

Strong correlation between diet and development of colorectal cancer

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1. ABSTRACT

Multiple factors have been described among the causes of non-hereditary colorectal cancer. In Western countries, the most common risk factors include upper-middle socioeconomic status and dietary regimens rich in proteins and animal fats. High consumption of red meats, smoked foods, cold cuts, or canned foods is believed to contribute to carcinogenesis as they directly affect epithelial turnover and cause metabolism of biliary acids. Dietary fibers have protective effects in that they capture the fats and biliary acids, thereby inhibiting their activity. Tobacco smoking acts both locally and systemically on the colorectal mucosa through the production of carcinogenic agents. Finally, the action of alcohol, in association with nicotine addiction, also increases the risk of developing colorectal tumors. Knowledge of dietary and environmental factors is of paramount importance in implementing preventive strategies for colorectal cancer.

2. EPIDEMIOLOGY AND INTRODUCTION

According to the International Agency for Research on Cancer data, colorectal cancer (CRC) is one of the most commonly diagnosed neoplasms in industrialized countries, with about 1 million new cases every year. Conversely, in non-industrialized areas, CRC risk reduces to 1 per 100,000 inhabitants (1). In Europe, colorectal carcinoma is the most frequent tumor in non-smoking subjects, accounting for 220,000 new cases per year, and constituting the second-most common cause of death from neoplasm after lung carcinoma in men and breast carcinoma in women (2). In Italy, the actual incidence rate of colorectal carcinoma is 35,000–40,000 new cases per year, with a greater prevalence in the Central-Northern regions compared to the South, probably due to different lifestyles and diets (3). For sporadic colorectal carcinoma, environmental factors, rather than genetic alterations, have a pivotal role in the etiology of the disease (4). In this respect, many retrospective

studies have observed that migrant populations moving from regions with low incidences of cancer to developed Western countries acquire the same risk levels as the native population within the first generation (5). An example of this is the increase in CRC incidence in Japan during the 20th century, when this population underwent an important and fast modification of diet, by adopting more Westernized dietary habits (5-7). The 2 most important physiopathological theories connecting diet to CRC are based on epigenetic modifications in the expression of genes regulating proliferation (i.e., apoptosis along with DNA repair) and on the hypothesized link between the metabolic status and the perpetuation of a chronic low inflammatory level in the colonic mucosa (8-14).

2.1 The epigenetic modifications and the “methylation and carcinogenesis pendulum model”

The sporadic nature of CRC is derived from the adenoma-carcinoma sequence, in which malignant tumors develop from a small proportion of adenomatous polyps, probably over a period of several decades (15-17). The molecular basis of the carcinogenetic sequence is relatively well established, compared with most human cancers (1517). The morphological changes in the adenoma-carcinoma sequence are associated with progressive acquisition of DNA mutations, including somatic mutations of proto-oncogenes or tumor-suppressor genes (18-19). For example, the “gatekeeper” mutation, a homozygous mutation of the APC gene, is thought to be the first genetic change in the adenoma-carcinoma sequence (18). Large adenomatous polyps and malignant tumors often have a mutation in the k-ras proto-oncogene. Additionally, mutations in the tumor suppressor gene *p53* appear to be typically associated with the transition to carcinoma (19). In addition to these somatic mutations, neoplastic progression in many tissues is also due to epigenetic modifications in the expression of the same genes that regulate proliferation, apoptosis, and DNA repair (14). The most studied epigenetic mechanism is the hypermethylation of the cytosine residues in CpG-rich sequences (CpG-islands) located within the promoter regions of expressed genes (20). This does not alter the DNA integrity, but the methylation of these sequences leads to the progressive silencing of the DNA-repair genes, such as DNA mismatch repair (*MLH1*) genes and tumor suppressor genes, with consequential abnormal cell proliferation (20-22). Many foods can alter this methylation equilibrium; it is hypothesized that certain dietary factors can interfere with this carcinogenesis pendulum model by preventing or promoting either promoter hypermethylation or global hypomethylation (4).

