The importance of an up-to-date evidence based diet planning for colorectal cancer patients

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The importance of nutrition goes well beyond cancer prevention. Nutrition of a cancer patient should be observed as an added component in the medical treatment. Yet, more specific nutritional guidelines are necessary, for not only aggressive cancers or later stages of cancer, but for the ones of slow progress as well. Adequate nutrition is maybe of higher importance after the diagnosis, and during recovery, between therapy cycles, or for cancer patients in remission.

Colorectal cancer (CRC) is the only cancer showing strikingly high correlation to the diet. Key findings of the two largest cancer cohort studies, confirmed that around 90% of CRC cases could be attributed to nutritional habits, with minor role of inheritance (1). These two studies are the European Prospective Investigation into Cancer and Nutrition (EPIC) and the United States study by the National Cancer Institute (NCI) from recruited members of the American Association of Retired Persons (AARP) into the NIH-AARP Diet and Health Study.

Despite all screening actions, statistical report on CRC incidence and mortality are truly dreadful, designating it as the third most common death cause of cancers world-wide (1) CRC incidence rates continue to rise, especially in transition countries (e.g. the Czech Republic, Slovakia), whereas rates stabilized or decreased in developed countries (e.g. the United States) (2). Early diagnosis is crucial for the survival, for CRC is usually fatal when diagnosed in the later stages of the disease.

RISK FACTORS

Risk factors for CRC are well known, and the most recent meta-analysis by Johnson et al. (3) strengthens the evidence that lifestyle and dietary habits play the most important roles in the overall risk of CRC. Compiled data presented in this meta-analysis found the highest risk for inflammatory bowel disease and history of CRC in first-degree relatives. On the other hand, the effect of lifestyle habits (i.e. low physical activity, cigarette smoking, increased body mass index [BMI]) and dietary habits (i.e. intake of red meat, low consumption of vegetables and fruits) overcome person's genetic predisposition (3).

From the perspective of the Republic of Serbia, these risk factors have been confirmed to play an important role (4). The author confirmed that most of CRC cares are preventable, and that cigarette smoking together with alcohol consumption presents the major contributable risk factors. If combined with intake of red meat, odds ratio are even higher (4).

LIFESTYLE RELATED RISK FACTORS

Meta-analyses for total physical activity (for an increase of 5 metabolic equivalent tasks [MET] h/d) showed a 3% decreased risk of CRC and an 8% decreased risk of colon cancer. For recreational activity (for an increase of 5 MET hour/week), decreased risk of CRC and colon cancers was found but did not reach statistical significance, whereas physical activity of 30 min/d showed an 11% decreased risk of CRC and a 12% decreased risk of colon cancer (5).

Obesity seems to be associated with more-aggressive CRC in a handful of studies (6). In addition, study by Campbell et al. (7) showed that prediagnosis obese BMI (≥30) relative to normal BMI (18.5-24.9) is associated with the higher risk of CRC mortality. It is suggested that prediagnosis BMI presents significant determinant of survival rate among patients with nonmetastatic CRC (7).

Risk of CRC is amplified in smokers, especially if combined with high intake of fruits and vegetables, as shown by the EPIC study (8). The EPIC study results show that former smokers have lesser risk than current smokers do, but for ex-smokers, the risk of CRC equalizes to the risk of never smokers after at least 20 years or more (9).

DIETARY RISK FACTORS

The official nutritional recommendations for CRC published in 2007 need update, due to the extensive literature evidences (5). One of the main goals of the Continuous Update Project (CUP) is to update existing recommendations according to the up-to-date evidence. Meta-analysis prepared by Perera et al. (5) compiled extensive evidence from 516 papers, and found convincing evidence that physical activity and foods containing dietary fibers decrease the risk of CRC. Intake of red and processed meat, consumption of alcohol (in men), body fatness, and abdominal fatness also show convincing evidence with increased risk of CRC. Adult-attained height is unlikely to modify the risk of CRC directly.

Extensive review of 32 epidemiologic studies by Randi et al (10) confirms earlier findings on some of accepted dietary patterns as being protective in terms of CRC risk. The Mediterranean diet (11), and the Healthy Eating Index-2005 (HEI-05), that assess adherence to the 2005 Dietary Guidelines for Americans (12) have been shown to have inverse impact on the risk of CRC (10).

Characteristics of dietary patterns that have been found to reduce risk of CRC are fruit and vegetable consumption, fat-reduced foods with reduced fat content, wholegrain, fish, and dairy products, with an estimated risk of 0.45 to 0.90. On the other hand, dietary patterns such as Western diet, consumption of processed pork meat, meat and potatoes, and traditional patterns have all been associated with higher risk of CRC; estimates varying from 1.18 to 11.7 (10). These findings are in accordance to the official updates on nutritional guidelines for CRC by CUP.

When discussing the issue of fruit and vegetable consumption, concerns are brought for the known pro-oxidative effect of several naturally presented nutrients. The EPIC study results presented by van Duijnhoven et al (8) showed inverse association between the highest quintile of

consumption of fruits and vegetables and the risk of CRC. The inverse risk was found in never and former smokers, but positive in current smokers. This modifying effect was found for fruit and vegetables combined and for vegetables alone (8). Considering kinds of vegetables, the results for cruciferous vegetables, such as broccoli, cauliflower, cabbage, kale, are most promising (13).

