

Primary prevention of colorectal cancer

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Colorectal cancer is the third most common malignant neoplasm worldwide. Epidemiological and laboratory animal studies have established a link between various nutritional factors and the etiology of this cancer. Recent studies in genetic epidemiology and molecular biology have shown that inherited genetic factors also play an important role in colorectal carcinogenesis. Thus, genetic-nutritional interactions may form the basis for the development of this cancer. Nutritional factors that appear to promote or attenuate the carcinogenic process in the colon include fat, excess calories, fibre, calcium, selenium, and various vitamins. Strategies for primary prevention of colorectal cancer should therefore be targeted to all populations who are at risk because of dietary and hereditary predisposition.

Based on current knowledge, recommended nutrition guidelines for reducing the risk of colon cancer include decreased fat consumption, adequate amounts of fruits, vegetables, and calcium, and avoidance of overweight. Research to further elucidate the role of diet in colorectal carcinogenesis should include randomized studies in humans, testing of various nutritional regimens, and the use of colonic adenomas and markers of cell proliferation and differentiation as end-points.

Introduction

Colorectal cancer is the third most frequently diagnosed malignant neoplasm worldwide (1). With an estimated annual incidence of 570 000,^a it constitutes 9% of all diagnosed cancers, ranking in frequency below gastric and lung cancers and equal with breast cancer. In developed countries colorectal cancer is the second most common malignancy, while in developing countries it ranks eighth.^a Although the causes of this widespread cancer are unknown, epidemiological and laboratory animal studies performed over the last few decades indicate a strong link with nutritional factors (2, 3). While the major thrust of research has been directed towards the diet,

recent evidence suggests that inheritance plays an important role, not only in the relatively rare familial colon cancer syndromes such as familial polyposis, but in the more common "sporadic" colon cancers as well (4). Thus, it appears that both dietary constituents and inherited predisposition are important factors in colorectal carcinogenesis.

The evidence that nutritional factors can promote or inhibit the development of colorectal cancer suggests that primary prevention may be essential for the control of this disease. Strategies for primary prevention can be more effective if targeted to populations at risk because of a hereditary predisposition and the consumption of diets which enhance the carcinogenic process in the colon.

The link between dietary components and colorectal cancer has been supported by epidemiological correlations (2, 5-10), case-control studies (2, 11-16), and experimental studies in animals (17-20). Dietary constituents that have been implicated include fat and excess calories, reduced dietary fibre, alcohol, relatively inadequate intake of vitamins (retinoids, ascorbic acid, alpha-tocopherol), minerals (calcium), and trace elements (selenium). In the USA, the National Research Council Committee on Diet, Nutrition and Cancer performed an exhaustive evaluation of the literature on the association between diet and cancer (2) and concluded that current evidence indicates a strong link between the two. A recent report on the relationship between diet and health concluded that one-third of cancer mortality may be related to diet (3). The Nutrition Research

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^a Granth, H. et al. *Time trends in mortality from cancer*. Unpublished WHO document WHO/CAN/88.5, 1988.

Council Committee suggested human intervention studies to clearly demonstrate that changes in diet could reduce the risk of cancer (21).