2.2 The link between the metabolic status and the perpetuation of a chronic low inflammatory level in the colonic mucosa

According to this theory, obesity and low physical activity, together with dietary factors, can induce a distorted metabolic status linked to a low level of chronic and asymptomatic inflammatory activity in the colonic mucosa, which leads to greater vulnerability to cancer development (13, 16). Adipose tissue is a source of a variety of proinflammatory signal factors and cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6).

These mediators, among others, create a systemic, low-grade inflammatory state, which is a substratum condition for carcinogenesis (11-12). Therefore, colon cancer may be considered one of the diseases related to “the Western life-style,” which includes non-insulin-dependent diabetes mellitus, cardiovascular disease, and metabolic syndrome (16).

3. OBESITY AND PHYSICAL ACTIVITY

For over 50 years, numerous studies, both retrospective and prospective, have provided substantial evidence that overweight and obesity can be directly associated with the risk of developing cancer of the digestive tract or other organs (23-26). A study by Lee *et al.* performed between 1962 and 1988 showed a direct correlation between body mass index (BMI) and increased disease risk. In particular, the risk increased in a statistically significant manner in patients with particularly low levels of physical activity (27). More recent studies performed by Diez and Boutron revealed that some factors, i.e., body weight, caloric intake, and physical activity, might independently influence both early and late stages of the adenoma-carcinoma sequence (28-29). Their data show that physical activity can reduce the risk of cancer by significantly affecting the development of adenomas. Additionally, a particularly high BMI is associated with an increased risk for large sessile adenomas, while a highly calorific diet can increase the risk for cancer, but not for adenoma (2829). In a recent prospective study conducted in approximately 400,000 European subjects, the researchers found that the physically active population had a 20%–25% risk reduction for colon cancer, in general, and a 30% reduction for right-sided colon neoplasms. Physical activity was defined as 2 hours of moderately intense exercise or 1 hour of vigorous exercise daily (30). Other studies have investigated the role of fat distribution as a more influential prognostic factor in the pathogenesis of CRC, as opposed to the degree of obesity as indicated by the BMI (3133). In fact, Moore *et al.* observed a direct correlation between higher-waist circumference and CRC in both men and women, independent of their BMI. The evidence was even more significant in the subgroup of patients with reduced physical activity (31). This correlation is also supported by a recent trial (EPIC trial), although the separate analysis of men and women makes the evidence less compelling (32). However, current evidence does not support the positive correlation between colon cancer and higher-waist circumference and waist-hip ratio in post-menopausal women under hormone replacement therapy. Furthermore, the positive correlation is not applicable to cancer of the rectum (33).

The mechanism involved in the obesity-colon cancer relationship seems to be an asymptomatic chronic inflammation of the colic mucosa, as already documented by numerous studies on carcinogenesis in chronic intestinal diseases (13, 34). In fact, non-steroidal anti-inflammatory drugs such as aspirin significantly reduce the risk of CRC by inhibiting cyclo-oxygenase-2 (COX-2). The pathophysiology involves the action of adipokines (leptin, adiponectin, cytokines, TNF- α , and IL-6) that activate many mucosal signals with subsequent activation of the transcription

factor κB (NF- κB), hyper-expression of the nitroxide synthase enzyme, and COX-2, with consequential suppression of apoptosis, a prerequisite for the activation of carcinogenesis (912, 3537). Another confirmatory test of this chronic inflammatory state is the elevation of calprotectin level, which can be assessed in neutrophils, lymphocytes, and macrophages (38). Presently, high levels of calprotectin represent an important diagnostic modality for determining the level of activity of chronic intestinal diseases, also correlating positively with age, obesity, and physical inactivity (38).

