

Revisión

Diet and colorectal cancer: current evidence for etiology and prevention

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Abstract

The etiology of colorectal cancer (CRC) involves the interaction of cell molecular changes and environmental factors, with a great emphasis on diet components. But the paths connecting lifestyle characteristics and the colorectal carcinogenesis remain unclear. Several risk factors are commonly found in western diets, such as high concentrations of fat and animal protein, as well as low amounts of fiber, fruits and vegetables. A large number of experimental studies have found a counteractive effect of fiber on neoplasia induction, especially in relation to fermentable fiber (wheat bran and cellulose). Epidemiological correlation studies have also indicated that a greater ingestion of vegetables, fruit, cereal and seeds is associated to a lower risk for colorectal neoplasia. Moreover, beneficial properties of fiber (especially from vegetable sources) were documented in more than half of case-control studies. Nevertheless, recent epidemiological data from longitudinal and randomized trials tended not to support this influence. Future research should evaluate what sources of fiber provide effective anti-neoplastic protection, carrying out interventional studies with specific fibers for longer periods. Red meat, processed meats, and perhaps refined carbohydrates are also implicated in CRC risk. Recommendations to decrease red meat intake are well accepted, although the total amount and composition of specific fatty acids may have distinct roles in this setting. Current evidence favors the substitution of long and medium-chain fatty acids and arachidonic acid for short-chain fatty acids and eicosapentaenoic acid. Excess body weight and excess energy intake inducing hyperinsulinemia have been also associated to CRC, as well as personal habits such as physical inactivity, high alcohol consumption, smoking and low consumption of folate and methionine. Thus, current recommendations for decreasing the risk of CRC include

DIETA Y CÁNCER COLORRECTAL: EVIDENCIA ACTUAL SOBRE LA ETIOLOGÍA Y LA PREVENCIÓN

Resumen

La etiología del cáncer colorrectal (CCR) implica la interacción entre los cambios celulares moleculares y los factores ambientales, con un gran énfasis sobre los componentes de la dieta. Pero los caminos que conectan las características del estilo de vida con la carcinogénesis siguen siendo inciertos. En las dietas occidentales se encuentran, habitualmente, diversos factores de riesgo como las concentraciones elevadas de grasa y proteínas de origen animal, así como cantidades bajas de fibra, frutas y vegetales. Un gran número de estudios experimentales han encontrado que la fibra contrarresta la inducción de neoplasia, especialmente en relación con la fibra fermentable (salvado de trigo y celulosa). Los estudios de correlación epidemiológica también han indicado que una mayor ingestión de vegetales, frutas, cereales y semillas se asocia con un riesgo menor de neoplasia colorrectal. Además, en más de la mitad de los estudios de casos-control, se documentaron las propiedades beneficiosas de la fibra (especialmente de origen vegetal). Sin embargo, los datos epidemiológicos recientes de estudios longitudinales y de distribución aleatoria no tendían a apoyar esta influencia. La investigación futura debería evaluar qué fuentes de fibra proporcionan una protección antineoplásica realizando estudios de intervención con fibras concretas, durante periodos más prolongados. Las carnes rojas y las procesadas, y quizás los hidratos de carbono refinados, también están implicadas en el riesgo de CCR. Están bien aceptadas las recomendaciones para disminuir la ingestión de carne roja, aunque la cantidad total y la composición de ácidos grasos concretos pueden tener efectos distintos en este contexto. La evidencia actual se decanta por la sustitución de los ácidos grasos de cadena larga y media y del ácido araquidónico por los ácidos grasos de cadena corta y por el ácido eicosapentaenoico. El exceso de peso corporal y el exceso de aporte de energía que induce una hiperinsulinemia también se han relacionado con el CCR, así como los hábitos personales como la inactividad física, el consumo elevado de alcohol, el tabaquismo y el consumo bajo de folatos y metionina. Por lo tanto, las recomendaciones actuales

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dietary measures such as increased plant food intake; the consumption of whole grains, vegetables and fruits; and reduced red meat intake.

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Key words: *Colorectal cancer, epidemiology, risk factors, fiber.*

Introduction

Although colorectal cancer (CRC) exhibits universal distribution, there is a higher incidence if the disease in developed, industrialized countries, such as North America, Northern Europe and New Zealand. The disease is less common in South America, Southeast Asia, Equatorial Africa and India⁵¹.

