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REVIEW ARTICLE

Dietary Lifestyle and Colorectal Cancer Onset, Recurrence, and Survival: Myth or Reality?

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Abstract
Background and Purpose Interest in the possibility that diet might help to reduce the risk of colorectal cancer dates back to 1970 based on both the large variation in rates of specific cancers in different countries and the impressive changes observed in the incidence of cancer in migrants from low- to high-risk areas. Here, we report the state of art of literature data about this topic.
Methods Three sections have been separately considered: chemoprevention of first tumor onset, chemoprevention of recurrence after surgery, and chemoprevention of polyp recurrence in the course of the follow-up of subjects with elevated risk. A particular attention has been pointed to dietary factors and survival, whose relevance is showing a growing interest.
Results The relationship between diet and colorectal cancer has been extensively studied about the onset, sometimes with controversial results. Its influence on recurrence and survival has been examined in only few studies.
Conclusions Literature data are convincing for a protective role on the onset of preneoplastic and neoplastic lesions for some foods such as fibers, vitamin A and D, folic acid, calcium, antioxidants, and promising perspectives for some substances such as phyto-estrogens. Less evidence-based data are available on the possibility to avoid the recurrence of the disease or to affect its mortality with dietary habits. Future perspectives will be directed be not only to identify new dietary style able to prevent the onset of neoplastic lesion of the colon but also to realize an effective chemoprevention.

Keywords Diet · Colorectal cancer/adenoma · Chemoprevention · Recurrence · Survival

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Introductive Remarks

The role of diet in the etiology of various type of cancer [1] remains an area of active research. Interest in the possibility that diet might help to reduce the risk of various types of cancer—including colorectal cancer—dates back to 1970 basing on both the large variation in rates of specific cancers in different countries and the impressive changes observed in the incidence of cancer in migrants from low- to high-risk areas [2, 3]. The importance of lifestyle factors in the development of cancer was also shown in studies of monozygotic twins (who share all genes). Inherited genetic factors were shown to be responsible for about the 15 % of all cancer cases. Carcinogenesis is a multistep process (from initiation to metastasis), so, for many years or decades, potentially cancerous cells remain vulnerable and only few will progress towards the malignant stage. This vulnerability makes possible to intrude and interfere at several stages of tumor development and thus prevent the onset of disease. Case–control, epidemiological, and laboratory studies have shown that some foods have chemoprotective properties related to their ability to block the development of precancerous cells into malignant cells by both direct and indirect mechanisms [4].

In this report, three sections will be separately considered: chemoprevention of first tumor onset, chemoprevention of

recurrence after surgery, and chemoprevention of polyp recurrence in the course of the follow-up of subjects with elevated risk. A particular attention will be pointed to dietary factors and survival, whose relevance is showing a growing interest.

Colorectal Cancer Chemoprevention

There is a close relationship between diet and colorectal cancer, the third leading cause of death in both men and women in USA, but the relevant components of diet are still not well known.

Dietary Fibers and CRC

The incidence of this cancer is generally high in populations with high intake of meat and low intake of staple plant foods [2], and it has been strongly recommended that dietary fibers might reduce neoplastic risk [3]. Burkitt hypothesized that a high fiber diet leads to an increase in fecal mass, thus accelerating intestinal peristalsis and reducing the time of exposure to luminal carcinogens [3]. Over the years, several mechanisms have been proposed to explain the anticarcinogenic action of the fibers as follows: the dilution of colonic carcinogens, the inhibition of cell proliferation and proto-oncogenes expression, and the promotion of colonocytes differentiation [5–7]. However, the protective role of the consumption of these foods against cancer is still controversial. Indeed, the World Cancer Research Fund (WCRF) report (2007) concluding that "there are limited evidences suggesting that fruit and non starchy vegetables protect against colorectal cancer" downgrades the previous report in which this association was defined as "probable." Nevertheless, the Department of Health (2003) recommends the consumption of fruit and vegetables at the dose of at least five portions per day, corresponding to overall 400 g [8, 9].

