

REVIEW ARTICLE

Colorectal cancer and chemoprevention

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Summary

Epidemiological studies have suggested that diet factors may increase or, on the contrary, decrease the risk of developing colorectal cancer. Hence, a multitude of diet factors such as folic acid, calcium, antioxidants, selenium, fibre and diets rich in fruit and vegetable and poor in fat have undergone intensive research as chemopreventive agents. In addition, the use of aspirin and other nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced risk in the development of adenomas and colorectal cancer. Nevertheless, the role of these

chemopreventive approaches in the prevention of adenomas in the general population and sporadic colorectal cancer is uncertain. At present and in anticipation of further developments with large intervention trials under way, chemoprevention should be restricted only to high risk individuals. A balanced healthy diet, combined with a healthy life-style, involving physical exercise, remain the gold standard for the general population.

Key words: chemoprevention, colorectal adenoma, colorectal cancer, cox inhibitors, dietary fibers

Introduction

Colorectal cancer is an important public health problem in the Western World and despite the progress made in early diagnosis and treatment, it remains one of the commonest epithelial cancers in both genders and is essentially incurable in its most advanced stages.

In view of the high morbidity and mortality associated with colorectal cancer and its treatment, the strategy of prevention in various modalities is of extreme importance to public health. A specific element of prevention is chemoprevention, that is the adminis-

tration of natural or synthetic compounds, aiming at blocking or reversing carcinogenesis or at least delaying the development of invasive carcinomas.

The concept of chemoprevention lies in the fact that carcinogenesis is a long-lasting (10 to 20 years) and multistage process, which requires accumulation of multiple genetic and phenotypic changes, starting from the initial onset of the disease up to the complete development of an invasive carcinoma. The identification of this extended process may increase our ability to intervene in order to prevent carcinogenesis.

Major differences in geographic distribution of colorectal cancer, as well as major changes in disease incidence and mortality in population groups immigrating from areas with low disease incidence to areas with increased incidence strongly suggest that environmental factors and diet play an important part in cancer development.

In a multitude of mainly retrospective epidemiology studies, diets rich in fruits and vegetables were related to a low risk of developing colorectal cancer, whereas diets containing mainly animal fat, red meat and alcohol were connected with a high risk [1-3].

Based on these facts, a multitude of diet factors have undergone intensive research as chemoprephy-

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lactic agents. These factors include folic acid, calcium, several antioxidants, selenium, fibre and diets rich in fruit and vegetable and poor in fat.

Chemoprophylactic agents

The most common mode of study is the effect these chemoprophylactic agents may have on inhibiting growth of adenomas in patients with a history of adenomatous polyps.

In one of these studies, administering 1200 mg of elemental calcium resulted in a small but statistically significant reduction in recurrence of large bowel adenomas. The recurrence rate in the group receiving calcium was 31%, while for the placebo arm it was 38% ($p=0.04$) [4]. Similar results were noted in a smaller study in Europe, but the difference was not statistically significant [5]. The preventive role of calcium lies on the effect it has on bowel lumen pH by its means of affecting bile salts' balance, which are identified as carcinogenic factors [6].

Dietary fibres are another important factor intervening in bile salt metabolism by means of increasing stool water content, thus reducing concentration of secondary bile salts, as well as altering bowel lumen pH, thus reducing the production of secondary bile salts [7].

Nevertheless, in a large randomized study there was no statistically significant reduction in the risk of developing large bowel adenomas in patients receiving a complementary diet of large quantities of wheat-bran fiber (13.5 g per day) against those receiving small quantities (2 g per day) [8].

In yet another large, multicenter, randomized study, a low fat diet, rich in fruits and vegetables failed to reduce the recurrence rate of adenomas [9].

Lack of a positive effect in reducing the risk of developing adenomas was evident in another study regarding administration of antioxidant vitamins (i.e. vitamin E, β -carotin, vitamin C) [10]. On the contrary, in a smaller study with a median follow up of 18 months, administration of the same agents showed a definite protection against adenoma recurrence [11].

Folic acid, a water soluble vitamin B, is a major dietary factor with an important role in preventing various malignancies including colorectal cancer. In a series of 15 retrospective studies, patients receiving adequate dietary folic acid intake showed a 40% reduction in the risk of developing colorectal cancer in comparison to those receiving minimal amounts of folic acid in their diet [12-14]. Furthermore, in a recent meta-analysis of studies from the USA, Cana-

da, Netherlands and Sweden including over 500,000 men and women, adequate dietary folic acid intake was associated with 20% reduction in colorectal cancer incidence in comparison to those with minimal folic acid intake [15]. This inversely proportionate relation between levels of folic acid and colorectal cancer risk could be modified further by alcohol intake, a well known folic acid antagonist [16], as well as by the use of other factors participating in folic acid metabolism like methionine and vitamins B6 and B12 [12-14]. Despite evidence of folic acid being an effective chemoprophylaxis factor and despite its safety and cost effectiveness [17], a safe and effective dose and most appropriate schedule of administration have not been defined. There are already numerous studies showing that complementary administration of high doses of folic acid to animals is related to tumour progression in subjects with tumour foci in target organs [18].