In the United States, these tumor are the second most prevalent neoplasia group among men (following lung cancer) and the third among women (following breast cancer and lung cancer). In 2003, around 147 thousand new cases of CRC were diagnosed and 57 thousand people died from the disease. According to estimates by the National Cancer Institute (INCA) for 2003 in Brazil, around 20 thousand new cases were diagnosed, leading to death in 8 thousand patients.

The epidemiology of CRC has aroused interest in recent years as a result of developments in genetics and molecular biology. The genetic alterations that lead to CRC may either be acquired (generating the so-called sporadic cancer) or hereditary. During this process, the accumulation of genetic alterations is essential and mutations in at least 4 or 5 genes are necessary for the development of a malignant tumor. The vast majority (75 to 85%) of patients have sporadic CRC, exhibiting no evidence of a genetically inherited disease in which the risk of developing CRC is high.

Nowadays it is well recognized that a complex interaction between individual genetic features and environmental factors, especially diet, is involved in the etiology of CRC. Therefore, prevention depends on dietary education as well as on tracking high-risk groups and treatment of pre-malignant lesions.

That worldwide of incidence and mortality of the disease suggest a co-existence of environmental causes of great impact, and studies on migran populations suggest that the risk for CRC is influenced by environmental exposure⁵⁰. Environmental mutagenic factors may determine which susceptible individuals will develop carcinoma. Thus, there is considerable interest in defining strategies and recommendations for preventing the development of CRC by modifications in eating habits and life style (smoking, sedentarism, etc.).

Among dietary properties, western diet stands out for being rich in fats, animal proteins and calories, as well as poor in fiber (fruits, vegetables and cereals). Red meat, processed meats and refined carbohydrates

para disminuir el riesgo de CCR incluyen medidas dietéticas como aumentar los alimentos de origen vegetal, el consumo de granos completos, vegetales y frutas y reducir el consumo de carnes rojas.

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Palabras clave: *Cáncer colorrectal, epidemiología, factores de riesgo, fibra.*

contribute toward a higher risk²⁹. From an environmental and behavioral perspective, risk factors also include a sedentary lifestyle, smoking, obesity, alcohol consumption, and ingestion of heterocyclic amines and aromatic hydrocarbonates²⁹. On the other hand, protective agents include calcium, vitamin D, folates, selenium, vitamins and anti-oxidants. In general, these are the main factors associated with CRC, though other elements may also influence its genesis (table I).

In summary, diet can influence the genesis of CRC through detrimental effects (fats), chemical preventive (fibers) and endocrines mechanisms (calories), among others. Thus, the present article aimed to review some mechanism of CRC carcinogenesis associated to specific diets, to describe the action of some nutrients over the colonic mucosa, to present evidence of chemical preventative effects associated to nutrition and to elaborate dietary recommendations for the prevention of CRC.

The role of fiber

The high consumption of saturated fats and animal protein associated with low fiber intake has traditionally been the main dietary characteristics implicated in CRC genesis. In this context, the elucidation of fiber action on the colon epithelium is important since it can suggest means for preventative interventions in the future. These mechanisms involve physical events (alteration of intestinal transit time, dilution of fecal *bolus*, physical or chemical adherence to mutagenic

Table I
Risk and protection factors of diet intake

| <i>Risk factors</i> | <i>Protective factors</i> |
|----------------------------|---------------------------|
| Fat | Fiber |
| Red meat | Fiber components |
| Saccharose | Calcium |
| Calories, tobacco, alcohol | Folate |
| Heterocyclic amines | Selenium |
| Aromatic hydrocarbonates | Vitamins |
| Other carcinogens | Anti-oxidants |

Table II
Anti-carcinogenic constituents present in fruits and vegetables

| <i>Constituent</i> | <i>Source</i> | <i>Protection mechanism</i> |
|---------------------|------------------------|--------------------------------|
| Anti-oxidants | All plants | reduce oxidative lesions |
| Folates | Green vegetables | reduce DNA hypomethylation |
| Glucosinolates | Cruciferous vegetables | Increase oxidase activity |
| Indoles | Cruciferous vegetables | Increase oxidase activity |
| Flavonoids | Fruits, vegetables | Anti-oxidant |
| Phenols | Fruits, vegetables | Inhibit nitrosamines |
| Protease inhibitors | Seed, legumes | Inhibit proteases |
| Isoflavones | Soy | Inhibit P450 enzymes |
| Garlic components | Allium vegetables | Induce glutathione transferase |
| Limonene | Citric fruit | Induce glutathione transferase |

agents) and secondary effects (generation of bacterial fermentation products — especially short-chain fatty acids— and alteration of the luminal pH)^{28,42}.

