Dietary chemoprevention of colorectal cancer

Ann. Ital. Chir., 2008; 79: 261-268

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AIMS AND BACKGROUND: *Colorectal cancer is the second cause of morbidity and death in Italy. Genetic and environmental factors, i.e. inappropriate nutrition, are strongly involved in the aetiology of colon cancer. In the present review the authors analyze the possible mechanisms by which certain nutritive factors may interfere with the complex process of carcinogenesis.*
METHODS: *The authors identify studies by a literature search of Medline from January 1, 1970, through December 31, 2006.*
RESULTS: *The mechanism of every protective compound is detailed, in particular the impact of antioxidant vitamins and minerals on tumor development. At present, the data suggest that vegetables are associated with lower risk and that their fibre content alone does not account for this association. Further, meat consumption is associated with an increased risk but this, too, is not explained solely by its fat content. Several microconstituents of the diet may be associated with reduced risk, including folate, methionine, calcium and vitamin D. Short chain fatty acids also contribute to colonic health. Nevertheless agricultural products contain several dangerous pesticides. Mutagenic compounds, particularly heterocyclic amines, produced when protein is cooked, plausibly explain the meat association.*
CONCLUSIONS: *Healthy nutrition is a necessary but not sufficient condition for colon cancer prevention: accepted the feasibility of an accurate control on every patient's diet, frequently the difficulty encountered in nutritional chemoprevention is to establish individual metabolic profiles.*

KEY WORDS: Chemoprevention, Colorectal neoplasm, Diet, Epidemiology.

Introduction

Colorectal cancer (CRC) is a major world-wide health concern, representing the second cause of morbidity and death in Italy. This pathology is most often found in people over the age of 50 and it has been estimated that the probability of developing colorectal cancer is 4% since birth until 70 years old. In industrialized countries, several environmental and nutritional risk factors are associated with colorectal cancerogenesis, expecially a low fibre, high fat/refined carbohydrate diet. Although cancer screening and surveillance provide opportunities for risk stratification, they achieve risk reduction only when coupled with effective interventions. Therefore, the incidence of many neoplasms could be reduced by a balanced diet.

Internationally there is wide variation in the incidence of colorectal cancer, with higher rates reported for western-lifestyle countries and lower rates reported elsewhere: in particular, there is a high incidence of colorectal cancer in the USA (44 cases per 100,000 persons per year), Europe (35/100,000), Canada and Australia; whereas a low number of cases is reported in Asia (3/100,000), Africa (5/100,000) and South America.[1] Observational studies on Japanese immigrants to the USA have shown that in the second generation emerged a higher risk of colon cancer than their counterparts who remain in Asia. Changes in cancer incidence associated with migration suggest parallel changes in environmental factors, nutrition or lifestyle habits.[2] This indirect evidence is strong

Pervenuto in Redazione Gennaio 2008. Accettato per la pubblicazione Maggio 2008.
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enough to make even the most skeptical doubter believe in the possibility of the influence of nutritional habits on carcinogenesis.

The results of the research on this matter are not decisive, supposing that they are not contradictory at all. Paradoxically, in our overeating society, food has frequently been adulterated with presumed beneficial substances (vitamins, calcium, selenium, etc.) and a big publicity campaign encourages people to buy it, but nutrition-related diseases have increased markedly during the last decades. Clearly excessive importance is often given to few aspects of a complex question. Dietetic guidelines suggested by the National Cancer Institute provide to include fruit and vegetables in everyday diet, to reduce fat intake to 30 percent of total calories, to increase complex carbohydrates, to drink alcoholics with moderation, to increase fibre intake to 20-30 g/day (until 35 g/day), to minimize the intake of salted, charred, cured or smoked foods and to avoid obesity.[3] Notwithstanding these reassuring certainties, the reverse of the medal should not be neglected: a big percentage of fruits and vegetables is contaminated at least with one type of pesticide.[4, 5, 6]

In order to reach a conscious nutritional (and molecular) chemoprevention, it is appropriate to evaluate the mechanisms of action of every nutrient. Thus, it is important to remember that not all mutagens are carcinogenic and that there is a noticeable inconsistency among the results of *in vitro* and *in vivo* tests. Dietary components with a potential protective role are antioxidants, calcium, vitamin D, folate, methionine, polyamine inhibitors, polyphenols and short chain fatty acids (SCFA). SCFA are the dominant anion in the colon and the primary energy source of mucosal colonocytes; their concentration can be strongly influenced by diet. Diet supplemented with anticarcinogens does not necessarily provide medical benefit, because every substance at high doses acts like a drug, with its peculiar side effects (e.g., excessive intake of fat-soluble vitamins).

