through the gastrointestinal tract, reducing the concentrations of intestinal carcinogens because of increased stool mass, diluting colonic contents, and enhancing bacterial fermentation, which leads to increased production of short chain fatty acids (acetate, propionate, and butyrate). The latter substances were found to induce apoptosis in CRC cells in rats. Dietary fiber has also been proved to have an anti-inflammatory function, lowering the production of interleukin 6, tumor necrosis factor α, cyclooxygenase 2, and gene expression of inducible nitric oxide synthase.

In addition, in an animal model of CRC, short-chain fatty acids interfered with numerous regulators of cell-cycle proliferation and apoptosis such as the beta-catenin, p53, p21, Bax, and caspase 3 genes. Thus, diets high in wheat bran, fruit and vegetables, citrus fruits, cruciferous vegetables, dark green vegetables, onions, garlic, and tomatoes might have a protective effect against colorectal adenomas and subsequently CRC [16]. Fruits and vegetables also contain many potentially protective substances that affect various biochemical pathways. Their benefits can be observed in inhibitory action at early tumor stages or at advanced or metastatic tumor stages [17–20].

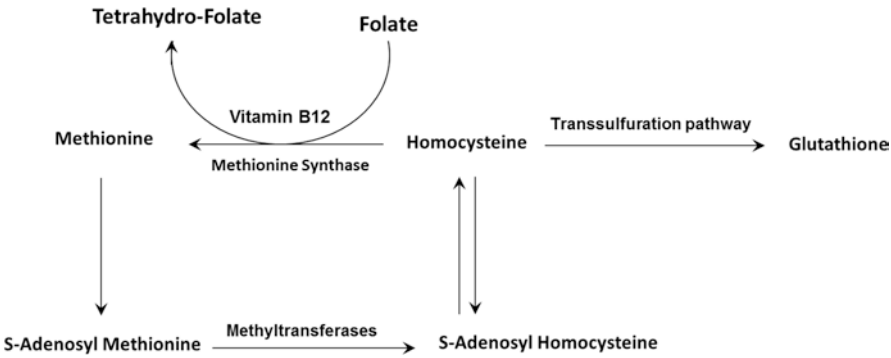

Fig. 1 Simplified schematic of the folate-dependent methionine cycle. Homocysteine is converted into methionine by methionine synthase, which utilizes vitamin B12 as a cofactor and acquires a methyl group from folate which is subsequently converted to tetrahydrofolate. Methionine is further converted to S-adenosylmethionine through the activity of methionine S-adenosyltransferase, the major methyl donor for all methyltransferases, which adds methyl groups to various acceptor molecules such as DNA, RNA, phospholipids, and proteins. S-adenosylmethionine is then converted to S-adenosylhomocysteine, which is reversibly converted to homocysteine in a reaction catalyzed by hydrolase. Homocysteine is remethylated back to methionine, or transsulfurated into glutathione biosynthesis pathway, based on the availability of folate and vitamin B12

2.3 Protective Role of B Vitamins (Folate, Vitamin B6, and Vitamin B12)

Folate deficiency results in genomic hypomethylation and defects in DNA synthesis, both of which can contribute to colonic carcinogenesis. Methionine and folate are required in the production of S-adenosylmethionine, the primary methyl donor, but when methionine levels are low, more folate is used as methyl tetrahydrofolate to form methionine (Fig. 1). The lower levels of methyl tetrahydrofolate might affect DNA synthesis, which could explain the protective effect associated with higher folate levels for those with low methionine intake [21, 22]. Interestingly, compared with people having a high methionine intake but low folate intake, those having high intakes of both methionine and folate were observed to have a significantly increased risk for CRC. The reduction in the CRC incidence in the United States and Canada might be a result of dietary folate supplementation that reduced the risk for colon adenoma development [23]. It was suggested that folate supplementation could be associated with a higher risk of adenoma recurrence and might even be harmful to patients with a prior history of colon cancer [23].