4. RED MEAT INTAKE

Although a correlation between high consumption of red meat and increased risk of CRC has long been postulated, there is no evidence to date supporting this relationship. There are numerous studies in the literature on this topic, some of which found no significant association, while some others reported an increased risk only for carcinoma of the colon and not of the rectum (39, 45-46). According to the results of a prospective study conducted in approximately 89,000 American women published in 1990 by Willett *et al.*, there is a relative risk of developing colon cancer of 1.9 for the highest quintile of meat intake, as compared with the lowest one ($P < 0.01$) (42). One of the most recent meta-analyses reviewed 15 prospective studies conducted on the consumption of red meat and 14 studies conducted on the use of preserved meat (for a total of approximately 15,270 cases considered). The study showed that the relative risk of developing CRC associated with the intake of high amounts of red meat is 1.28 (CI, 1.15–1.42) and, for those who consume preserved meat, it is 1.20 (CI, 1.11–1.31) (47). Similarly, other studies have linked the risk of developing colon cancer not only to the use of red meat, but also to the way of cooking it, with particular emphasis on temperature, time, and degree of cooking (4849). On their study on screening-detected colorectal adenomas, Rashmi Sinha *et al.* showed that red meat, broiled meats, bacon, and sausage have been associated with an increased risk of adenoma of the colon (descending and sigmoid colon), non-advanced adenomas, and single adenomas (48). The mechanisms underlying the relationship between diets based on red meat cooked at high temperatures and the onset of CRC remain unknown, although several possible explanations are proposed. The ingestion of meat cooked at high temperatures, such as frying and grilling, leads to the formation of numerous and proven carcinogenic substances such as polycyclic amines and polycyclic aromatic hydrocarbons such as benzopyrene. Moreover, many preserved meats contain relatively high levels of nitrite. Nitrate, along with proteins and heme, contribute to the production of nitrosamines, responsible for mutagenic action (4954). Red meat is also a rich source of iron, which itself is associated with an increased risk of colorectal carcinoma, as a major intracellular pro-oxidant. In this regard, it is considered that the heme derived from the ingestion of red meat can directly damage the mucosa of the colon, as opposed to white meat that does not seem to be correlated with an increased risk of carcinoma (53). In conclusion, although evidence from several studies shows a direct correlation between the high consumption of red or preserved meat and the onset of

CRC, no significant risk reduction has been observed in vegetarian patients in either Europe or the U.S. (54). Therefore, it is less likely that the mere use of red meat can fully explain the high incidence of CRC in industrialized Western countries, as compared to developing regions (Asia and Africa).

5. GLYCEMIC INDEX, GLYCEMIC LOAD, AND INSULIN RESISTANCE

Many authors report a strong epidemiological correlation of CRC and non-insulin-dependent diabetes mellitus with altered postprandial glucose tolerance (16, 55). Some authors suggest a direct link between an altered metabolic status and the perpetuation of a chronic low inflammatory state in the colonic mucosa, which, in turn, may be the basis of CRC development (13, 16). The presence of insulin resistance—a condition characterized by impaired glucose tolerance, elevated plasma insulin levels, and elevated insulin-like growth factor 1—seems to be correlated with a high susceptibility to colon cancer. This association would also be supported by the insulin-driven hyperproliferation of colonic epithelial cells (in rat models). In addition, the *in vitro* exposure of CRC cells to insulin leads to an increased rate of proliferation and impaired apoptosis, both of which favor tumorigenesis (5658).

Clinically, the 2 most important parameters determining glycemic intake are glycemic index and glycemic load (59). The glycemic index is a direct measurement of the blood-glucose elevation induced by the consumption of a particular carbohydrate type, in comparison with the one induced by a standard food carbohydrate such as glucose. The widespread use of refined carbohydrates in western diets leads to higher glycemic indexes than that used in other foods such as legumes and grain cereals. The glycemic load is the product of the glycemic index of the food and the total amount of carbohydrate consumed in the meal. Franceschi *et al.* reported a direct association between CRC risk and the highest quintile of glycemic index and glycemic load (OR = 1.7 and 1.8, respectively) (60). Conversely, a recent meta-analysis, including cohort- and case-control studies, found no significant associations between CRC risk and the different degrees of glycemic indices and glycemic loads.