Overall, the scientific data do not show a clear association between fruit and vegetables and the risk for colorectal cancer, although they are compatible with a small reduction in risk. The European Prospective Investigation into Cancer and nutrition (EPIC), a multicenter cohort study recently conducted in 10 European countries [10], demonstrated a 30 % reduction in colorectal-cancer risk, using age, sex, body mass index (BMI), total caloric intake, and dietary record as correction factors. The results of other large prospective studies have been less clear (8,081 cases, Park et al. [11]; 2,110 cases, Nomura et al. [12]; 2,974 cases, Schatzkin et al. [13]), and large prospective studies have suggested that high intakes of fruit and vegetables have at least a small inverse association with the risk for colorectal cancer. In the Women's Health Initiative (WHI) randomized trial, the intervention was a low-fat eating pattern aimed at reducing dietary fat intake and increasing consumption of vegetables, fruits, and grains; there was an average increase in fruit and vegetable intake of 1.1 servings per day, and the dietary intervention did not cause any significant change in the incidence of colorectal cancer after 8 years [14].

High-Fat Diet and CRC

The greater consumption of "fats, oils, and snacks" by African Americans in comparison to the consumption by White people allowed to postulate that total dietary fat affects the risk of developing colorectal cancer, but the majority of the studies do not confirm the association [15–17]. It is possible, however, that it is not overall fatty acid consumption but perhaps specific fatty acid subgroups that may be relevant to the etiology of colon cancer. For example, some studies have found that the consumption of n-3 polyunsaturated fatty acids may be inversely associated with colorectal cancer [18, 19], although the results are not completely convincing [18–21]. Few studies examined the association between colorectal cancer and *trans* fatty acid consumption [18–20, 22] and reported inconsistent results. Fatty acids are substrates for eicosanoid production, and eicosanoids can activate proinflammatory pathways that promote colon carcinogenesis. Prostaglandin E2 (PGE2), formed from arachidonic acid by constitutive cyclooxygenase 1 (COX-1) and inducible cyclooxygenase 2 (COX-2) in the colonic mucosa, plays an important role in the expansion of cell populations in the colonic crypt and subsequent formation of adenoma [23–27] Cyclooxygenase (COX) inhibitors conversely block proliferation, induce apoptosis, and inhibit angiogenesis in the colon [28]. Inhibition of both COX-1 and COX-2 appears to be effective for preventing polyp formation and greatly reduces colon cancer risk [29, 30]. It appears that reducing the level of PGE2 levels in normal tissue could lead to a reduced risk of polyp formation, and PGE2 has been identified as an appropriate prevention endpoint [31, 32].

Proteins and CRC

A comprehensive review by the WCRF and the American Institute for Cancer Research concluded that "the evidence that red meat and processed meat are a cause of colorectal cancer is convincing" [8]. The panel thus recommends: "Limit intake of red meat and avoid processed meat," which is a challenge for the meat processing industry [33]. Epidemiological and three clinical studies suggest that red meat and processed meat intake increases the risk of colorectal cancer. [34–36]. The average relative risk associated with consumption of red meat is moderate but significant in the three meta-analyses (relative risk=1.17, 1.35, and 1.28, respectively), as is the risk associated with consumption of processed meat (relative risk=1.49, 1.32, and 1.20,

respectively). These meta-analyses estimated that one gram of processed meat increases the risk of colorectal cancer 11 times, six times or twice more than 1 g of fresh red meat, respectively, for the three meta-analyses [37]. Several mechanisms have been assumed to explain the relationship between the risk of colorectal cancer and red meat intake. Red meat enhances the formation of putative carcinogenic N-nitroso compounds in human feces [38, 39]. Meat cooked at a high temperature contains mutagenic heterocyclic aromatic amines that induce colon, mammary, and prostate tumors in rodents and monkeys [40]. However, these aromatic amines might not play an important role in colorectal cancer incidence, since (a) chicken intake is a major contributor of aromatic amines intake, but it is not associated with the risk [41], and (b) doses of aromatic amines that induce cancer in animals are 1,000–100,000 times higher than the doses found in human food [42]. Red meat also contains heme, the iron-bearing prosthetic group of myoglobin. Dietary hemin (heme stabilized by a chlorine atom, also called ferriprotoporphyrin IX chloride) increases colonic epithelial proliferation and induces cytotoxicity of fecal water in rats [43]. Dietary hemin, hemoglobin, and heme in meat promote a dose-dependent formation of preneoplastic lesions in the colon, aberrant crypt foci and mucin depleted foci [44–46]. In addition, dietary heme increases amounts of lipid hydroperoxides in fecal water and cytotoxicity of fecal water [44, 46].