Nutritional factors

Fats

Current data indicate that increased fat consumption is associated with enhanced carcinogenesis in the colon. Colon cancer mortality in different countries around the world show a linear relationship with total dietary fat availability (22). Although not all the countries are well fitted on the graph, the direct correlation is striking. Estimates of dietary fat intake show that populations with a high fat consumption have higher death rates from colorectal cancer (9, 23). Studies in migrants from areas with diets low in animal fat and protein to areas with a "western" type of diet with high fat show an increased incidence of colon cancer compared to that in their country of origin. This increase in risk was demonstrated in migrants from Japan to Hawaii (24) and from Poland to Australia (25). Numerous case-control studies have also supported the association between fat intake and colorectal cancer (16, 27-29). However, other epidemiological data did not confirm this association, particularly when different regions of the same country were studied. Thus in the USA the per capita fat consumption in individual states showed no direct association with mortality from colon cancer (30); also, the incidence of colon cancer in Utah was found to be significantly lower than the average U.S. incidence, in spite of a similar per capita fat intake (31). A prospective cohort study assessing the intake of nutrients for 28 days found no difference in fat intake (as a percentage of calories) between those who subsequently developed colon cancer and those who did not (32). A recent review on the link between dietary fat and colon cancer was inconclusive (33). The inconsistency in the epidemiology data may be due to the fact that in most epidemiological studies the dietary factors protecting against colon cancer, such as fibre, had not been adequately considered. Indeed, in a study from Scandinavia (34) the rate of colon cancer was found to be markedly higher in a Danish population than among Finns, in spite of similar fat intakes; the Finns had a substantially higher fibre intake than the Danes, which suggests that fibre may have modified the damaging effect of fat. It is therefore important to control for other components of the diet when assessing the risk from a single nutrient.

Most epidemiological studies did not correlate colon cancer with a specific dietary fat, but rather with the total fat consumed. Another source of inconsistency in the epidemiological data may be in the type

of fat used to elucidate the correlation between fat intake and colon cancer; while some studies incriminate animal fat consumption, other data suggest that vegetable fats (35) show the strongest positive correlations. When colon cancer is induced in laboratory animals by dimethyl-hydrazine, diets with a high concentration of vegetable oil and polyunsaturated fat are associated with a higher incidence of colon cancer (20). In contrast, highly polyunsaturated fish oils and mono-unsaturated olive oil have been shown to have no colonic tumour enhancing effect in animals (36). Two recent European case-control studies suggest that mono-unsaturated fatty acids may actually exert a protective effect against colon carcinogenesis (37, 38).

The biochemical basis of the cancer-promoting action of dietary fat in the colon has not been established. Several mechanisms have been proposed: (1) dietary fat induces an increase in biliary sterols and these compounds damage the colonic epithelium and induce hyperproliferation (39, 40); (2) carcinogenesis is enhanced by lipid peroxidation radicals generated from fat metabolism (41); (3) certain fatty acids promote carcinogenesis by becoming incorporated into cell membranes and by inducing changes in the membrane fluidity and in the response to carcinogenic compounds in the colon; (4) overabundance of linoleic acid increases the synthesis of certain prostaglandins which can act as cancer promoters by stimulating cell proliferation; (5) dietary fat determines the characteristics of the gut bacterial flora which play an important role in the metabolism of carcinogens; and (6) the cancer-promoting effect of fat is not specific to its chemical composition but is attributed to its caloric density. Fat being the most calorically dense among the macronutrients is thus the most carcinogenic.

It has not been determined to what level dietary fat should be restricted in order to achieve significant attenuation of the carcinogenic process in the colon. The average fat content in the American diet and some western European diets is about 40% of total calories (42, 43). This is in contrast to Third World diets in which only 10-25% of total calories are in the form of fat. Animal studies show a dose response of carcinogen-induced colon tumours when dietary fat is increased from 10% to 40% of total calories (21).

In spite of the inconsistencies in the evidence relating colorectal cancer to fat intake, the data, when considered as a whole, support the hypothesis that increased dietary fat plays a role in enhancing colonic carcinogenesis. Randomized intervention studies in humans are required to establish this relationship firmly.