6. SMOKING AND ALCOHOL

Smoking causes more than 400,000 deaths in the US each year, approximately one-third of which are due to neoplasms (61-62). Although a correlation between smoking and the onset of adenomatous polyps has been established, many cancer research, control, and prevention associations in the US have not included cigarette smoking among the risk factors for CRC (63-66). Recent studies reevaluating the epidemiological data of regular tobacco smokers have refocused on this association (67-71). Chao reported a significant increase in cancer risk after a period of 20 years of smoking, in both men and women; this risk was directly proportional to the period of nicotine addiction and the average daily number of cigarettes smoked, while a sharp risk reduction was reported after quitting smoking (62). In

addition, in the multivariate analysis on the prevalence of CRC in tobacco smokers conducted by Anderson, regular smokers were more likely to have an adenomatous lesion or a colorectal neoplasm, as compared to those who had never smoked. These findings were associated with a significantly higher risk for rectal and left colon neoplasm (72). Moreover, in the population analyzed by the authors, smoking represented a greater risk for CRC than a family history of CRC (72). A recent prospective study by Lieberman, investigating the risk factors associated with advanced colonic cancers and the onset of hyper-plastic polyps in 3,121 asymptomatic patients between 50 and 75 years of age, showed a significant association between smoking and the risk for cancer. In particular, the risk was higher for current smokers who smoked more than 25 packages per year, and for former smokers who used to smoke more than 49 packages annually (73).

In 2007, a prospective study by Paskett *et al.* examined the association between the risk of invasive CRC and active and passive exposure to cigarette smoke. The authors studied a group of 1,468,777 healthy women divided in 3 subgroups according to their smoking habits. They demonstrated a statistically higher association between cancer and smoking ($P = 0.05$), age of starting smoking ($P = 0.03$), number of cigarettes smoked per day ($P = 0.006$), and duration of nicotine dependence ($P < 0.001$) (74). A further multivariate and site-specific analysis related to tumor localization indicated a significant increase in the risk of cancer of the rectum, compared to cancer of the left colon, in smokers. No statistically significant correlation was found with regard to passive exposure to cigarette smoke (74).

Other studies have clarified the etiopathogenetic synergism between smoking and alcohol intake. The effects of cigarette smoking on the possibility of CRC onset are exacerbated when associated with alcoholism (75).

7. DIETARY FIBERS

A high consumption of dietary fiber seems to have a protective effect against CRC. Thus, rural populations manifest a low incidence of CRC because of their typical diet containing very high levels of non-digestible polysaccharides derived from unrefined plant cell walls (76-77). The mechanism of action is complex and seems related to the synergism between functional bulk laxative effects and an increased growth of commensal bacteria by anaerobic fermentation. This leads to the release of many short-chain fatty acids such as acetate, propionate, and butyric acid into the colonic mucosa (78). Among them, butyric acid is a biologically active product thought to suppress mitosis by promoting the histone deacetylase enzyme inhibitor (102 in Johnson), which increases differentiation and stimulates apoptosis (78). Cumming *et al.* reported an inverse relationship between total fecal weight and the risk of CRC among patients consuming different levels of dietary fiber (79). In contrast, Fuchs *et al.*, Pietinen *et al.*, and Terry *et al.* did not detect any protective effects of fiber intake in their prospective studies (80-82), even though it is argued that the hypothesis has not been adequately tested because of the relatively small statistical power of those

prospective studies. A large trial designed to overcome these limitations, the EPIC study, suggests a possible protective role of dietary fibers against CRC in most of the developed world, but only when consumed for long periods of time and in large quantities (85).