Thus, fiber deficiency increases intestinal transit time and raises the concentration of luminal contents, allowing a longer contact of the colonic mucosa with harmful and carcinogenic agents. Among such agents, fatty acids metabolites (bile salts) are generated by the metabolism of animal fat and protein. These elements lead to important epithelial alterations that may develop neoplastic cells in the colon¹³.

Some vegetables may provide greater benefits for the prevention of CRC, such as broccoli, cauliflower and brussels sprouts. These food sources contain high levels of sulphoraphan, elements that induce detoxification enzymes that increase the aqueous solubility of corporeal toxins and their subsequent elimination. More recently, it has been pointed out that various constituents found in fiber sources (especially fruits and vegetables) perform metabolic actions with anti-carcinogenic effects (table II).

An increase in dietary fiber also raises the concentrations of short-chain fatty acids (SCFA) formed through bacterial fermentation. These products have an important role in colon metabolism especially butyrate. It has been demonstrated induction of cell lineages differentiation, trophic effects on the epithelium, intracellular anti-neoplastic action and inhibition of hyper-proliferative epithelial growth¹¹.

Furthermore, soluble fibers may delay starch absorption, reducing the glycemic load and consequent post-prandial hyperinsulinemia, which is linked to colon carcinogenesis²².

In 1969, Burkitt¹⁰ verified that the incidence of cancer among rural black Africans was lower than that among westerners who ingested a more processed diet. The author postulated that diet had an effect on the greater incidence of CRC among the white population, and that less processed foods and a higher

amount of fiber had a protective effect on the black population. Since these original considerations, epidemiological, observational and interventional studies have collected diverse data regarding the relation between fiber ingestion and CRC.

Historically, a large number of epidemiological observations involved ethnic groups that had migrated countries where food consumption habits differed from those in their country⁵¹. The evolution of CRC incidence in African black that migrated to the USA has become a classic citation in the literature. In the USA, a diet rich in fat and poor in fiber increased significantly the CRC mortality, going from 2.5/100 thousand inhabitants, figures that are immensely superior to those found among Asian peoples. Other studies in Israel have also shown that the incidence of cancer among Jewish descendants of Americans and Europeans is higher than the average of the rest of the population who have distinct eating habits.

Literature data regarding fiber and CRC exhibits a huge body of evidence favoring its consumption. In an excellent review, Shankar and Lanza⁴³ found 40 studies from 1980 to 1991 that evaluated this relation. Thirty-two of them demonstrated an inverse relation between a higher consumption of fiber and the incidence of tumor. According to an observational epidemiological study that grouped a sample of 519,978 adults in 22 urban centers of Europe showed that an increase in diet fiber content reduced the risk of CRC by 25%⁶. The supposed protective effects of fiber have also been recognized in meta-analyses^{26,48} and other review studies^{25,49}.

Case-control and longitudinal epidemiological studies offer most of the evidence concerning fiber and CRC, because they are easier to carry out than interventional experiments. Two meta-analysis uniting 13 and 20 case-control studies demonstrated that diets rich in fiber reduce the risk of this cancer^{15,26}. According to Howe and cols.²⁶, the risk of colon cancer in

the United States could be reduced by 31% if there were an ingestion of 25g of fiber per day. Other meta-analysis of 12 case-control studies selected by Trock and cols.⁴⁸ pointed out the advantages of a greater ingestion of fiber in comparison to a lower consumption. A recent, large review confirmed that case-control studies lend support to the protective effects of high concentrations of fibers against colorectal neoplasias⁵¹. Peters and cols.³⁷ also demonstrated that fiber (especially seeds, cereals and fruit) is associated to a lower risk of colon adenomas in more than 30 thousand patients.