Fibre

The hypothesis that a diet high in fibre may protect against colon cancer was first proposed by Burkitt & Trowell, who observed that African blacks who consumed high fibre diets had lower death rates from large bowel cancer than whites, whose fibre intake was low (44). Some epidemiological studies support this hypothesis (15, 45–48) but others are inconsistent (29, 49, 50) with it. The inconsistency of the data has been pointed out in the report of the U.S. National Research Council (2), and in a more recent report by a committee of the Federation of American Societies for Experimental Biology (51). The inconsistency may be due to the fact that dietary fibre is not a specific chemical entity but rather a diverse group of compounds which originate in plants and are resistant to the action of human digestive enzymes. Different fibres have different physiochemical properties and can affect the colonic milieu and colonic mucosa in various ways. Indeed, some fibres may have little physiological effect in the colon, their main action being in the small bowel. Most epidemiological studies on the correlations between fibre and colon cancer examined fibre-containing foods in general rather than specific fibres. In some studies, the risk for colorectal cancer was related to specific fibres or specific fibre-containing foods. Thus, consumption of cruciferous vegetables (broccoli, cauliflower, cabbage, Brussels sprouts) was found to be protective against colon cancer (45). Animal models have shown that specific dietary fibres (bran (52) and cellulose (53), but not pectin (54)) protect against carcinogen-induced colon cancer. Consumption of some fibres has been shown to induce changes in the colonic mucosa suggestive of enhancement of the carcinogenic process. Thus, increased DNA synthesis, mucosal mass and cell migration were associated with consumption of wheat bran, guar, and pectin, but not oat bran (55). It must be emphasized that this response may not be universal and may depend on species, sex, or other factors. Considering the diverse physiochemical make-up of dietary fibre, it is likely that if indeed there is a protective effect it may be specific to certain fibres.

The mechanisms by which fibre can exert a protective effect against colon carcinogenesis have not been elucidated. Possibilities include: (1) reduction of transit time in the colon, thus reducing the exposure of the colonic mucosa to intraluminal carcinogens; (2) binding and dilution of carcinogens in the colonic lumen (such as bile acids), thus neutralizing their harmful effects; (3) changes in the colonic bacterial flora which metabolize bile acids; and (4) decrease of pH in the colon by certain dietary fibres

(such as pectins), which are metabolized in the colon to short-chain fatty acids, causing deionization of potentially harmful free fatty acids and bile acids.

The protective effect of dietary fibre against colon cancer could be additive to that of a reduction in dietary fat. Usually, diets low in fat tend to have a high fibre content. In experimental conditions, in normal humans, the reduction of fat in the diet resulted in an increased fibre consumption (M. Shike et al., unpublished data), since fats were replaced by complex carbohydrates and other foods.

Calories

Animal studies and a few epidemiological data suggest that excessive caloric intake and body weight may increase cancer risk in various organs. Tannenbaum's early work (56, 57) in animals, and more recent data, demonstrated that caloric restriction and decreased body weight inhibit chemically induced tumours, including colon cancer (58, 59). International epidemiological correlation studies (9) and case-control studies (13, 16) suggest that increased caloric consumption and increased body weight enhance the risk for colorectal cancer. A study by the American Cancer Society (60) found that the body weight index (which is presumably related to caloric intake) correlated positively with colon cancer incidence. A similar finding was noted in Japanese men living in Hawaii (61). However, other epidemiological studies did not find a correlation between body weight and colon cancer (62). In a recent symposium on calories and energy expenditure in carcinogenesis (63), it was concluded that "overnutrition is directly related to high risk of cancer". It must be noted, however, that there is a complex relationship between caloric intake, energy expenditure, body weight, and the hormonal milieu. The studies cited above lend support to the hypothesis that excess calories and increased body weight can enhance carcinogenesis, but additional data are required to separate the effects of calories from the specific effects of fat, and to determine whether the effect of calories is independent of the metabolic rate and body weight. This is particularly important since it has recently been shown that an inherent low metabolic rate can result in decreased caloric expenditure and a tendency towards obesity (64), underscoring the complex relationship between caloric intake, metabolic rate, and obesity. If indeed increased caloric intake enhances carcinogenesis, it remains to be determined whether the primary factor is the direct effect of the calories, the metabolic rate, or the body weight and composition.