8. FRUITS AND VEGETABLES

The 21st century began with the slogan that daily fruit and vegetable intake could reduce the risk of many cancers. In fact, the report on diet and cancer of the World Cancer Research in 1997 showed convincing evidence of the protective effects of fruits and vegetables against gastrointestinal cancer (83). Subsequently, the International Agency for Research on Cancer in 2003 formulated more cautious conclusions based on the limited evidence of cancer-preventive effect of fruits and vegetables on gastrointestinal cancers (84). Today, the true significance of fruit and vegetable consumption as protective factors against CRC remains controversial, as large prospective studies have been completed and no statistically significant correlation is found. The EPIC prospective study on diet and cancer produced only weak evidence of protective effects of fruits and vegetables against gastrointestinal tract cancers (85). The supposed benefit of high intake of fruits and vegetables against CRC is based on the biological activity of flavonoids in the modulation of carcinogen metabolism and inflammatory pathways (86). Among the flavonoids, the most important are the flavanols, including epigallocatechin (EGC) gallate, the putative main anticarcinogenic component of green tea, which is thought to be able to inhibit at various stages the activation of NF- κ B, one of the most important components of inflammatory pathways (84). A recent meta-analysis published by Sun *et al.* found statistical evidence for the protective effect of green tea against colon cancer, but found no evidence supporting the protective effect against rectal cancer (88). The same group has analyzed the relationship between urinary metabolites of tea polyphenols and the risk of CRC in a cohort of 18,244 Chinese men. The authors found that a higher level of EGC and 4-*o*-methyl-EGC in urine is associated with a significantly lower risk of colon cancer, but not of rectal cancer (88).

9. FISH AND N-3 POLYUNSATURATED FATTY ACIDS

A high dietary intake of n-3 polyunsaturated fatty acids from oily fish can protect against CRC by inhibiting the expression and activity of COX-2 and by reducing the production of proinflammatory eicosanoids. This action is similar to the known protective mechanism of aspirin and other NSAIDs (46, 89). The EPIC study showed an inverse association between fish intake and CRC risk, especially in people consuming more than 40 g of fish per day (46). However, in a recent systematic review, MacLean *et al.* found no benefit of high fish intake in protecting against CRC (90).

New epidemiological evidence shows that the protective effects of fish may be associated with particular genetic polymorphisms of some key proteins such as perox-

isome proliferator-activated receptors and COX-2 expression (9293).

10. FOLATE

Folate is a B vitamin contained generally in fresh fruits and green vegetables and is essential for normal DNA synthesis and replication as well as for epigenetic regulation of gene expression (9495). Folate deficiency causes genomic instability and chromosomal breaks, and aberrant DNA methylation might lead to cancer (96). In previous epidemiologic and clinical studies, the risk of CRC was directly related to low levels of folate (97-100). Multiple case-control and observational cohort studies report a reduction of 30%–40% in CRC risk for patients with high levels of folate consumption compared with patients with the lowest intake (99101). Recently, however, animal studies have suggested that high levels of folate might promote colorectal oncogenesis by enhancing pre-existing adenomatous polyps (102). The protection provided by folate supplementation in the diet might depend on the stage of colorectal carcinogenesis. Hence, folate may generally have a protective role against neoplasia in normal colorectal mucosa, but it may also enhance pre-existing adenomatous lesions (102, 103).

11. CONCLUSION

According to the studies analyzed, it can be concluded that Western diets and high levels of energy intake can be considered as relevant risk factors in the development of CRC, together with positive family history and the presence of adenomatoid lesions. In the Western population, obesity and lack of physical activity represent the most important risk factors for developing colon cancer. In particular, waist circumference and waist-to-hip ratio are strongly associated with colon cancer in both men and women, suggesting that fat distribution is still one of the most important risk factors. Processed and broiled meats also increase CRC risk by producing cancerous factors such as N-nitrous compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons. The results regarding the effect of smoking on CRC are discordant between studies. Some authors have reported a greater risk for colon and rectal cancer for smokers than for patients with a family history of cancer. However, no significant associations between CRC risk and the highest glycemic index have been shown in a recent systematic review. There is weak evidence regarding the protective effects of fruit and vegetable consumption together with fish and n-3 polyunsaturated fatty acid intake. In order to undertake adequate primary prevention, it is of paramount importance to recognize the role of environmental factors in the development of CRC. This should include the treatment of obesity, a reduction in the intake of fats, increased consumption of fruits and vegetables, and moderation in the intake of alcohol.

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