As previously noted, food rich in dietary fibers show convincing evidence of reducing the risk of CRC. Grains, fruits, and vegetables present significant source of dietary fibers in daily diet. However, the opinion is that not all fibers are made the same, and that type of fiber consumed is extremely important (1). Per every 10 g of fibers a day, 10% lower risk for CRC and 11% lower risk for colon cancer was found, with higher decrease in men (12% in men *vs.* 8% in women) (5). Cereal fiber showed 10% decreased risk, and for 3 servings of wholegrain per day, 21% decreased risk for CRC and a 16% decreased risk for colon cancer (5). The Cochrane review by Asano and McLeod (14) after looking at dietary fiber RCTs came with the conclusion that increase intake of fibers will not affect incidence or recurrence of adenomatous polyps within a two to four year period, in patients with no previous history of CRC (14). Pooled analysis by Park et al. (15) on 730,000 patients with CRC, followed up between 6 and 20 years, showed a nonsignificant decreased risk for the groups that consumed the most dietary fiber (15).

Fiber dilutes fecal content, decreases transit time, and increases stool weight, but the precise mechanisms for its probable protective role are still not clearly understood. The gut flora produces fermentation products, especially short-chain fatty acids (e.g. butyrate) which are shown to induce apoptosis, cell cycle arrest, and differentiation in experimental studies (15). Additionally, colonic microbiota is considered to play an important link in the colonic carcinogenesis cascade. Diet affects dynamic balance between beneficial and detrimental microbial metabolites, leading to so called dysbiosis (16). Interestingly, intake of coffee is considered to modulate macrobiota of colon (17). It was proposed that it has potential probiotic effect, due to in vivo metabolism and composition of coffee chlorogenic acids and dietary fiber, including melanoidins. Studies suggest that coffee may reduce CRC risk, increase colon motility, and antioxidant status (17).

Note that intake of fiber is strongly correlated with intake of folate, which is essential for methylation reactions in the human body. Reduced DNA methylation may contribute to the loss of normal control of proto-onco-gene expression, and DNA hypomethylation presents a constant characteristic of early CRC (18). If low intake of folate is combined with excessive intake of ethanol, the risk is even higher since ethanol interferes with folate bioavailability (18).

POTENTIALLY EFFECTIVE FOODS AND NUTRIENTS

Probable inverse effect on CRC risk was found for garlic, and intake of milk and calcium, including dietary and supplemental one (5). Garlic is a newly proposed food showing consistent, dose-response effect to elevate the risk for CRC due to its allyl sulfur components. Animal studies demonstrate that allyl sulfides effectively inhibit colon tumor formation and also can inhibit cell growth in laboratory experiments (5). The more recent EPIC study results strengthen the evidence of protective role of dairy products on CRC risk, with no observable difference among milk and dairy products of different fat content (19). Intake of calcium has shown strong inverse relation to total cancer risk, risk of cancers of digestive system, especially CRC. The inverse relation was found for total calcium intake, calcium from diet, and supplemental calcium (20).

Some studies suggest that nonstarchy vegetables, fruits, and foods containing vitamin D may act protectively against CRC. On the other hand, for some foods like cheese or foods containing iron, animal fats, or sugars findings suggest possible causative effect on CRC. Additional suggestions are made for fish, foods containing folate, and selenium (5). Due to lack of strength, no specific recommendations can be drawn out for any of the above-mentioned nutrients (5).

Intake of selenium in form of supplement was suggested by Bjelakovic et al. (21) to have the potential benefit on gastrointestinal cancer occurrence. But the more recent Cochrane review by Dennert et al. (22) did not find convincing data on beneficial effect of selenium supplementation after analyzing RCTs, but rather inconsistent. However, from the epidemiological point of view, the same group of authors did find lower mortality and cancer incidence odds ration with higher selenium exposure, which was more emphasized among men.

Several nutritional components naturally present in foods have been proposed by numerous studies, *in vitro* and *in vivo* to have the potential beneficial effect on carcinogenesis. So far several vitamins were explored, such as vitamin A, C, E, and D, β-carotene, and folic acid. In vivo studies were focusing on supplementation. Even though the evidence in animal studies and cancer cell cultures show potential effect of mentioned vitamins, human studies failed to show this effect. Antioxidant supplementation in gastrointestinal cancer patients was not found to have significant effect on mortality, as reported in the Cochrane review by Bjelakovic et al. (21). However, for β-carotene in combination with vitamin A and E mortality was significantly increased (21). Additionally, vitamin and mineral supplementation did not show any effect in terms of cancer prevention (23). Lower incidence of cancer was found in men taking multivitamin supplements for more than 10 years (pooled unadjusted relative risk of 0.94). On the other hand, this systematic review by Fortmann et al. (23) published in November 2013 did confirm that β-carotene increases lung cancer risk in smokers.

DIETARY APPROACH

Planning a diet for cancer patient needs to combine all relevant information in order to maximize medical therapy. Nutritional guidelines need constant update, because of a large number of ongoing studies reporting new findings of potential foods and nutrients. In terms of planning a diet for a cancer patient, individual approach has been shown to have the highest potential (24). Study by Ravasco et al. (24) showed that individual nutrition counseling shows the best effectiveness at improving long-term prognosis in CRC patients. This effectiveness includes better nutritional status, intake of nutrients closer to recommendations, lesser late radiotherapy toxicity, better quality of life, and higher survival than in cases when individual nutritional counseling was not provided (24). Individual approach should surely be combined with patient's preferences (25).

In conclusion, individualized diet plan based on updated recommendations that will consider patient's preferences could significantly improve how they handle medical treatment, their recovery, and the overall quality of life.

Conflict of interest

We declare no conflicts of interest.

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