Minerals, vitamins, and trace elements

Recently, it has been hypothesized that calcium can protect the colonic mucosa from intraluminal compounds that irritate it and lead to neoplastic changes (65). Calcium is thought to neutralize the damaging effects of bile and free fatty acids which are considered to be strong cancer promoters in the colon (66–68). Although most of the bile acids are absorbed in the terminal ileum, small amounts reach the colon in a conjugated form with taurine and glycine. The colonic bacteria deconjugate these complexes releasing free bile acids, which they subsequently dehydroxylate to tumour-promoting secondary bile acids. Free fatty acids are present in significant amounts in the colon, originating both from non-absorbed dietary fat and from the sloughing of mucosal cells. It has been suggested that calcium in the colon forms insoluble complexes with fatty acids and bile acids, thus blocking their irritating effect on the colonic mucosa (65, 67, 68). Direct induction of terminal differentiation of mucosal cells has also been proposed as a possible mechanism for the protective effect of calcium (69). In considering the theoretical role of calcium, its effect on *vitamin D* metabolism must be addressed. It has recently been shown that 1-25-dihydroxy-vitamin D is a differentiating agent in various cancer cell lines (70). Increased calcium intake and absorption may result in a decrease in the circulating levels of 1-25-dihydroxy-vitamin D. Whether such a decrease may have an inhibitory effect on cell differentiation remains to be determined.

Numerous epidemiological studies assessed the risk for colorectal cancer in relation to calcium intake. In a 19-year cohort case-control study in the USA involving 2000 men working for the same company, an inverse correlation between colorectal cancer incidence and calcium consumption (assessed from 28-day food diaries obtained at the beginning of the study) was found (32). In another large population study involving 8000 men in Hawaii no correlation was noted (71). The epidemiological data do not demonstrate a consistent protective effect from ingestion of calcium and calcium-containing foods (72). This may be partly due to variations in the amounts of fat, fibre, and other constituents in the diet. It is conceivable that calcium exerts a protective effect only when the diet is high in fat and low in certain dietary fibres. Experimental evidence from laboratory animals show that calcium can protect the colonic mucosa from the damaging effects of bile acids (67, 73) and fatty acids (72), which lead to enhanced cell proliferation. Preliminary human intervention studies also indicate that calcium supplementation may inhibit the carcinogenic process. In an uncontrolled study in subjects at high risk for colon cancer,

the elevated cell proliferation indices of the colonic mucosa decreased by 50% and shifted to a quiescent pattern after the administration of oral calcium supplements (1250 mg/d) for 2–3 months (74). The cell proliferation indices shifted from the high-risk patterns to low-risk patterns. Theoretical considerations and some epidemiological and experimental data support the hypothesis that calcium may exert a protective effect against colon carcinogenesis and justify further research in this area.

There is now increasing interest in the role of other micronutrients, such as vitamins A, C, E, and selenium (2), in protecting against carcinogenesis. *Vitamin A* and related compounds have been found to have potential anti-neoplastic effects, particularly in the lung (75). Epidemiological studies found an inverse correlation between indices of vitamin A intake and colorectal cancer (76, 77). Assessment of the intake of vitamin A in these studies was based mainly on vegetable consumption. Therefore, the correlations are non-specific and could be related to vegetable constituents other than vitamin A.

Vitamin C is an antioxidant abundant in fruits and vegetables. It has been proposed that vitamin C can inhibit formation of fecal mutagens and thus protect the colonic mucosa. This hypothesis was confirmed in one study (78) in which the effects of both vitamin C and E were studied. In a report on patients with familial polyposis, supplementation with vitamin C decreased the number of recurrent rectal polyps following polypectomy (79). Numerous epidemiological studies suggest a protective effect of foods high in vitamin C content against cancer in various organs. Experimental studies in animals also demonstrate a beneficial effect of vitamin C against carcinogenesis.