In the present review the authors try to identify scientific evidence in support of the recommendations to avoid colorectal cancer development, in a nutritional chemopreventive setting.

Material and Methods

We identified studies by a literature search of the Medline database (from January 1, 1970, through December 31, 2006) with the following Medical Subject Heading (MeSH) and subheading terms: "colorectal neoplasms", "colorectal neoplasms / epidemiology", "colorectal neoplasms / chemistry", "colorectal neoplasms / pathology", "colorectal neoplasms / prevention and control", "chemoprevention", "chemoprevention / adverse effects" and "diet therapy". We also reviewed reference lists of the identified pubblications for additional pertinent studies. No language restrictions were imposed. The 67 studies considered for inclusion were case-control or cohort studies, clinical trials and review articles about the possibilities of nutritional chemoprevention of large bowel cancer. In case of multiple publications from the same population or cohort, only data from the most recent report were included.

Results

In the 1970's Burkitt promoted the hypothesis that dietary fibre protected against colorectal cancer, and that increases in cancer rates may have been due to an increased intake of refined cereals, protein, fat and sugar.[7] Dietary fibre is the indigestible portion of plant foods. There are two important types of fibre: insoluble and water-soluble. Water insoluble fibres remain unchanged during digestion; they may increase stool bulk and stimulate intestinal transit, thereby reducing epithelial exposure to intraluminal carcinogens. They can be found in fruits with edible peel or seeds, vegetables, whole grain products, cereals, bran, buckwheat and legumes. A grain fibre supplement (19.5-22.5 g/day) inhibits benign large bowel neoplasia in patients with familial adenomatous polyposis.[8] Dietary wheat bran fibre also reduces [^{3}H]thymidine rectal mucosa cell labelling in patients with resection for colorectal cancers.[9] Water-soluble fibre (such as pectins, mannans, guar gums, amylose, raffinose) undergo metabolic processing via fermentation, yielding end-products, such as short chain fatty acids (acetic, propionic and butyric acids), methane, carbon dioxide. Soluble fibre can be found in fruits (such as apples, oranges and grapefruits), certain vegetables (such as broccoli and carrots), legumes (such as dry beans, lentils and peas), barley, oats and oatbran. Other important determinants in short chain fatty acid production are dietary residues reaching the lower gut: resistant starch, digestion-resistant oligosaccharides (greatly present in the leguminosae), polyalcohols (such as sorbitol and several sweeteners), fructose and lactose in case of lactose intolerance. A direct source of butyrate is the diet, where it is present at low levels in many fruits and vegetables, but its richest source is from milk fat (butter) which contains 3-4% butyrate as glycerol esters termed tributyrin.[10] Although large luminal butyrate concentrations vary prominently by individual differences in the composition of intestinal microflora, it has been reported an increase of butyrate anyway, following the intake of resistant starch. Referring to a normal diet and to the amount of bacterial cells produced in the colon, one can estimate that about 15-60 g carbohydrate is fermented per day, yielding 150-600 mmol SCFA. The average intraluminal concentration of SCFA has been estimated to be between 100 and 170 mM.[11] The concentration of individual SCFA is greatly influenced by the diet. In colonocytes, fatty-acid oxidation governs