In case-control studies, patients with CRC are identified in a given period of observation and are paired with demographic controls from the population. Previous exposure of the colon mucosa to dietary elements is quantified by means of inquiries into eating habits and food composition tables. Next, the odds ratio is calculated, measuring the possibility of developing the disease after exposure to a variable risk and comparing it to the base risk. However, the greatest problem with this type of study is the error that arises when patients with cancer modify their perception of their dietary habits. As a result, the study no longer reflects the real situations to which the individual were exposed⁵⁰.

Nevertheless, the literature data are not unanimous in regards to the supposedly protective effects of fiber against CRC. While epidemiological and experimental studies unite favorable evidence, a number of longitudinal prospective studies and interventional series have not confirmed the idea. It should be pointed out, however, that the possible beneficial effects have not yet been attested due to the imprecision of the dietary ingestion measurements, the small number of patients and short periods of study^{20,42}.

Longitudinal studies begin with the recruitment of a large number of volunteers, called cohort. The ingestion of fiber is quantified through inquiries and food composition tables. The cohort is accompanied in a systematic and prospective fashion, and the cases of adenomas, precursor lesions and colorectal cancer are identified. The critical point is that the information from the dietary inquiries becomes progressively less up-to-date over time and there is the further possibility of participants abandoning the study before its conclusion⁵⁰.

The Nurses Health Study¹⁶ was developed over a period of 20 years. It assessed dietary exposure through the use of semi-quantitative questionnaires and standard food composition tables. The relative risk of CRC or adenomas demonstrated no differences among the five levels of ingestion of dietary fiber (9.8 to 24.9 g/day). Although there was a risk reduction with the ingestion fiber present in fruit (without any statistical significance), the consumption of vegetable fiber was surprisingly associated to a higher risk.

In USA, a prospective study with a cohort of nearly 16,500 men³⁸ found no significant association between

the ingestion of fiber (total, cereal or vegetable) and the appearance of adenomas, though there was a (non-significant) reduction with a greater consumption of fruit fiber. In another important research²⁷ (*Iowa Women's Health Study*), the total ingestion of fiber was not associated with the risk of CRC. This was also the conclusion of a national tracking study carried out in Norway¹⁷.

Moreover, although the consumption of vegetables has been associated to a lower risk of adenomas and cancer in western patients⁵, results of the association of CRC with vegetables are as yet inconsistent in oriental countries³³.

An explanation for the conflicting results between case-control and longitudinal studies may lie in the fact that the types of fibers differ in their effects on increasing fecal mass, altering the intestinal transit time and promoting fermentation. Furthermore, as few new cases of CRC were identified during longitudinal studies, it is possible that the lack of significant difference may be a consequence of statistical error.

A large number of interventional studies (both on animals and humans) have also addressed the issue. In an elegant experiment, Galloway and cols.¹⁹ demonstrated that the risk of developing CRC in mice depends on the type of diet employed, varying from 3.6% (low-fat, high fiber content diet) to 64% (employing a diet with a high fat content and low in fiber). Despite some limitations, animal models of colorectal neoplasia are very important to investigate the effects of dietary factors on carcinogenesis, but experimental results cannot be directly extrapolated to humans. Besides the diet and gastrointestinal tract in mice being distinct from humans, the carcinogens used to deflagrate the malignant neoplasia are not the same. Thus, many of the conflicting results found in the literature may be explained by the differences between natural history of tumors in humans and the development of experimental tumors.

In general, protective effects have been demonstrated, especially with fiber sources that are not particularly fermentable, such as a cellulose and wheat germ, whereas other soluble fibers generally increase CRC carcinogenesis²⁸.

Considering the importance of secondary bile acids in the pathogenesis of colon cancer, the modulating effect of different types and quantities of fiber have been studied in relation to the type of dietary fat in healthy human volunteers. Reddy and cols.³⁹ verified that a dietary supplementation of 10 grams of wheat and rye germ (27 grams of fiber per day) determined a significant reduction in fecal bile acids, especially secondary acids, during the period of fiber ingestion when compared to the control period without fiber.

In an interventional study carried out on patients that had undergone operations for colon cancer³⁵, the offer of 20 grams of fiber from psyllium seed powder (*plantago ovata*) per day for three months promoted an increased production of butyrate and acetate. The con-

centration of fecal butyrate increased 42%, an effect that was dependant on the continuation of the treatment.