Carbohydrates and CRC

It is believed that a decreased intake of carbohydrates reduces the risk for colonic polyp formation [47]. Complex long-chain carbohydrates are considered highly protective in contrast to saccharose [48]. Some studies confirm that persistent hyperglicaemia and the subsequent insulin release are stimuli for hyperproliferation of colon epithelium and risk factors for the development of CRC [49]. In contrast, other studies did not observe this association [50]. Complex long-chain carbohydrates must supply the 40–60 % of all energy intake, while refined saccharose must supply less than the10% according to specific recommendations from a population study [48]. The results of this study support the notion that saccharose and sweets are risk factors for intestinal polyps and cancer, while complex long-chain carbohydrates have protective effect.

Calcium–Vitamin D and CRC

There is increasing evidence suggesting that calcium and vitamin D play important roles in reducing the risk of colorectal cancer. Calcium and vitamin D are biologically linked, and both have shown promise as preventive agents of colorectal cancer [51–53]. Animal models and cell cultures have provided evidence that these micronutrients may act by influencing apoptosis. For example, compared with mice on a standard diet of 0.5 % calcium, increasing the concentration to 1.0 % resulted in higher levels of apoptosis in the distal colorectal epithelium. In human colorectal adenoma and cancer cell lines, the active metabolite of vitamin D [1,25 (OH)2D3] was found to induce apoptosis in a dose-dependent manner [54]. Two studies [55, 56] assessed calcium (1,000–1,500 mg/day) plus vitamin D (400–1,100 IU/day) in general populations (n=37,016). There was no significant effect on the relative risk of colorectal cancer (RR, 1.08; 95 % CI, 0.87–1.34). However, the duration of follow-up was 4–7 years, which may be insufficient to detect an effect on cancer incidence. However, two trials conducted on calcium intake (1,200–2,000 mg/day) in individuals with a history of adenomas (n=1186) demonstrated a statistically significant 18 % reduction in the risk of adenoma recurrence after 3–4 years of follow-up (RR, 0.82; 95 % CI, 0.69–0.98) and a nonsignificant reduction in the risk of advanced adenomas (RR, 0.77; 95 % CI, 0.50–1.17) [57, 58]. Miller et al. [59] recently support the vitamin D proapoptotic activity in 803 consecutive patients undergoing colonoscopies recruited for a study designed to examine risk and etiologic factors for colorectal adenomas. Patients with adenomas in the highest versus lowest tertile of dietary calcium intake had 3.4 times higher odds [95 % confidence interval (CI), 0.9–12.9] of elevated apoptotic scores. However, in adenoma-free patients, high calcium intake was not related to apoptosis (OR, 1.2; 95 % CI, 0.6–2.7). In contrast, the highest level of 25-hydroxyvitamin D was associated with higher apoptosis in adenoma-free patients (OR, 2.6; 95 % CI, 1.1–6.2).

Folic Acid and CRC

Folic Acid (FA) is one kind of water-solubility vitamin, which has been believed to be chemopreventive agent that can provide methyl- group to DNA, thus impact DNA synthesis and DNA methylation [60]. Abbreviations in DNA synthesis often lead to DNA mutation, DNA strand break, and the impairment of DNA repair, which finally result in cancer formation [61]. However, there were conflicting data whether FA can inhibit or promote colorectal adenoma (CRA) from clinical or preclinical studies. Epidemiologic studies show that FA is significant associated with lower risk of colorectal cancer, supporting FA as a protective agent for colon mucosa [62]. Nevertheless, several large prospective studies in 99,523 participants in the American Cancer Prevention Study II (CPS-II) Nutrition Cohort [62] and a double-blind, randomized clinical trial conducted by nine clinical centers incorporating 1,091 participants for 3 years follow-up [63]. However, the Aspirin/Folate Polyp Prevention Trial demonstrated about the

67 % of increased risk of advanced lesions with high malignant potential as well as an increased risk of having multiple adenomas among the FA supplementation group (1 mg/day for 6 years) [64]. Furthermore, many researchers consider that the role of FA might be two-sided, i.e., the prevention in early stage of adenoma formation and the promotion in latest age depending on the time of FA administration.

