Dietary Lipids and Cancer

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Abstract: For many years, epidemiological studies continued to suggest that high fat diets are linked to an increased incidence of certain cancers. However, whether the oncogenic properties of fat are associated with their quantity rather than the quality has become debatable. Epidemiological studies have been suggesting that n-6 polyunsaturated fatty acids (n-6 PUFA) and saturated fats are more likely to increase the incidence of cancer, whereas monounsaturated fatty acids (MUFA) and n-3 polyunsaturated fatty acids (n-3 PUFA) are more likely to prevent or decrease the chance of carcinogenesis. A firm conclusion cannot be drawn yet because of insufficient research. This paper reviews the current knowledge of the effects of saturated fats, different types of unsaturated fats, and fat-soluble vitamins on the etiology of cancer.

Key Words: *cancer; saturated fats; monounsaturated fatty acids, MUFA; n-3 polyunsaturated fatty acids, n-3 PUFA; n-6 polyunsaturated fatty acids, n-6 PUFA; arachidonic acid, AA; eicosanoids; anti-inflammatory; anti-proliferative effects.*

Background

For more than fifty years dietary fats have been known to play a substantial role in the etiology of cancer [1]. Dietary habits seem to be more easily modified than tobacco smoking cessation or physical exercise habits [2]. Different studies have suggested that a high consumption of fat is related to an increased incidence of breast, colon, pancreatic and prostate cancer [1]. However, this finding is no longer accepted because the oncogenic properties of fat are independent of their caloric content. Much research has indicated that dietary intake of monounsaturated fats, (e.g. olive oil) [1, 3] or n-3 PUFA (e.g. fish oil, flaxseed oil) [4-6] is inversely correlated with the development of colorectal cancer. It has also been documented that diets high in animal fat and n-6 PUFA contribute to an increased risk of colorectal [7], colon [8] and breast cancer [9].

The mechanism by which dietary n-3 and n-6 PUFA protect or enhance tumor development, respectively, has not been fully investigated, but most of the proposed mechanisms are based on the metabolic fate of these fats and the subsequent biosynthesis of eicosanoids, which exert control over several systems. Fats, particularly saturated fats, may affect hormonal status, modify cell membrane structure and function, cell signaling transduction pathways, and gene expression, and they may even modulate functions of the immune system [10]. It has become necessary to determine the roles of fatty acids in the development of or protection against human cancer. This article will discuss the relationship between cancer on the one hand, and dietary saturated fats and various types of unsaturated fats on the other hand, as well as indicate the mechanisms by which different fatty acids induce or prevent carcinogenesis.

1. Saturated Fats

During the past several decades, it has been shown that high intake of saturated fat, animal fat, and meat is associated with an increased risk of colorectal [11] and breast cancer [12]. These findings are supported by studies that compared risk factors for colon and rectal cancer and showed that dietary animal fat may be associated with increased risk of colon cancer [13-15]. However, a large cohort study followed 483,109 men and 619,199 women over 14 years failed to link meat consumption to increased risk of pancreatic cancer [16]. Another prospective study found that saturated fat intake and butter consumption were strongly correlated with an increased risk of pancreatic cancer, whereas energy and carbohydrate intake were inversely proportional to development of pancreatic cancer [17]. Additionally, a multiethnic cohort study showed a 50% increase in pancreatic cancer risk with diets that were high in pork or total red meat but no increased risk was found with dietary intake of poultry, fish, dairy products, eggs, saturated fat or cholesterol [18]. This study indicated that mutagenic compounds produced during the cooking or preservation of food could be the link between consumption of red or processed meat and the increased risk of pancreatic cancer. Although burned and singed meat contains high concentrations of carcinogens and mutagens, a clear link to increased rates of cancer has not been found [19].

A study published in 2007 compared the incidence of colorectal cancer between African Americans (n=17), Native Africans (n=18), and Caucasian Africans (n=17). It found that higher risks of colorectal cancer and mucosal proliferation rates were associated with higher dietary intake of animal products and with larger colonic populations of bacteria producing potentially toxic hydrogen and secondary bile-salts [20].