Controlled randomized studies are data sources of considerable interest. However, in dietary studies, the different base diets make comparisons difficult between intervention and control groups. Most of the available studies were limited (from two to four years) and included small population samples taken from high-risk groups.

The so-called adenoma-carcinoma sequence is the conceptual basis of a number of interventional studies that have investigated the preventive potential of diet among individuals with a greater risk for cancer, such as a patients with polyps and adenomas. After polypectomy, patients present a 50% chance of developing additional polyps within a period of three years. In this setting, nutritional intervention studies have not demonstrated reduction in the development of further polyps (*Phoenix Colon Cancer Prevention Trial*², *Polyp Prevention Trial*⁴¹).

In the *Wheat Bran Fiber Study*², 1,429 individuals from the Phoenix area (USA) were randomized to receive cereal supplements (13,5 vs. 2 grams of fiber per day) for 3 years after having polyps removed in the previous 3 months. Colonoscopy performed after 1 and 4 years demonstrated no differences between the two groups. The same occurred in an analysis of 2,079 patients with previously resected adenomas, in whom Schatzkin and cols.⁴¹ compared the use of a diet rich in fiber and poor in fat to the use of the habitual diet. Other series also obtained statistically non-significant reduction in the development of adenomas (*Australian Polyp Prevention Project*³¹, *Toronto Polyp Prevention Trial*³²).

These studies demonstrated that an increased ingestion of fiber among high-risk populations for short periods of time did not reduce the recurrence of adenomatous polyps. Nevertheless, interpretation of these data requires many considerations. It is known that the natural history of CRC is a long duration process, where the evolution of one tiny polyp can take decades. Given enough time, the ingestion of fiber over a longer period and the evaluation during a greater follow-up could detect differences on the studied population. But the current interventional studies have not examined this aspect yet.

Individual susceptibility to colorectal neoplasias varies, as the presence of a personal and family history increases this risk. However, the stratification of this risk is yet imprecise. Thus, although controlled randomized studies with fiber and CRC involving high-risk populations have not demonstrated any significant effect, there must be subgroups of individuals that are more susceptible to dietary manipulation.

Specific genetic mechanisms may be responsible for the malignant transformation of polyps, since just 5 to 10% of these adenomas may become cancer when

not removed. Considering the possibility that different diets may have distinct effects on the molecular mechanisms within the polyps, future studies should evaluate the manipulation of diet on this particular group of polypoid lesions.

Finally, the effects of fiber on colorectal carcinogenesis cannot be examined separately. It is now recognized that vegetables and other agents such as vitamins and anti-oxidants have important benefits, and different types of fiber may have either synergic¹ or antagonistic²⁴ effects on colorectal neoplasias. Despite the controversy regarding protection from CRC, the current recommendations on increasing the average fiber ingestion of the population are sensible in that there is the recognition of the fiber effects on improving overall health, reducing the risk of heart disease, hypertension, hypercholesterolemia, diabetes and other chronic illnesses³⁴.

Thus, one must consider that the generic grouping of all types of fiber as "dietary fiber" may mask or confound its potential biological effects⁴².

Influence of fat

For millions of years, food from vegetal sources was the basis of human diet. With the advent of the industrial revolution 200 years ago, dietary habits in industrialized nations began to change through the refinement of food sources containing a large amount of fiber along with an increase in fat consumption. In this context, meat became a symbol of opulence among members of society. Subsequently, this greater amount of elements from animal origins increased the incidence of many illnesses such as a cancer, heart disease, diabetes and others.

Diverse evidence suggests that fat in the diet is associated to a greater risk of CRC. In countries with high incidence of CRC, the fat content in the diet represents about 40% of the total calories. This contrasts with low incidence regions where the fat content is just 15 to 20% of total calories³³.

The quantity and composition of specific fatty acids influence this risk³⁶. There is a strong association between CRC and the consumption of red meat (beef, lamb, pork and processed meats such as sausage, hamburger, ham and bacon). It has been suggested that this increased risk is due to the greater production of bile acids, formation of carcinogenic agents and toxic effects inducing the proliferation of colonocytes²⁹.