Antioxidants and CRC

There were 12 studies on the role of antioxidants in colon carcinogenesis in general population (n=148,922), with treatment follow-up durations between 5 and 12 years [65]. Across the nine studies comparing antioxidants to no antioxidants, there was no difference in the incidence of colorectal cancer (RR, 1.00; 95 % CI, 0.88–1.13). The single study that assessed the effect of antioxidants on adenoma incidence in the general population also did not demonstrate a statistically significant effect. Of 14 analyses for different combinations of antioxidants in the general population, one study reported a statistically significant increase in relative risk of adenoma incidence in participants receiving vitamin E or vitamin E plus betacarotene; however, this should be interpreted with caution because it differs from the large number of undertaken analyses [66]. However, there were seven studies of antioxidants (including vitamins A, C, and E, beta-carotene, or selenium) in individuals with a history of adenomas (n=1,706) with treatment and follow-up durations of 2–5 years. Doses and combinations varied between studies with a large difference among the various combinations despite no statistically significant differences in relative risk of adenoma recurrence were demonstrated, either when all antioxidants were overall analyzed (RR, 0.78; 95 % CI, 0.54–1.14) or when specific combinations were assessed separately [65, 66]

Phytoestrogens and CRC

Dietary phytoestrogen intake has been suggested to be inversely associated with CRC risk [1, 67–69]. The decisive role of dietary habits and lifestyle in colorectal carcinogenesis comes from epidemiological studies showing a rapid increase in colon cancer incidence among the Asian-born population in the USA relatively shortly after their immigration in relation to the changes of dietary habits. Indeed, soy-containing food are characterized for their content in phytoestrogens, the most common being genistein and daidzein [70]. Phytoestrogens are a heterogeneous group of polyphenolic plant-derived compounds classified, based on their chemical structure, into four major classes: isoflavones, flavonolignans, lignans, and coumestans. In food, phytoestrogens usually occur as inactive precursor molecules undergoing different metabolic conversion by intestinal microflora into hormone-like compounds. These substances structurally and functionally resemble 17-β estradiol, and we know by several epidemiological, experimental, and clinical evidences that estrogens act as protective agents in CRC through one of their well-characterized two receptor subtype (ERs) named ERβ [71]. This receptor is the one associated with estrogen-mediated anticarcinogenetic effects, and it is distinguished from the other receptor subtype, ERα, that is the subtype related to estrogens side effects and that is responsible to drive proliferation in the absence of a balancing effect of ERβ. In CRC, the silencing of ERβ expression has been reported to parallel dedifferentiation and stage worsening, and ERβ induction has been proposed as a possible therapeutic target in CRC chemoprevention [72, 73]. With the only exception of coumestans—particularly coumestrol—binding both ERs with an affinity comparable to natural estrogen, phytoestrogens have been described for a higher selectivity for ERβ and a less marked affinity for ERα than natural estrogens. The flavonolignan silymarin and the lignans have been shown to have no or very low affinity to ERα, respectively [74, 75]. Recently, a prospective cohort study in Japan reported an inverse association between soy food and isoflavone intake and CRC risk in men and postmenopausal women in the highest quintile of soy food and isoflavones intake, after adjustment for dietary intake of calcium and n-3 polyunsaturated fatty acid, BMI, physical activity, alcohol use, and other lifestyle factors [76]. In a prospective study including about 70,000 Chinese women, Yang [68] recently demonstrated that total soy food intake was inversely associated with CRC risk. Each 5-g/day increment in intake of soy-containing foods (as assessed by dry weight assessment of components) was associated with an 8 % reduction in risk. A recent meta-analyses on currently available epidemiological studies suggests that consumption of soy foods is associated with a reduced colorectal cancer in women but not in men. However, major limitations in drawing conclusions remained on the absence in most studies of the use of a validated questionnaire. When frequency of intake was reported, only a few evaluated intake quality, and the measurement units varied across studies [1]. In comparison to isoflavones, lignans occur at much higher levels in the typical western diet. Unfortunately, epidemiological studies addressing lignans in CRC chemoprevention and risk reduction are almost completely unavailable. Adelcreutz was the first to suggest that lignans may be protective not only against breast but also colon cancers. This hypothesis was supported by studies showing a higher lignan excretion in individuals consuming a diet suggested to lower colon cancer risk or for those living in areas with low colon cancer risk [77]. Kuijsten et al. studied the association between plasma enterolignans (enterolactone

