

Colorectal cancer: is it possible to prevent it?

Tiesiosios ir gaubtinės žarnos vėžys: ar įmanoma jo išvengti?

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Introduction and Background

Colorectal cancer (CRC) is among the most common human malignancies and remains a leading cause of cancer-related morbidity and mortality [1]. Colorectal cancer is the third most common cancer in the UK: its incidence increases with age, the median age at diagnosis being over 70 years.

Colorectal carcinogenesis is a multistep process characterized by molecular and cellular alterations that result in an identifiable precursor lesion – the adenomatous polyp. The transition from normal mucosa to adenoma and its subsequent progression to carcinoma are protracted events that offer opportunities for preventive interventions. Suppression or reversal of the carcinogenic process in the colorectum with nonpharmacologic or pharmacologic agents, i.e. chemoprevention, is an area of considerable research interest and activity [1].

Discussion

Chemoprevention is defined as the employment of drugs or natural compounds to prevent the development of benign or malignant tumors [2]. Epidemiological studies have shown that individuals reporting a regular intake of aspirin and other non-steroidal anti-inflammatory drugs have a reduced risk of developing colorectal polyps and cancer.

There have been several large epidemiological and observational studies to evaluate the possible protective effects of >200 agents [3]. Some studies have showed that a regular and continued use of non-steroidal anti-inflammatory drugs (NSAIDs), predominantly of aspirin, is associated with significant reductions in both colorectal adenoma and carcinoma incidence. NSAIDs were first shown to be effective in patients with familial adenomatous polyposis (FAP). Subsequent randomized trials in FAP have demonstrated that sulindac and the selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, can significantly regress the existing adenomas, and resulted in the Food and Drug Administration (FDA) approval of celecoxib for an adjunctive management of these patients.

Apoptosis in the colonic epithelium appears to be progressively inhibited during colonic carcinogenesis [4]. Evidence is now growing that the induction of apoptosis is one of the ways in which NSAIDs prevent cancer, and they may well exert their chemopreventive effects in the colon by restoring a normal frequency of apoptosis in the colonic mucosa.

The selective COX-2 inhibitor, celecoxib, at a dose of 400 mg twice daily, has been shown to reduce the mean number of polyps by 28% in patients with the rare genetic disorder – familial adenomatous polyposis [5]. This has led to the approval by the US Food and Drug

Administration of the use of celecoxib for the reduction of polyp numbers in patients with familial adenomatous polyposis (together with endoscopic surveillance or surgery). Studies are currently ongoing on the effectiveness of COX-2 inhibitors in preventing the recurrence of sporadic colorectal adenomas, either when used as a sole therapy or in combination with other agents [7].

Pending the expected release of results from several phase III trials in the near future, chemoprevention for colorectal cancer can only be practically considered in the very-high-risk population like those with familial adenomatous polyposis and ulcerative colitis, in conjunction with surveillance colonoscopy.

A number of studies have found a reduction in the risk of colorectal adenomas and cancer with a long-term dietary supplementation with folic acid.

Women who had regularly taken multivitamins (containing folic acid) for at least 15 years showed the greatest reduction in the risk of developing colonic cancer [6]. Nevertheless, there are no prospective studies to support the idea that a long-term multivitamin use influences the risk of rectal cancer. Folic acid is currently being investigated in prospective trials to further evaluate its potential efficacy as a chemopreventive agent.

Calcium, vitamin D, and some minerals (gamma-tocopherol and selenium) have protective effects, and daily exercise for > or =30 min results in a significant decrease of risk.

Diets high in animal fats and red meat have been found to be associated with an increased risk of colonic adenomas and colorectal cancer. Although the exact mechanism is unclear, it may be related to increased concentrations of secondary bile acids within the colon, which may increase cell proliferation in the colonic mucosa and have been found to be carcinogenic in animal models. Recently, a higher calcium intake was found to be associated with a significantly lower risk of distal but not proximal colonic cancer.

It is estimated that up to 80% of colorectal cancers may be preventable by dietary change. As an adjunct to chemopreventive agents, experiments in animals appear to support the use of low-fat diet regimes (preferably with higher intakes of omega-3 fatty acids) as a desirable approach to the primary prevention of colorectal cancer in the general population. High-galactose fruit and veg-

etable fibers, selenium and folic acid supplementation, and low-fat diets may well be the dietary interventions that could reduce the risk of colorectal cancer [8].

The risk of developing colorectal cancer is influenced by several acquired risk factors, including environmental exposures and the comorbid medical conditions that are partially genetic in nature (165). Acquired risk factors include the following categories: 1) dietary factors, 2) lifestyle factors, 3) side-effects of medical interventions, and 4) comorbid medical conditions. The dietary factors that potentially increase the risk of CRC include low fruit, vegetable, or fiber intake, high red meat or saturated fat consumption, and exposure to caffeine or alcohol. Of these factors, the significance of low fruit, vegetable, and fiber intake has been called into question because of contradictory results from large observational studies and negative results from randomized trials. The association of high red meat or saturated fat consumption with increased CRC risk is supported by the preponderance of observational data. Lifestyle factors include the lack of exercise, alcohol drinking, and smoking. The association between inflammatory bowel disease and CRC is well established, and it forms the basis for widely adopted colonoscopic surveillance recommendations from national medical organizations.

Conclusions

Further research would be useful to investigate the longer-term risk–benefit balance for those potentially effective chemopreventive agents; for example, whether there is a dose level that gives a significant benefit without unacceptable toxicity, what treatment durations are required, whether an effect on CRC can be demonstrated, and for how long the benefits are maintained after the intervention is stopped. Larger studies that follow up participants over long time periods (e.g., 20 years) and assess CRC incidence as an outcome would be valuable. Also, studies in which participants take these interventions for longer durations (e.g., 10 years or more) would be valuable to assess the risk–benefit balance associated with long-term chemoprevention.

Within the general population, even for studies with a relatively short treatment duration, a long-term follow-up is essential if the primary outcome is CRC incidence.

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