In a randomized clinical trial, it was found that folic acid supplementation at a dose of 1 mg daily is harmful, causing an increase, by a factor of 2.3, in the total number of colonic adenomas and an increased risk, by a factor of 1.7, for advanced colonic adenomas [24]. Physiologic levels of folic acid play a protective role and that intense supplementation could lead to progression of small preexisting adenomas. Moreover, especially in the elderly population, folic acid supplementation

at high doses (1000 μg/day) appears to enhance the risk of neoplasms [24]. Vitamin B6 (pyridoxal phosphate) is an important protective anticancer nutrient that is found in numerous grains, fruits, and vegetables. In a meta-analysis of prospective studies, it was suggested that a 49% decrease in CRC risk for every 100 pmol/mL is assocaited with an increase in serum level of pyridoxal phosphate concentration [25]. To summarize, diets rich in folate, vitamin B6, and vitamin B12 might prevent colorectal carcinoma.

2.4 Role of Calcium and Vitamin D

Vitamin D, a fat-soluble vitamin, is synthesized mostly endogenously from skin exposure to ultraviolet sunlight. Some comes from the diet as the provitamin cholecalciferol (D3), which is found naturally in oily saltwater fish, liver, and egg yolk. The plant-derived provitamin ergocalciferol (D2) is found in foods such as mushrooms. Food fortification can provide an extra source of vitamin D. The active form of vitamin D, which is synthesized by hydroxylating provitamins in the liver and kidneys, is 1,25-dihydroxyvitamin D3 (calcitriol). The use of calcitriol in experimental studies has been shown to induce differentiation and inhibition of tumor cell proliferation in various types of cancer cells; however, because of the development of toxic hypercalcemia, such use is limited. For those reasons, calcitriol analogues are usually used [26]. Epidemiologic studies show that deaths from CRC are higher in areas with less sunlight. Also, populations consuming higher amounts of fresh fish, shellfish, calcium, and vitamin D have lower rates of CRC [27]. A meta-analysis suggested an inverse association between circulating levels of 25-hydroxyvitamin D3 and risk of CRC. In countries in which vitamin D-fortified foodstuffs are available (for example, the United States and some Scandinavian countries), the prevalence of vitamin D deficiency is between 1.6% and 14.8% in various age groups. In countries with an insufficient dietary supply of vitamin D or in which foodstuffs are not supplemented, dietary intake of vitamin D is generally low [28].

2.5 Sedentary Life Style and Obesity

In a meta-analysis of CRC risk factors, data from 2309 colon cancer patients and 66,199 CRC patients in 23 studies was used to investigate the relationship between body mass index and risk of CRC. Body mass index and CRC were found to be significantly associated (relative risk: 1.10 per 8 kg/m^2) [29]. A meta-analysis used data from 5994 colon cancer patients and 5099 CRC patients in 21 studies to examine the relationship between physical activity and CRC. Without adjustment for any covariates, a significant negative correlation between CRC risk and physical

activity was observed (relative risk: 0.88 per two standard score; 95% confidence interval: 0.86–0.91) [30]. In developed countries during the past few decades, physical activity levels for both adults and children have steadily declined. Those declines in physical activity level are suggested to be a result of more time spent watching television and playing computer games and of a decrease in opportunities for physical activity in schools and communities.

3 Non-modifiable Risk Factors for Colon and Rectum Cancer

Several risk factors are associated with the incidence of colorectal cancer. Those that an individual cannot control include age, inflammatory bowel disease, history of CRC in first-degree relatives, and hereditary factors. People with a family history of colorectal cancer have a significantly higher risk of having the disease compared with people without such a history. Risks increased in a number of cases including patients with relatives' diagnosed young, patients with relatives having colonic cancers, and those with more than one affected relatives. The incidence of CRC is low under the age of 45 years. The chance and the risk of this disease elevates with age, as it is well accepted that the diagnosis rate is higher in old people aged 65–84 years. Moreover the average lifetime risk of having CRC is two to three times more in people with a first-degree relative who has an adenomatous polyp or colon cancer than in the general population.

3.1 Hyperhomocysteinemia and Oxidative Stress

Oxidative stress is a condition under which the intracellular antioxidant (GSH), antioxidant enzymes (glutathione peroxidase, superoxide dismutase, and catalase), and dietary antioxidants are not counter balancing the reactive oxygen species-mediated cellular oxidative damages (lipid peroxidation, protein inactivation, and DNA breakdown), eventually leading to many chronic diseases such as CRC [31]. Oxidative stress as a consequence of increased production of nitrogen or oxygen reactive species has been demonstrated in inflammatory bowel disease and CRC. Major etiologic factor for the development of CRC is chronic inflammation of large intestine and rectum. Infectious agents or inflammatory bowel disease, an independent risk factor for CRC, may result in this inflammation. Another consequence if this inflammatory bowel disease might be the localized response to tissue stressors which may include premalignant lesions, adenomatous polyps. Metabolic conditions like nutritional deficiencies which promote systemic or localized inflammation could increase the inflammatory response within large intestine and rectum.