and enterodiol) and the risk of colorectal adenomas in a Dutch case–control study. *N*=532 cases with at least one histologically confirmed colorectal adenoma and *N*=503 controls with no history of any type of adenoma were included. When incident cases (*N*=262) were included, a substantial reduction in colorectal adenoma risk was observed among subjects with high plasma enterolignans [78]. On the other hand, 221 cases of colorectal cancers were diagnosed in the EPIC-Norfolk cohort study, and no association with serum or urinary lignans was found [79]. Barone et al. [80] recently demonstrated that ERβ levels are significantly lower in the colonic mucosa of male ApcMin+/− mice than in their wild-type littermates and that supplementation with a patented blend of phytoestrogens (silymarin—a flavonolignan titered at 30 % silibin, and lignans flaxseed extract titered at 40 % secoisolariciresinol) and insoluble fibers (Eviendep™, CM&D Pharma Limited, a Nestlè Health Science Company) fully restored the ERβ-deficient expression [messenger RNA (mRNA) and protein] to the wild-type levels. The supplemented blend also reduced the development of intestinal neoplasia: There was a significant 34 % reduction in polyp number and size throughout the small intestine and large bowel, together with less severe dysplasia. These observations strengthen the notion that decreased ERβ expression may be a biomarker of intestinal neoplasia onset and progression in APCMin+/− mice. Moreover, they suggest that both ERβ and adenoma burden can be modulated by phytoestrogen and insoluble fiber supplementation. The evidence could be of relevance to human FAP, since the ApcMin+/− mouse is regarded as a validated animal model for human disorder.

Alcohol and CRC

We believe that chronic alcohol abuse is a major risk factor for gastrointestinal polyps and cancer formation in esophagus, stomach, colon, and rectum. High alcohol intake (>21 U/week) of beer, wine, and spirits significantly increases the risk for colon polyps and cancer. These findings are probably due to the effect of acetaldehyde, which damages colorectal mucosa and elevates cell regeneration. FA and methionine deficiencies in chronically alcohol abuser are also risk factors for development of CRC [81]. Alcohol is an inducer of cytochrome P-405 2E1, which contributes to increase the production of free radicals. Alcohol diminishes the transformation of retinol into retinoic acid, and as a result, cell proliferation is upregulated [82].

Microbiota and CRC

Evidence is emerging that the intestinal microbiota is intrinsically linked with overall health, including cancer risk. Despite its composition is not fixed, but it can be affected by several dietary components. Dietary modifiers, including the consumption of alive bacteria (probiotics), nondigestible or limited digestible food constituents such as oligosaccharides (prebiotics) and polyphenols, or both (synbiotics), are recognized modifiers of the numbers and types of microbes and have been reported to reduce experimental colon cancer risk. Microorganisms also have the ability to generate bioactive compounds from food components. Examples include equol from isoflavones, enterodiol and enterolactone from lignans, and urolithins from ellagic acid, which have also been demonstrated to retard experimentally induced cancers. The gastrointestinal microbiota can also affect both sides of the energy balance equation, namely, by influencing either energy utilization from the diet and host genes that regulate energy expenditure and storage. Because of the link between obesity and cancer incidence and mortality, this complex relationship deserves great attention. Thus, a complex relationship exists between the intestinal microbiota and colon cancer risk, which can be modified by dietary components and eating behaviors [83].

Dietary Influence in CRC Recurrence and Survival

CRC survival is poor, with an overall 5-year survival rate of approximately 45 %. Stage at diagnosis and possibility of resection of the tumor are the main prognostic factors. Sex, age at the time of diagnosis, tumor site, and socioeconomic status have also been discussed as determinants of survival. Although the relationship between diet and CRC has been extensively studied, its influence on survival has been examined in only few studies. This information is important because many individuals who have been diagnosed with colorectal cancer are motivated and have been shown to adjust their dietary and physical activity habits [84–86]. In particular, this association has been investigated in 12 observational studies [87–100]. Seven of these studies examined dietary factors that referred to the time before cancer diagnosis [87–91, 93–96], and five studies investigated postdiagnosis dietary factors [92, 97–100].

These studies, however, did not allow clear conclusive remarks for some limitations such as the general conditions of the patients, the lack of homogeneous group assembling, the impossibility of establishing the real causes of death, and the presence and severity of malnutrition.

Macronutrients and Alcohol in CRC Survival

In two studies comparing high with low total calories intake before CRC diagnosis, an association between total energy intake and a lower risk of all cause death at 2 [87] and 5 years [89] of survival was demonstrated. Zell et al. [90] counteract these observations evaluating prediagnosis

energy intake with overall survival after 7–9 years of follow-up. This study further demonstrated that regular compared with infrequent wine consumption was associated with a lower risk of all-cause mortality in nonsporadic colorectal cancer [90]. However, no association was shown for total alcohol consumption with all-cause mortality in other two studies in colorectal [88] and colon [92] cancer, respectively.