In one animal study, 120 male F344 rats were injected weekly with azoxymethane, a carcinogen, and fed a high-fat diet containing 20% mixed lipids (HFML). Treatment with HFML for 38 weeks was significantly associated with increased colonic aberrant crypt foci (ACF), early putative preneoplastic lesions of colon neoplasia, increased cyclooxygenase-2 activity (COX-2) and

suppressed colonic apoptosis [21]. This large-scale study was the first to show the effect of HFML on colonic carcinogenesis in a well-established animal model. However, these data failed to elucidate how the HFML diet induces tumor formation in the colon.

In another similar study, F344/N rats were fed a diet containing 19% animal fat (beef tallow) and exposed for 26 weeks to tribromomethane (TBM), a drinking water contaminant. A significant and nearly two-fold expansion in ACF was observed in animals whose diets were high in fat compared to those fed a normal diet [22].

The mechanisms by which fats promote tumorigenesis are not fully understood. However, current knowledge indicates that a high fat intake results in increased production of bile acid, which is converted by intestinal bacteria into secondary bile acid and cytotoxic compounds. These compounds may enhance the proliferative activity of the colonic epithelium [1, 20, and 23] by increasing ornithine decarboxylase, which is involved in cell division. They also seem to speed up secondary cellular transduction signals, such as protein kinase C, and modify membrane fluidity by changing the phospholipid composition of the cell membrane, prostaglandin metabolism, and local inflammatory responses, along with increasing COX-2 activity and decreasing apoptosis [21, 23-25].

It has been suggested that diets rich in meat and other animal products may be low in plant foods, such as fruits, vegetables, and whole grain cereals [26]. Thus, such diets may have a lower content of certain anti-carcinogenic compounds, such as antioxidants and phytoestrogens or other phytochemicals that exhibit some antiproliferative activity [27, 28].

2. Monounsaturated Fatty Acids

Great effort has been made to clarify the association between consumption of MUFA, particularly oleic acid, and breast-cancer risk. Oils that are rich in MUFA, particularly olive oil, are considered to be the healthiest type of fat. To corroborate the protective role of olive oil by showing a decreased risk of cancer, a case-control study was conducted between 1999 and 2001 on 755 women: 291 cases with breast cancer and 464 controls. It was found that the consumption of ≥ 8.8 g of olive oil per day significantly correlated with a lower risk of breast cancer [29]. In agreement with these observations, a case-control study conducted in Greece showed that the increased intake of olive oil was associated with a lower risk of breast cancer [30]. Likewise, Galeone, et al., conducted a multicenter case-control study in Italy and Switzerland between 1992 and 2000 on 1394 colon cancer patients, 886 rectal cancer patients, and 4765 controls. Their findings demonstrated that olive oil might decrease colon cancer risk but not rectal cancer risk [31].

Olive oil has been shown to reduce the risk not only of breast and colon cancer, but of many other neoplasms as well. In one case control study, 754 individuals with initial primary cancer in the oral cavity and pharynx, together with 1775 controls, were followed between 1992 and 1997 [32]. It was found that consumption of 0.7 g of olive oil daily was associated with a lower risk of oral cancer [32]. In contrast, Elahi, et al., did not observe a protective effect of olive oil against development of breast cancer [33].

In general, the mechanisms underlying the protective role of olive oil against cancer seem to rely on the polyphenolic compounds, the tocopherol content of olive oil, and its fatty acid structure, which prevents free radical-initiated peroxidation. Moreover, Romero, et al., demonstrated *in vitro* that these substances exert a strong bactericidal activity against eight strains of *Helicobacter pylori* (the primary cause of peptic, gastric, and duodenal ulcers). Among these phenolic compounds, the dialdehydic form of decarboxymethyl ligstroside aglycon exhibited the strongest bactericidal effect at a concentration as low as 1.3 µg/ml. These results raise the possibility of considering virgin olive oil a chemo-preventive agent for peptic ulcer and gastric cancer [34]. Furthermore, it was hypothesized that olive oil may regulate cancer-related oncogenes. Colomer, et al., showed that exogenous supplementation of cultured breast cancer cells with physiological concentrations of oleic acid (OA) significantly reduced the overexpression of HER2 (Her-2/neu, erbB-2), a well-characterized oncogene playing a key role in the etiology and progression of breast carcinomas [35].