Vitamin E and selenium function as antioxidants and could protect against carcinogenesis by neutralizing the damaging effect of free radicals, particularly those originating from fat metabolism. In chemically induced colon cancer in mice, animals ingesting large amounts of vitamin E had fewer tumours compared to those taking small amounts (80). Two epidemiological studies found no correlation between plasma vitamin E levels and risk for cancer in all sites (81, 82). In a prospective study from Switzerland, low plasma vitamin E levels (as well as vitamin C) were found to correlate with an increased risk for colon cancer (83). The average per capita selenium intake in 27 countries was found to be inversely correlated with the combined mortality from all cancers, as well as specific mortality from colon cancer (84). In a prospective case-control study in Finland, low serum selenium was associated with an increased cancer risk in all sites (85). A recent case-control study (26) gave

further support to this hypothesis that low serum selenium is inversely associated with cancer. In laboratory animals, selenium was found to have an inhibitory effect against colonic mutagens (87).

It is clear that current epidemiological and experimental animal data support the concept that the diet plays an important role in the carcinogenic process in the colon. There are numerous dietary compounds which seem to affect this process. These nutrients can interact in a complex manner, enhancing or attenuating each other's effects. Furthermore, the intake of one nutrient may result in changes in the intake of others. It is likely, therefore, that primary prevention of colon cancer will entail a formulation of the diet as a whole, rather than addition or deletion of a specific nutrient. It is also becoming evident that an inherited genetic predisposition is an important determinant in colorectal carcinogenesis. Thus, the understanding and consideration of nutrient-genetic interactions are essential for achieving progress in the control of colorectal cancer.

Dietary recommendations

With the increasing recognition of the role of diet in the pathogenesis of various diseases, the concept that a "good diet" could promote health is now prevalent, both in the medical community and in the public. Consequently, there have been numerous nutritional recommendations to the public in various countries aimed at prevention of diseases in which the diet is thought to play an important role (87-93). Some of the recommendations were aimed at formulating a general healthy diet while others focused on prevention of certain diseases, such as cardiovascular diseases or cancer.

The efficacy of most nutritional recommendations has not been proven by rigorous clinical trials. Therefore, there is controversy whether such recommendations should be made to the public. It is possible, nevertheless, to formulate interim guidelines based on current data and on basic nutritional principles. It is prudent to formulate such guidelines since the research base is substantial and full understanding of diet and cancer relationships will not be achieved for many years. Dietary guidelines for prevention of colorectal cancer should be recommended along with measures of secondary prevention (94).

Guidelines

(1) *Reduce the fat consumption.* This applies to both animal and vegetable fats, which should constitute no more than 25% of the total calories.

(2) *Ensure adequate intake of high fibre foods* including vegetables, legumes, fruits, and whole grain cereals. Dietary fibre intake should amount to at least 25 g/day.

(3) *Balance energy intake and expenditure.* Avoid excess body weight.

Strategies for research

Role of nutrition factors in colorectal carcinogenesis

Recent advances in the understanding of the biology of colon cancer and in the methodologies of nutrition studies make it possible to examine the link between colon cancer and the diet in human intervention studies with appropriate randomized design. Current data from epidemiological and animal studies allow formulation of hypotheses that can be tested in humans.

The ideal end-point of studies on the effect of nutritional modifications on colon carcinogenesis would be a decrease in the occurrence of colorectal cancers. These studies, which require prolonged follow-up and extremely large numbers of participants, would be prohibitively expensive. Markers of premalignant transformation of the mucosa, such as indices of cell proliferation and differentiation and certain features of adenomas, can be used as substitutes. Advances in colonoscopic techniques now make it possible to examine the entire colonic mucosa, take biopsies and remove polyps with relative ease. Consideration of genetic-nutritional interactions promises a more precise elucidation of the factors which play an important role in colon carcinogenesis. Studies can now be targeted to populations at risk, with appropriate controls for inherited predisposition. The understanding of the advantages and limitations of various dietary assessment techniques makes it possible to obtain more precise data on the diet. Analysis of the diet has been markedly facilitated by computerized programs which can be used on personal computers. Additional work is needed to develop biological markers of dietary intake.

Recommendations

(1) The importance of randomized human intervention studies (with a double-blind design when possible) should be emphasized.

(2) The nutritional change whose effect is being studied must be well defined (quantitatively and qualitatively).