Instead, a large postoperative adjuvant chemotherapy trial in 1,009 stage III colorectal cancer patients assessed diet midway through therapy and 6 months after its completion. Analyses were extensively adjusted for several prognostic factors, including the tumor stage, clinical perforation, and bowel obstruction at the time of surgery. Subjects in the highest quartile compared with subjects in the lowest quartile of a Western dietary pattern (meat, fat, refined grains, and dessert) had a higher risk of all-cause mortality (HR, 2.32; 95 % CI, 1.36, 3.96),

Proteins and CRC Survival

Only a study analyzed the correlation between survival and meat consumption before diagnosis and demonstrated the known association between a higher meat consumption and the risk of all-cause mortality in familial but not sporadic colorectal cancer cases [93]. However, another study in 39 colorectal cancer patients found no association for low compared with high energy or protein intake 3 weeks after diagnosis with 1 year of survival. [101].

Fibers and CRC Survival

The relationship between prediagnosis dietary fiber intake and mortality for colorectal cancer was investigated only in three studies. Two of them demonstrated no statistically significant association. By contrast, the other one—the oldest—demonstrated that the highest quartile of dietary fiber intake was associated with decreased survival (HRR=1.53) for CRC when compared with the lowest quartile. No associations for a prudent dietary pattern, which was characterized by high intakes of fruit and vegetables, poultry, and fish, were observed in postdiagnosis CRC.

Fatty Acid and CRC Survival

Skeie et al. [94] demonstrated an association between whole-year daily use of cod liver oil and daily use of other dietary supplements before CRC diagnosis with all-cause mortality in colorectal cancer cases.

Vitamin D and CRC Survival

A cohort study evaluated blood concentration before diagnosis of vitamin D [95]. Colorectal cancer-specific mortality was not significantly related to plasma 25(OH)D concentrations (HR, 0.61; 95 % CI, 0.31, 1.19). Results were similar for all-cause mortality. Nevertheless, another large cohort study analyzed dietary vitamin D influence after CRC diagnosis. This study including 1,017 colorectal cancer cases, observed a lower risk with higher predicted 25 (OH)D concentrations for colorectal cancer-specific mortality (HR, 0.50; 95 % CI, 0.26, 0.95) and all-cause mortality (HR, 0.62; 95% CI, 0.42,0.93) [100] .

Folate and CRC Survival

A cohort-study evaluates blood AF concentrations before CRC diagnosis [96]. Colorectal cancer-specific mortality was significantly lower for the highest quintile than for the lowest quintile of plasma folate concentrations (HR, 0.42; 95 % CI, 0.20, 0.88). AF concentrations were not associated with all-cause mortality in this study. In another study in 93 colorectal cancer patients with unresectable metastases, patients with serum cobalamin concentrations below the median had a lower risk of all-cause mortality than patients with serum cobalamin concentrations above the median [99]. Folate concentrations were not associated with all-cause mortality in this study.

Antioxidants and CRC Survival

One study investigated plasma concentrations of antioxidants before potentially curative resection or chemotherapy and/or supportive care [98]. This study included 53 patients with primary operable colorectal cancer and 53 patients with unresectable liver metastases. Patients with unresectable liver metastases with plasma retinol concentrations above the median were shown to have a lower colorectal cancer-specific mortality than patients whose plasma retinol concentrations were below the median. No association was observed for a-tocopherol, lutein, lycopene, α-carotene, and β-carotene plasma concentrations, and no association was reported for patients with primary resectable colorectal cancer.

Dietary Influence and Neoplastic Polyp Recurrence

Because the adenoma recurrence rate after polypectomy is approximately 40–50 % [101–103], the prevention of recurrent adenomas could significantly contribute to reduce CRC incidence. Factors associated with recurrence of these lesions, including adenoma and patient charateristics, are not fully understood; however, a series of studies have demonstrated an increased recurrence of adenomas in individuals with a history of multiple adenomas [104]. Thus,

reducing the incidence or recurrence of any or multiple adenoma formation, it is a plausible target for preventing colorectal cancer. Recent prospective cohort studies and dietary intervention trials of adenoma recurrence have predominantly yielded null result [105–108]. A number of factors could be responsible for the observed inconsistency in results. First, development of colorectal cancer is a multistage process, and the timing of initiation of the diet or the duration of the intervention may not be appropriate for the prevention. Second, the inconsistencies may be due to confounding by other nutritional or lifestyle factors, measurement error, recall bias, or unknown confounding factors. Another potential reason for the lack of effect in dietary intervention trials is the low level of compliance among participants.