3. n-3 and n-6 Polyunsaturated Fatty Acids (n-3 PUFA)

Several studies have associated high intake of n-6 fatty acids (e.g. corn and safflower oils) with a poor outcome in cancer patients [36, 37], whereas high consumption of n-3 fatty acids (e.g. fish and flaxseed oils) has been linked to a favorable outcome [38, 39]. To confirm these observations, 30 patients with colorectal adenomas were randomly placed in a control group or in a treatment group receiving a highly purified eicosapentaenoic acid (EPA) in free fatty acid form (2 g/day). After three months of treatment, crypt cell proliferation was reduced and apoptosis

was increased in normal colonic mucosa of the EPA-treated group as compared to the control group [40]. The authors suggested that metabolism of EPA may lead to the production of 3-series prostaglandins, such as PGE3, which have an inhibiting effect on cell proliferation and COX-2 activity, along with reduction in the mucosal levels of n-6 fatty acid. However, this study did not provide any further insight into the mechanism by which n-3 fatty acids such as EPA elevate mucosal colonic apoptosis [40]. On the contrary, Cheng, et al., showed that EPA and docosahexaenoic acid (DHA) supplementation significantly increased the production of the apoptosis-enhancing protein Bax, indicating that upregulation of Bax protein within normal mucosa could be one mechanism by which EPA increases mucosal apoptosis in the colon [41].

The ameliorative influence of n-3 fatty acids on cancer has also been documented in animal studies. Twenty male F344 rats were fed either high fat fish oil (HFFO) or high fat corn oil (HFCO) diets for 8 weeks and injected with azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF). Rats fed the HFFO diet had a lower incidence of AOM-induced ACF in the proximal colon than rats fed the HFCO diet. In addition, the activity of hepatic glutathione s-transferase (GST), an antioxidant enzyme, and plasma levels of PGE-2, one of the primary prostaglandins formed from the metabolism of AA, were significantly reduced in rats fed the HFFO diet relative to those fed the HFCO diet. This study indicated that HFFO diets could compromise the antioxidant status of the cell by augmenting lipid peroxidation [42]. Flaxseed oil (FO) is a good source of n-3 fatty acids. Supplementing AIN 93G diet with 10% and 20% of flaxseed meal (FSM) or 7% and 14% of FO decreased the incidence of AOM-induced ACF in Fisher 344 male rats [43]. n-3 PUFA may hinder carcinogenesis by a molecular mechanism, such as increased or decreased production of free radicals and reactive oxygen species, repression of AA-derived eicosanoid synthesis, attenuation the expression of vascular cell adhesion molecule (VCAM-1), believed to promote the adhesion of circulating tumor cells to the endothelium, influences on transcription factor activity and signal transduction pathways, modification of estrogen metabolism, and mechanisms involving insulin sensitivity and membrane fluidity, as reviewed [9].