There exists only scant associations between diet and the risk of a progressive accumulation of genetic damage. Nitrous components (nitrosamines) are found in foods that contain nitrates or that have been exposed to nitrous oxide, such as processed meats⁸. Heterocyclic amines are formed on the surface of the meat when it is cooked over a direct flame or at high temperatures and are activated metabolically. It is believed that local bioactivation of heterocyclic amines in the

colon contributes to the development of cancer, inducing mutations in the APC and K-ras genes^{29,46}.

In a systematic review about the risk of CRC and red meat, Sandhu and cols.⁴⁰ included prospective cohort studies and excluded case-control and ecological studies, grouping a total of 601,000 participants and 3,617 cases. They observed that a daily increase of 100 grams of meat was associated to a 14% increase in CRC risk. Also, a daily increase of 25 grams of processed meat (cured or with nitrates) was associated to a 49% greater risk. The authors observed that the independent effect of meat consumption on CRC risk was evaluated in just a small number of the studies.

Thus, the limitation total fat consumption may be important in cancer prevention. There is a recommendation to limit the ingestion of red meat below 80 grams per day, especially for those individuals with a high CRC risk (genetic diseases and certain life style factors). Limiting the consumption of processed meat is especially advised, replacing it with fowl, fish, beans and legumes²⁹.

In a recent review, Nkondjock and cols.³⁶ demonstrated that high concentrations of short-chain fatty acids (SCFA) and eicosapentaenoic acid (EPA) seem to protect against the development of CRC, while medium-chain fatty acids (MCFA) and arachidonic acid (AA) may be associated to greater risk. Long-chain saturated fatty acids (LCSFA) do not seem to be related to this risk, whereas associations of the tumor with monounsaturated fatty acids (MUFA), trans fatty acids and polyunsaturated fatty acids (PUFA) such as linoleic acid (LA), alpha-linoleic acid (ALA), docosahexaenoic acid (DHA), and the omega-3/omega-6 ratio do not seem convincing. Thus, substituting foods with high MCFA and AA content for diets rich in SCFA and EPA is suggested for reducing this risk.

Western diets are deficient in omega-3 fatty acids, in which the n-6/n-3 ratio between fatty acids varies from 15:1 to 16.7:1¹². This distortion is implicated in the pathogenesis of cardiovascular diseases and cancer, as well as inflammatory and immunological diseases, with the recognition that the modulation, of this ratio to 2.5:1 reduces rectal cellular proliferation in cancer patients⁴⁵. However, little is yet known on the therapeutic doses of omega 3 fatty acids. It is believed that these doses depend on the severity of the illness resulting from genetic predisposition.

Calories, excess weight and smoking

The excessive consumption of calories is strongly related to the high indices of colon cancer in western countries. The implicated mechanisms in this relation are the increases intestinal transit time, concentrations of fecal bile acids, epithelial proliferation, hyperinsulinemia and the development of resistance to insulin. Diverse studies have assessed the relation between saccharose ingestion and CRC, and 15 epidemiologi-

cal studies (among 17) identified a positive association; one found a null relation⁸.

There is evidence that in industrialized nations obese individuals have a relatively higher risk for CRC. This phenomenon has been explained by the chronic hyperinsulinemia theory. This alteration is generated by caloric diets with western characteristics (saturated fats and refined carbohydrates), leading to a peripheral resistance to insulin. A high concentration of circulating serum insulin may have a mitogenic action on colonocytes, cellular proliferation and apoptosis²². Furthermore, it may increase the availability of insulin-like 1 growth factor (IGF-1) that promotes cellular proliferation.

Lack of physical activity, excess body weight and central deposition of adiposities have been also considered consistent risk factors. In a national cohort study¹⁴ uniting 13,420 individuals, 222 incidental cases of CRC were diagnosed. Assessment of the risk increased progressively with excess weight estimated by the body mass index (BMI), where the risk varied from 1.79 for a BMI between 22 and 24 to 2.79 for a BMI above 30. From these data, the institution of regular physical exercise can be indirectly recommended as a preventative behavioral measure against CRC.

Although smoking has often been associated to the development of colorectal adenomas, its relation with CRC has only been mentioned in recent years. Giovannucci and cols.²² suggested that smoking acts as an initiating agent for CRC, increasing the risk of adenomas after 20 years and cancer after 35 years of the addiction. This risk is greater in the right colon⁴⁴.