Hyperhomocysteinemia, possibly through inflammatory mechanisms is an established independent risk factor for vascular disease. It is not very clear whether hyperhomocysteinemia has a role in promoting the development of CRC. Hyperhomocysteinemia might be directly linked with inflammation and CRC. It may be due to decreased absorption or increased requirements for folate and other nutrients required for one-carbon and homocysteine metabolism. Homocysteine may induce an inflammatory response in cultures of human intestinal microvascular endothelial cells [32, 33]. There could be a link between CRC and folate through homocysteine.

Adequate consumption of folate and vitamin B_{12} is crucial for supporting several metabolic pathways, especially the methionine cycle, Fig. 1 [33]. Under conditions of low folate and vitamin B_{12}, methionine synthase (a key enzyme in the methionine cycle) becomes hypoactive leading to an accumulation of precursors, including homocysteine, and eventually to the impairment of homocysteine dependent-transsulfuration to GSH, the major intracellular antioxidant, and it has been proved that glutathione depletion is often associated with oxidative stress [33]. Folate and B12 are the dominant nutritional modifiable environmental risk factors in relation to CRC development.

Folate is involved in the transfer of one-carbon units in the de novo synthesis of thymidylate, purines, and methionine. Adequate folate consumption is therefore essential for the synthesis, stability, and repair of DNA and normal cell division. Vitamin B_{12} acts as a coenzyme for methionine synthase (MTR) in the conversion of homocysteine to methionine, a folate-dependent reaction that creates the substrates for de novo nucleotide synthesis and S-adenosyl-methionine, a universal methyl donor. A methyl group from 5-methyltetrahydrofolate, produced by the enzyme methylenetetrahydrofolate reductase (MTHFR), can be transferred to homocysteine by MTR to form methionine and tetrahydrofolate. Deficiency of folate and B_{12} could also result in hyperhomocysteinemia. Several studies suggested that elevated blood concentrations of homocysteine (hyperhomocysteinemia) are a pathological metabolite marker for oxidative stress and for CRC [33].

3.2 Genetic Risk Factors

Less than 10% of patients have an inherited predisposition to CRC, and these cases are subdivided according to whether or not colonic polyps are a major disease manifestation. The diseases with polyposis include familial adenomatous polyposis (FAP) and the hamartomata's polyposis syndromes (e.g., Peutz-Jeghers, juvenile polyposis) [4], while those without polyposis include hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome I) and the cancer family syndrome (Lynch syndrome II) [34]. These conditions are associated with a high risk of developing CRC, and the genetic mutations underlying many of them have been identified. The third and least well understood pattern is known as "familial" CRC. Up to 25% of affected patients have a family history of CRC, but the pattern

is not consistent with one of the inherited syndromes described above. Individuals from these families are at increased risk of developing CRC, although the risk is not as high as with the inherited syndromes. It was proposed that this group of patients represents individuals with genetic changes with an autosomal recessive pattern of inheritance. Indeed the discovery that biallelic mutations of the base excision repair gene, the MutY human homologue (MYH) resulted in an increased risk of colorectal adenomas and cancer led to the first description of an autosomal recessive cancer syndrome [35].

4 Conclusion

Colon and rectum cancers are one of the most common incident cancers and a common cause of cancer death worldwide. B vitamins (folate and vitamin B_{12}) status is a major determinant of serum homocysteine as it is elevated in CRC patients with folate or vitamin B_{12}. Although supplementation of B vitamins combats hyperhomocysteinemia, yet its etiologic relationship to hyperhomocysteinemia-mediated oxidative stress in relation to CRC remains poorly understood. Accumulated evidence suggests that aging is associated with increased production of free radicals, resulting in increased oxidation of lipids, proteins, and genetic material. Oxidative conditions cause progressive structural and functional alterations of cellular organelles and changes in redox-sensitive signaling processes, such cellular conditions contribute to increased susceptibility to a variety of diseases, including inflammation and cancer. Primary and secondary prevention, with attention to a healthy lifestyle, physical activity, and screening should be enhanced in the general population. Modifiable and non-modifiable risk factors for colon and rectum cancer synergize for the pathogenesis of colon and rectum cancer.

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