processes such as ATP generation, lipogenesis, absorption of sodium, acetylation of histones and detoxification of xenobiotics. Moreover, butyrate enhances the physiological cell proliferation in the basal crypt compartments, thus decreasing the rate of aberrant crypt foci, due to the shifting of the zone of proliferation to the apical part of intestinal glands. The mechanism for locally mediated colonotrophism seems to be multifactorial and may include increases in visceral blood flow, aerobic oxidation of SCFA for energy, increased production of enterotropic hormones, and stimulation of the enteric nervous system. While butyrate increases proliferation of normal colonic epithelium, it decreases proliferation and induces apoptosis of neoplastic colonocytes in vitro and in vivo: it inhibits DNA synthesis and arrests the growth of neoplastic colonocytes in the G1 phase of the cell cycle, thus reducing their cloning efficiency, but it leaves the differentiation of normal colonocytes unchanged.[12-17] Therefore, butyrate could seem an inhibitory mediator of the aberrant crypt foci (ACF) – adenoma – carcinoma sequence. Moreover, butyrate and other SCFA provide energy for colonocytes, have anti-inflammatory properties and stimulate colonic fluid and electrolyte absorption.[18-22] A lack of SCFA can lead to colonic inflammation, thus playing a critical role in the pathogenesis of Inflammatory Bowel Disease (IBD). Recent data suggest that short chain fatty acid enema therapy is effective in chronic radiation proctitis because it stimulates colonic repair and collagen biosynthesis, thus accelerating the process of healing.[23, 24]

Non-genotoxic measures which are likely to upregulate apoptosis in pre-neoplastic/neoplastic cells also include antioxidant polyphenols.[25, 26] They are abundantly present in tea, chocolate, red wine, oranges, cherries, strawberries, apricots and tomatoes. Anyway, the efficacy of antioxidant therapies has been equivocal: some antioxidants exhibit a prooxidant activity under certain conditions and potential carcinogenicity under others.[27] One possible explanation could lie on the heterogeneity of polyphenols and of their effects.

Calcium binds bile and fatty acids in the form of insoluble soaps, which effectively sequesters these mutagenic substances from harmful contact with epithelial cells. Calcium rich foods are milk and dairy products, it being understood that calcitriol is the necessary hormonal stimulus of its active intestinal absorption. Calcium supplementation significantly normalizes fecal bile acid profiles after colon cancer surgery. In addition, it may directly inhibit epithelial proliferation within the colorectum by modulating protein kinase C activity, stabilizing membranes, or modifying K-ras mutations. Many epidemiological studies show moderate and fairly consistent inverse associations between calcium intake and CRC risk.[28, 29] Baron[30] reported a statistically significant 19% reduction in patients with recurrent adenomas and a 44% reduction in advanced adenomas among individuals taking a calcium carbonate supplement. It is interesting to note that chemopreventive effects were observed as early as one year after the beginning of the treatment, suggesting that calcium acts relatively quickly.[31] Moreover, supplemental calcium has been reported to suppress induction of the tumor-promotion enzyme ornithine decarboxylase (whose activity is increased in colorectal neoplasms): this fact constitutes another potential mechanism of anticancer action of calcium.

Epidemiological studies provided the suggestion of a link between CRC risk and vitamin D concentrations.[32] The chemopreventive properties of vitamin D may relate to its ability to modulate calcium absorption, gene expression and cell proliferation.[33, 34, 35] A large epidemiological study of the American Cancer Society cohort reported a 29% reduction in CRC risk among individuals with the highest vitamin D intakes from supplemental sources or diet (cod-liver oil, eel, sardine, tunny, salmon, mackerel, eggs, mushrooms, cacao).[36]