Reduction of colorectal cancer risk has been demonstrated in epidemiology studies involving diets rich in selenium [19]. Similar studies involving selenium as a chemoprophylactic agent are now in progress. Currently, a large study is in progress involving 64,500 postmenopausal women, examining prevention of cancer, cardiovascular disease and osteoporotic fractures. In particular, the study started in 1992 and is due in 2007, assessing the following: 1) the effect of low fat diet in breast and colorectal cancer as well as in coronary disease; 2) the value of hormonal replacement therapy (HRT) in reducing coronary events and osteoporotic fractures; and 3) the reduction of colorectal cancer and osteoporotic fractures by administering calcium and vitamin D [20].

A major obstacle to epidemiology studies assessing the effect of chemoprophylactic agents is the massive number of the population required, as well as the long observation periods. A major question is whether various factors like the patient's lifestyle and diet are important, mainly during one's childhood or early adult life.

The progress made in molecular biology and the better understanding of the basic stages of carcinogenesis have identified specific targets. One of these targets is the enzyme cyclooxygenase (COX) which encompasses 2 isoenzymes: COX-1 and COX-2. COX-1 is necessary for the function of healthy tissues, whereas COX-2 increases in cases of infection or malignancy [21]. Overexpression of COX-2 typically occurs in preinvasive stages of carcinogenesis, creating a specific target for chemoprophylaxis. Hence, in numerous preclinical and more than 15 clinical studies, COX inhibitors have been successful in causing regression of

premalignant lesions. Furthermore, in more than 25 retrospective and prospective studies it has become evident that using aspirin and other NSAIDs caused reduction in the risk of developing adenomas and colorectal cancer and mortality by 40-50% [22]. Only 2 studies failed to verify reduction of colorectal cancer risk by the use of aspirin [23,24].

Despite the convincing data written above, NSAIDs are not being used in clinical practice in view of their side-effects (peptic ulcer, worsening renal and liver function, antiplatelet effect) and the fact that chemoprophylaxis is given to healthy, asymptomatic individuals. The NSAIDs side-effects are related to COX-1 inhibition, not participating in carcinogenesis. Consequently, the discovery of COX-2 selective inhibitors (celecoxib, rofecoxib), has drawn new pathways in colorectal cancer chemoprophylaxis.

In a recent randomized study involving 8,000 patients, celecoxib caused 40-50% fewer symptomatic peptic ulcers compared to non-selective COX inhibitors [25]. Moreover, in another series of pre-clinical studies, COX-2 selective inhibitors reduced the incidence of crypts and colonic cancer in animal models [26,27].

Based on the safety profile of COX-2 inhibitors a multitude of studies looked into their use as chemopreventive agents. Hence, in a randomized trial performed by the US National Cancer Institute, involving 88 individuals with familial adenomatous polyposis (FAP) who received celecoxib for 6 months, there was a significant reduction in the number and size of adenomas, with a toxicity profile comparable to the placebo arm [28]. Celecoxib was shown to improve the endoscopic appearance of the duodenum, as well as the large bowel and the rectum, reducing the risk of malignancy for both organs. In view of the above data the FDA approved the use of celecoxib in FAP.

The results of this study led to a widened role for celecoxib in the prophylaxis of sporadic colorectal cancer. There are a multitude of trials underway, administering NSAIDs or COX-2 inhibitors along with other chemoprophylactic or dietary agents, like folic acid, selenium etc [29].

As far as the prevention of sporadic colorectal cancer is concerned, the use of low dose aspirin (325 mg every other day for a period of 5 years) in a large, controlled, randomized study failed to display a reduction in the incidence of new cases of colorectal cancer (relative risk=1.15; 95% C.I. 0.80-1.65). This study is the only completed study for the prevention of colorectal cancer to date [30].

It is common practice to try new chemopreventive agents initially in high risk patient groups and only

administer the agent to the general population if the initial results are positive. These agents should be safe and effective in preventing more than one malignancies or other diseases.

COX inhibitors are ideal candidates in view of their beneficial effect in treating arthritic pain and preventing cardiovascular events and cataract [31-33].

For the time being and in anticipation of further developments with large intervention trials underway, it is evident that chemoprevention should be restricted to high risk individuals. A balanced healthy diet combined with a healthy lifestyle involving physical exercise, remains the gold standard for the general population.

Furthermore, the prevention of colorectal cancer should be performed by monitoring the group aged over 50 with endoscopy or faecal occult blood.

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