Chemical prevention

Observation studies on individuals at risk have suggested that the use of certain supplements and drugs (non-steroid anti-inflammatory drugs, post-menopausal hormonal reposition therapy, folic acid and calcium) can prevent the development of CRC^{18,47}. However, no evidence is strong enough to recommend their routine utilization. Although anti-oxidants are hypothetically cancer preventive agents, a controlled randomized study on anti-oxidant vitamins (beta carotene, vitamin C, vitamin E) demonstrated no effects on the incidence of CRC²³.

In one observational study, the use of folic acid supplements for more than 15 years determined a 75% reduction in the relative risk of CRC²¹. Since folate participates for DNA synthesis, its deficiency may cause abnormalities in its synthesis and repair mechanisms. The combination of an early initiation of smoking habits, high consumption of alcohol (which is an antagonist of the methyl group) and a low availability of folates generate hypomethylation of the DNA that is recognized as an early event in colorectal carcinogenesis^{3,22}.

Similarly, it is suggested that the link between calcium and bile acids in the intestinal lumen can inhibit carcinogenic effects. A randomized controlled study⁴ on the daily supplementation of 1,200 mg of elementary calcium over 4 years demonstrated a 19% reduction in the risk of recurring adenomas in a presumably medium-risk population. However, it is not yet known whether this finding applies to individuals at high risk as determined by genetic alterations⁹.

Among 23 epidemiological studies on calcium intake, 17 found an inverse association, nine of which with statistical significance. In regards to vitamin D, 10 of 12 studies demonstrated an inverse relation, five of which with statistical difference⁶.

These findings raise the idea that there may be other reasons for consuming drugs such as aspirin and folic acid (to prevent cardiovascular diseases) or ingesting calcium and estrogen (to prevent osteoporosis). However, the consumption of agents with chemical prevention properties can present potential adverse effects. Thus, cautious consideration should be taken concerning the risk/benefit relation before general recommendations are made. In the case of anti-inflammatory drugs, the risk of digestive bleeding and cerebral hemorrhages should be weighed against their possible benefits. More recently, studies have been developed with less toxic drugs such as sulindac and celecoxib (cyclo-oxygenase inhibitors) to investigate their effectiveness and adverse effects²².

Finally, recent meta-analysis studies have demonstrated that vitamin E (alpha-tocopherol) may have more consistent protective effects, while the inverse associations between vitamin C and beta-carotene with CRC are yet considered weak^{30,51}.

Broad-based prevention

The data presented in this review show that diverse dietary components and behavioral characteristics may be associated to a higher risk of CRC, with variable levels of consistency. So, after identifying the risk factors (environmental or genetic) involved with CRC, primary prevention should be accomplished with modifications in lifestyle, habits and diet composition, such as:

- Reduction in fat ingestion to 30% of the total calories.
- Consumption of fiber in quantities of 20 to 30 grams per day.
- Inclusion of a large variety of fruit and vegetables in the diet.
- Limitation of alcohol consumption.
- Breaking smoking habits.
- Controlling obesity (reduce calories from all sources).
- Practicing regular physical exercise.

Evidence of the effectiveness of primary prevention by way of dietary measures is as yet questionable⁵¹.

Nevertheless, the observation that a large number of dietary and behavioral factors associated to the risk of CRC are similar to those of cardiovascular diseases and other tumor emphasizes the possibility that these modifications can bring additional benefits to people's the quality of life²².

Secondary prevention also has a critical role in reducing CRC mortality. It involves identification of risk groups (screening), treatment and follow-up of patients with pre-malignant lesions. The Brazilian Society of Coloproctology recommends the following program: (for more information visit www.combateaocancer.org.br or www.sbcpro.org.br):

- Proctological examination after the age of 40 or 50 years (depending on the risk group);
- fecal occult blood test after the age of 50 years;
- flexible sigmoidoscopy every 3 to 5 years after the age of 50 years; abnormal findings require colonoscopy.

Recent developments in molecular techniques may have some potential to identify high risk populations for CRC by selecting individuals that should be screened, and thus improve the cost-benefit relation of these efforts. In the future, one expects to modulate the risk of CRC by dietary changes that could influence its carcinogenesis mechanisms.

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