(3) When a specific nutritional intervention is being studied, its effect on the intake of other nutrients must be considered.

(4) Nutrients interactions (fat-calcium, fat-fibre, fat-calories), which may have crucial effects on the colonic mucosa, must be taken into account in human intervention studies.

(5) Biological markers of dietary intake (e.g., blood and tissue levels of nutrients, and functional assessment of nutrients) should be used in evaluating the effects of nutrients.

(6) Well-defined intermediate markers of carcinogenesis, such as measures of cell proliferation and differentiation and certain features of adenomas (see below), can be utilized as end-points in human intervention studies.

(7) Development of colon cancer is a lengthy, multiple-step process. A nutritional intervention may affect one stage but not another. Thus, multiple end-points (representing various stages in the neoplastic transformation) should be utilized concomitantly in intervention trials.

(8) When the adenoma is used as an end-point, its pathological features and "malignancy potential" (number, size, tubular and villous component, and dysplasia) should be well defined.

(9) In human intervention studies, the genetic predisposition of the subject to colonic neoplasms must be well defined. Data should be obtained on the family history of colon cancer and adenomas.

(10) Molecular genetic and cytogenetic alterations may be inherited or result from the action of nutritional factors. The effects of the diet on the genetic material should be studied.

(11) Small, well-controlled metabolic studies can be used to elucidate the biology of the response of the colonic mucosa to changes in the diet.

(12) Studies of chemically-induced colon cancer in laboratory animals should continue in order to better understand the mechanisms and formulate new hypotheses regarding diet and colon cancer.

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Résumé

Prévention primaire du cancer colo-rectal

Par sa fréquence, le cancer colo-rectal se classe au troisième rang des néoplasmes malins dans le monde (il représente 9% de tous les cancers diagnostiqués), et il est encore plus fréquent dans les pays développés. Des études épidémiolo-

giques et l'expérimentation animale ont montré qu'il existe un lien étroit entre les facteurs nutritionnels et ce cancer. Des observations récentes semblent indiquer que des facteurs génétiques héréditaires peuvent aussi intervenir non seulement dans le syndrome relativement rare du cancer familial du côlon, mais également dans la genèse du cancer sporadique du côlon. Il paraît donc de plus en plus plausible que des interactions entre les facteurs génétiques et nutritionnels jouent un rôle fondamental dans l'étiologie du cancer colo-rectal.

Etant donné que des facteurs nutritionnels paraissent capables de favoriser ou d'inhiber le développement du cancer colo-rectal, la prévention primaire pourrait avoir une place essentielle dans la lutte contre cette maladie. Les stratégies de prévention primaire devraient viser les populations que l'on juge à haut risque en raison d'une prédisposition héréditaire ou d'un régime alimentaire favorable au développement du cancer du côlon.

Différents facteurs diététiques ont été mis en cause dans la genèse de cette maladie, notamment les lipides et les régimes trop riches en calories ou trop pauvres en fibres, ainsi que les carences en vitamines (rétinoïdes, acide ascorbique, alpha-tocophérol), en minéraux (calcium) et en oligo-éléments (sélénium). Il n'existe cependant aucune preuve indiscutable de l'influence réelle de ces facteurs. Une telle preuve ne pourrait être obtenue que par des études d'intervention contrôlées chez l'homme, avec répartition aléatoire des sujets. Les progrès accomplis récemment dans la compréhension de la biologie du cancer du côlon et des différents stades de son développement permettent désormais d'envisager des études de ce type, dans lesquelles il serait possible d'utiliser comme indicateurs des marqueurs intermédiaires, par exemple des indices de la prolifération et de la différenciation des cellules, ou le taux de récurrence des adénomes du côlon. Les recommandations d'ordre diététique que l'on peut formuler en vue de réduire le risque de cancer colo-rectal sont les suivantes: réduire la consommation de lipides, augmenter la consommation d'aliments riches en fibres, absorber suffisamment de calcium et éviter la surcharge pondérale.

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