Most fruits and vegetables contain antioxidants, vitamins and minerals. Representative examples such as carotenoids, retinoids, ascorbic acid, alpha-tocopherol, selenium and zinc can neutralize free radicals, thus reducing oxidative DNA damage.[37] Vitamin C can also inhibit nitrosamine formation in vitro and in vivo. In addition, certain studies suggest that antioxidants may inhibit tumorigenesis by stimulating the immune system.[38] Fruits and vegetables are good sources of vitamins: for example, carrots, apricots and green leaves vegetables are rich in provitamin A, in the same way as cauliflowers, broccoli, oranges, tomatoes, kiwi contain a large amount of vitamin C. Wheat germ oil is very rich in vitamin E, but there are different types and quantity of this vitamin in several vegetable oils (in decreasing order of percentage: palm, soybean, corn, canola, safflower, sunflower, peanut, olive oil, coconut); tocopherol is also present in yolk. Main dietary sources of selenium are plant foods, fish, shellfish, red meat, grains, eggs, chicken, liver, garlic, Brewer's yeast, wheat germ, and enriched breads. How much selenium is present in the various foods depends on how much of the mineral was in the soil where the plants grew or the animals ate. Soil impoverishment and food processing cause a significant decrease in zinc bioaccessibility as well. That is why it is important to choose natural foods as much as possible. In particular, zinc is found in oysters, shellfishes, beef, wheat cereals, yeast, bran, wheat germ and pumpkin seeds. Retinoids are vitamin A derivatives and have been the most studied chemopreventive compounds; topical and systemic therapy have got a poor clinical tolerability which is not acceptable for reducing cancer risk in healthy subjects. Natural and synthetic retinoids have got a hepatotoxic potential related to excessive intake of the vitamin.

High doses of antioxidant supplementation may be deleterious in subjects in whom the initial phase of cancer development has already started, and they could be ineffective in well-nourished subjects with adequate antiox-

idant status.[39, 40] A phase II trial evaluating antioxidant combinations reported reductions in colorectal adenoma proliferation and recurrence.[41] The SU.VI.MAX (SUpplementation en Vitamines et Mineraux AntioXydants) study, a double-blind, randomized, placebo-controlled, primary prevention trial, designed to test the effect of a combination of antioxidant vitamins and minerals, at doses considered to be nutritional (120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 microgram selenium and 20 mg zinc) in reducing cancer and ischemic vascular disease incidence in 13,000 middle-aged subjects, has recently delivered its verdict. After 7.5 years, low-dose antioxidant supplementation lowered total cancer incidence in men, but not in women. It may be explained by the lower baseline antioxidant status in men.[39, 40] Besides, De Cosse[42] showed the possibility of inhibition of benign large bowel neoplasia (polyps) in patients with familial adenomatous polyposis treated with vitamins and a grain fibre supplement.
Fresh fruits and vegetables are also rich in folate, whereas red meat, chicken and fish have relatively high concentrations of methionine. Folate and methionine both supply methyl groups necessary for DNA synthesis and repair and for gene expression. Case-control and prospective studies suggest that dietary folate and methionine exert chemopreventive effects against colorectal carcinogenesis.[43, 44, 45] The amount[46] and duration[47] of intake may influence the degree of protection that these dietary components confer: indeed, a lower risk for colorectal neoplasms has been observed among participants with the highest levels and the longest periods (more than 10 years) of folate intake.[48-54] Nonetheless, dietary and genetic factors may modulate the proposed chemopreventive effects of folate and methionine; certain studies have shown that heavy alcohol consumption and polymorphisms in methylenetetrahydrofolate reductase (MTHFR) may reduce the availability of methyl groups, thus altering the chemopreventive effects of folate and methionine.[55-58]
Many studies have shown the association between gastrointestinal cancer risk and high-fat diet. High consumption of red and processed meat is associated with an increased risk for colorectal cancer, according to several meta-analysis studies.[59-61] In particular, the two main factors that influence the production of pyrolysis products in cooked meats are time and temperature; consequently, the excess risk is mostly confined to intake of roasted, grilled and possibly fried red meat. These results are consistent with cooking practices that produce carcinogens such as heterocyclic amines and polycyclic aromatic hydrocarbons, which lead to the formation of DNA adducts; it has been reported the detection of adducts in malignant human colorectal tissue.[62-65]
Beneficial agricultural products contain several pesticide residues, as well as there are benefits and risks in red meat intake. A substance that should be regarded as if it is carcinogenic to human colic epithelium is the organophosphate insecticide chorpyrifos.[66] Nevertheless, scientific evidence is rather narrow to this end, probably because these dietary contaminants are not carcinogens by themselves, but they result carcinogenic proportionally to their concentrations. Probably, hormesis should be revalued in nutritional context: it is a biological and toxicological theory according to which there is a stimulatory response from low dose or concentration of a non-essential substance which results in an increase in biological function of individual organisms, but at higher doses/concentrations produces toxic effects.[67]