In general, n-6 PUFA appear to possess some carcinogenic properties. However, conjugated linoleic acid (CLA), a naturally occurring n-6 fatty acid found primarily in ruminant meat and dairy products, has been demonstrated to protect against cancer in animal models of chemical carcinogenesis and to inhibit the proliferation of human cancer cell lines [44]. Different mechanisms may be suggested for how CLA inhibits carcinogenesis. First, it is incorporated into the cell membrane as oleic acid and metabolized as linoleic acid, influencing linoleic acid desaturation and elongation. Thereby, it modulates prostaglandin metabolism. Second, it can decrease synthesis of insulin-like growth factor (IGF) II and down-regulate extracellular signal-regulated kinase-1/2 pathway and IGF-I receptor signaling [45]. Third, CLA may increase free retinol levels by enhancing the level of cellular retinol-binding protein (CRBP) mediated by activation of peroxisome proliferator-activated receptor (PPAR)-alpha (PPAR-alpha), known to be a transcription factor for CRBP [46]. In addition, CLA, particularly the t10c12 isomer, suppresses cell proliferation, and induces apoptosis and expression of the pro-apoptotic gene nonsteroidal anti-inflammatory drug-activated gene 1 in human colorectal cancer cells [47]. Furthermore, there are indications that CLA may inhibit growth of cancer cells through induction of cyclin-dependent kinase inhibitor p21CIP1/WAF1, a tumor suppressor protein [48].

4. Fat-soluble vitamins

There are four families of fat-soluble vitamins: A, D, E, and K. These vitamins have been studied in animals and in humans to assess their influence on the growth of cancer cells of different origins. Ohlsson, et al, studied the effect of fat-soluble vitamins on seven cell lines that were obtained from patients with pancreatic adenocarcinoma. They found that the number of pancreatic cancer cells decreased after treatment with vitamin A and D analogues, especially when high concentrations were used. However, combining retinoids with the vitamin D analogue EB 1089 did not enhance its effect. Moreover, vitamin E succinate repressed cell growth in three out of seven cell lines, whereas vitamin K1 increased the number of pancreatic cancer cells in three out of seven cell lines. This study concluded that high concentrations of vitamin A and D analogues attenuated the cell numbers in pancreatic cancer cell lines, whereas vitamins E succinate and K1 had little if any effect [49]. Vitamin K analogues have also been shown to inhibit cancer cell growth through increased protein kinase phosphorylation, a process important in modulation of cellular transduction signals [50].

Vitamin E has been linked to inhibition of the growth of cancer cells [51] as well as to inhibition of UV-induced DNA damage and carcinogenesis

in animal models [52], probably by enhancing the glutathione-dependent enzyme system [53]. Following a secondary analysis of the α-tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), it was reported that male smokers who daily received 50 µg of vitamin E (α-tocopherol) had a 41% decline in prostate cancer mortality and a 36% decline in its incidence [54]. In the same line, a large epidemiologic cohort study found that daily intake of 100 µg vitamin E by smokers and those who had recently quit smoking reduced the risk of metastatic or fatal prostate cancer by 44% compared with others who did not receive the vitamin E supplement [55].

Similarly, high values of serum provitamin A and carotenoids were associated with low risks of mortality from lung, stomach, colorectal and liver cancer among a group of Japanese aged from 39 to 85 years and followed for 11.7 years [56]. Vitamin A may attenuate carcinogenesis through its essential role in controlling cell proliferation and differentiation [57]. Taken together, mechanisms underlying the protective effect of fat-soluble vitamins remain uncertain. However, the antioxidant properties of some vitamins and their ability to induce apoptosis may play a significant role in prevention or inhibition of cancer cell growth, respectively. Retinol and provitamin A carotenoids may also decrease cancer risk through other mechanisms, such as inducing cellular differentiation [58].

Conclusion

The studies described here and elsewhere indicate that monounsaturated fat, n-3 PUFA, and fat soluble vitamins may have a profound influence on the prevention and/or suppression of cancer, whereas saturated fat and n-6 PUFA may increase the risk of carcinogenesis. Monounsaturated fat and n-3 fatty acids should be preferred over animal fats and other vegetable fats in the diet. Inconsistency in the literature with regards to the impact of n-3 PUFA on cancer might be due to a) the frequent lack of proper design in studies on humans, b) the supplement dose is often too low or too high, c) inability to define the target populations due to collection of insufficient data from the participants, so that they may not adequately represent the target populations of interest, d) inadequate sample size. Further studies are needed to determine the inductive or protective mechanisms of dietary fats on carcinogenesis in well-designed human studies.

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