Total Calories and CRC/Adenoma Recurrence

In the previously mentioned postoperative adjuvant chemotherapy trial in 1,009 stage III colorectal cancer patients assessing diet midway through therapy and 6 months after its completion, it was also demonstrated that subjects in the highest quartile compared with subjects in the lowest quartile of a Western dietary pattern (characterized by high intakes of meat, fat, refined grains, and dessert) had a higher risk of recurrence (HR, 2.85; 95 % CI, 1.75, 4.63) and recurrence and/or death (HR, 3.25; 95 % CI, 2.04, 5.19).

Fibers and CRC Recurrence

The Polyp Prevention Trial (PPT) was designed to test the effect of a low-fat, high-fiber, and high-fruit and high-vegetable dietary intervention on the recurrence of adenomas in the colon [108]. Sansbury et al. [109] examined the effect of strict adherence to a low-fat, high-fiber, and high-fruit and high-vegetable intervention over 4 years among participants (n=1,905) in the US PPT (1991–1998) on colorectal adenoma recurrence. The authors observed a 35 % reduced odds of adenoma recurrence among super compliers compared with controls (odds ratio=0.65; 95 % confidence interval, 0.47, 0.92). Findings suggest that high compliance with a low-fat, high-fiber diet is associated with reduced risk of adenoma recurrence. The PPT trial-based cohort provides also evidence that dry beans may be inversely associated with advanced adenoma recurrence.

Fatty Acids and CRC Recurrence

Methy et al. [110] assessed the risk of overall adenoma recurrence associated with dietary consumption of total fat, subtypes of fat, and specific fatty acids (oleic acid, linoleic acid, and alpha-linolenic acid) in a sample composed of 523 patients with confirmed adenomas at the index colonoscopy, 35–75 year old, who completed the European fiber-calcium intervention trial and had an initial dietary assessment using a qualitative and quantitative food questionnaire. The overall 3-year recurrence rate was 22.6 % (118 out of 523 patients). There was no significant association between overall adenoma recurrence and either total fat, subtypes of fat, or specific fatty acids. However, polyunsaturated fatty acids and linoleic acid were both moderately but significantly associated with distal and multiple recurrence. No significant association was observed with recurrence of proximal or advanced adenomas. A recent Japanese trial [111] investigated whether dietary instruction optimizing the fat energy ratio suppressed the recurrence of colorectal tumors in 373 men and women. At entry, each participant completed a three-consecutive-day food record on which dietary instruction was given to restrict fat energy ratio to 18–22 %. Unexpectedly, the recurrence of tumor increased as the subjects reduced their fat intake. Furthermore, in men, the risk of tumors decreased significantly as the intake of linoleic acids per body weight increased. For women, similar trends were observed. These results suggest that extreme fat restriction is highly likely to promote the recurrence of colorectal tumors, which may be partly attributed to linoleic acid deficiency.

Proteins and CRC Recurrence

Martinez et al. [112] prospectively assessed the relation between type of meat, meat preparation method, doses, and colorectal adenoma recurrence among 869 participants in a chemoprevention trial with ursodeoxycholic acid. Most meat variables assessed were positively but softly associated with the recurrence of few adenomas. In contrast, the recurrence of advanced or multiple adenomas was more strongly associated with some evaluated meat exposure variables. Significant association was detected for the recurrence of advanced lesions among individuals in the highest when compared with the lowest tertile of intake for pan-fried red meat (OR=1.85; 95 % CI=1.10–3.13) and well/very well done red meat (OR=1.71; 95 % CI=1.02–2.86). Significant positive association was also shown for the recurrence of multiple adenomas and the following variables: processed meat (OR=1.83; 95 % CI=1.10–3.04), pan-fried red meat (OR=1.63; 95 % CI=1.01–2.61), well/very well done red meat (OR=1.68; 95 % CI=1.03–2.74), 2-amino-3,4,8-trimethylimidazo[4,5,-f]quinoxaline (OR=1.74; 95 % CI=1.07–2.82), and 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (OR=1.68; 95 % CI=1.03–2.75). These results support a meat mutagen exposure hypothesis as a potential mechanism for recurrence of clinically significant adenomatous polyps. Furthermore, a large multicenter randomized controlled trial [113] reassessed to check whether meat

intake and a reduction in its consumption were associated with the recurrence of adenomatous polyps of the large bowel in 1,905 treated subjects and 947 controls who had one or more histologically confirmed colorectal adenomas removed within 6 months before randomization. The analysis did not provide any evidence to suggest that a lower intake or a reduction in total and red meat consumption during a period of 4 years reduced the risk of adenoma recurrence (including multiple or advanced adenoma), whereas the data suggested that a high intake of fish was associated with a low risk of adenoma recurrence.