Discussion and Conclusion

Almost all malignant neoplasms present, among their risk factors, an unbalanced diet containing numerous as much as unknown carcinogenic substances, hormones and environmental polluters. Molecular prevention should become increasingly valued as we confront the wide spectrum of neoplastic and cardiovascular disease – the prevalent health-care challenges in Western societies.
The complex interactions among diet, gut microflora and host tissues influence large-bowel health. Elaborate cocktails of nutrients exert combined physiological and biological effects on intestinal epithelial cells and the majority of colon bacteria causes a great number of metabolic reactions with nutrients and host molecules. Individuals have a distinct gut bacteria profile that may result in each individual having a different capacity to utilise dietary components and a resulting different risk profile for disease.
Firstly, a correct diet aimed chiefly at cancer prevention should include a reduction of the intake of polluters as much as possible. Nowadays, advertised food products undergo processing steps which interfere with their organoleptic qualities of these meat products and with the biochemical balance of the individual.
There is a noteworthy relation between reduced colorectal cancer risk and total fruits and vegetables intake; the reason of this association lies in the beneficial effect of dietary fibre, vitamins, minerals, antioxidants and in the presence of numerous antimutagens in several food products (such as cauliflowers, cabbages and Bruxelles cabbages, etc). Very interesting is the relatively recent discovery that short chain fatty acids are antiinflammatory and antineoplastic active molecules. Butyrate concentration should be increased with diet, sooner than with local or systemic administration. Across-the-board recommendations to eat every macro and micronutrients in a balanced and various diet are valuable in order to prevent or relieve colorectal cancer. The intake of one or few beneficial elements (vitamins, minerals, antioxidants, etc) regardless of the individual metabolic environment, it would not only come to naught, but it would also be harmful.

Accepted the feasibility of an accurate control on every patient's diet, anybody could develop a large bowel cancer in spite of an appropriate diet. In part this is a problem of single or associated alimentary contaminants which could reach a concentration superior to the maximum tolerated dose (MTD). On the other hand the answer to this enigma should be searched in the difficulty we find when we study the individual metabolic profile, without ignoring any potential protective effects of dietary compounds. Dietary chemoprevention is otherwise a necessary but not sufficient condition for colon cancer prevention, which is also influenced by carcinogens, familiar and genetic profile, age, gender, race, health status (e.g., metabolic syndrome) and last, but not the least, physical exercise.

Riassunto

Il tumore del colon e del retto è tra i tumori a più elevata incidenza in Italia e nel mondo occidentale, rappresentando la seconda causa di morbilità e morbosità per neoplasia. Numerosi fattori di rischio ambientali e dietetici sono strettamente correlati con lo sviluppo del cancro colorettale. Attraverso una revisione della letteratura, gli autori hanno analizzato i possibili meccanismi attraverso cui alcuni nutrienti interferiscono con il complesso processo della cancerogenesi, individuando l'evidenza sperimentale che ne giustifichi l'indicazione nell'ambito della prevenzione coloproctologica.

I dati attualmente a disposizione suggeriscono che il consumo di frutta e verdura è associato con un ridotto rischio di sviluppare neoplasie e che il contenuto in fibre di questi alimenti non giustifica di per sé tale associazione. Il consumo di carne è correlato, invece, ad un aumentato rischio oncologico e ciò non è analogamente riconducibile al solo contenuto in grassi. Esistono, inoltre, diversi micronutrienti, come folato, metionina, calcio e vitamina D, che possono ridurre il rischio di neoplasia colorettale. Ulteriore contributo alla salute dell'apparato digerente è fornito dagli acidi grassi a corta catena.

D'altro canto, i prodotti agricoli contengono numerosi pesticidi dannosi. Inoltre, sostanze mutagene, in particolare amine eterocicliche, prodotte dalla cottura delle proteine, spiega plausibilmente il rischio correlato all'assunzione di carne. In ultima istanza, a fronte della possibilità di una chemioprevenzione alimentare, rimane la difficoltà di definire per ogni paziente un profilo metabolico individuale globale.

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