Calcium and CRC Recurrence

The supplementation with calcium versus placebo at 3 g/day for 48 months reduced adenoma recurrence by 24 % ($p<.05$) in a randomized trial [114]. Supplemental calcium at 3–4 g/day appears to reduce the incidence of recurrent adenoma by 22 % (versus placebo) over 3–4 years [115]. In a recent report from the WHI, no reduction in CRC risk was found in women supplemented with 1 g of calcium carbonate and 400 IU of vitamin D3 per day over a 7-year period, casting doubt on calcium chemopreventive activity [116]. However, several factors could have contributed to the negative results of the WHI study, including the doses of calcium, which were one third of those usually employed in adenoma chemopreventive trials, the relatively high intake of calcium in the placebo group, the average CRC risk of the population studied, the relatively short duration of follow-up for a cancer end point, and overlapping interventions.

Antioxidants and CRC Recurrence

In a large beta-carotene supplementation trial of adenoma recurrence, similar in design to the PPT, participants in the beta-carotene supplemented group (20 mg/day), and placebo group experienced a similar rate of adenoma recurrence by intent to treat analysis [117]. In a subsequent analysis, stratified by smoking and drinking status, a significant protective effect from beta-carotene supplementation was observed in non smoking and non drinking individuals [118]. Steck-Scott et al. [119] examined the relation between serum and dietary carotenoids/vitamin A and adenomatous polyp recurrence in a subcohort of 834 participants in "Polyp Prevention Trial." Baseline dietary intakes of alpha-carotene and vitamin A from food with/without supplements were inversely associated with few recurrence (p for linear trend=0.03—alpha-carotene; p=0.004 and p=0.00—intakes of vitamin A). Compared to the lowest quartile of averaged beta-carotene concentrations, the OR of multiple adenomas for the highest quartile was 0.40 (95 % CI=0.22–0.75) with an inverse trend (p=0.02). The risk was inversely related to averaged alpha-carotene concentrations and right-sided polyps; alpha-carotene intake and recurrence of few, multiple and right-sided polyps; beta-carotene intake and multiple adenoma recurrence; vitamin A from food (with supplements); and each adverse endpoint. Thus, alpha-carotene and vitamin A may protect against recurrence in nonsmokers and nondrinkers or be indicative of a healthy lifestyle factor able to reduce the risk.

Phytoestrogens and CRC Recurrence

Di Leo et al. [120] recently conducted a randomized, double blind, placebo-controlled trial on the effect of a short-term (60 days) supplementation with a patented blend of phytoestrogens (sylimarin and lignans) and dietary fibers (Eviendep™) in patients with sporadic adenomas at average risk for CRC, in advance of their surveillance colonoscopy. The patients were naive of any previous and concomitant hormonal or anti-inflammatory chemoprevention. An increased ERβ (mRNA and protein) and apoptotic activity (TUNEL) was detected in the treated group, whose compliance with the dietary treatment was objectively monitored by means of urinary enterolignan assessment. Eviendep™ was optimally tolerated, and no adverse event was recorded during the study period as related to Eviendep™ exposure. Moreover, Eviendep™ did not induce/potentiate ERα expression in the colonic mucosa demonstrating its specificity for ERβ and supporting the overall safety profile of the product.

Conclusive Remarks

The role of diet in the etiology of various type of cancer [1] remains an area of active research.

Literature data are convincing for a protective role on the onset of preneoplastic and neoplastic lesions for some foods such as fibers, vitamin A and D, folic acid, calcium, antioxidants, and promising perspectives for some substances such as phyto-estrogens.

Less evidence-based data are available on the possibility to avoid the recurrence of the disease or to affect its mortality with dietary habits. Indeed, available data are limited by some relevant factors such as confounding aspects, i.e., overall nutritional or lifestyle factors, measurement error, recall bias, or unidentified confounding features. Another potential reason for the lack of effect in dietary intervention trials may be the low level of compliance among participants.

Future perspectives will be directed be not only to identify new dietary style able to prevent the onset of neoplastic lesion of the colon but also to realize an effective chemoprevention. Moreover, evidence based data are needed from future study to identify dietary and chemopreventive factors able to act on disease recurrence and survival.

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