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Properties of dietary fatty acids and implications on cancer

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ABSTRACT

Cancer, recognized as a major noncommunicable ailment, exhibits a substantial global morbidity and mortality rate. Dietary fatty acids' effect can be varied upon the structure of components. Saturated fatty acids (SFAs) and Monounsaturated fatty acids (MUFAs) intakes have positive relation with the risk of different types of cancers. However, this conclusion alters based on the type of polyunsaturated fatty acids (PUFAs). Omega-3 fatty acids illustrate protective effects against cancer, while omega-6 fatty acids have pro-inflammatory activities. Moreover, omega-3: omega-6 fatty acids plays a crucial role related to cancer. Ketogenic diet is contraindication for some types of cancer. This diet in cancer patients can be used as secondary treatment, and complications peculiarly cancer cachexia could be improved which increases life quality of cancer patients. In conclusion, decreasing the risk of cancer will be possible by shifting fatty acids consumption toward more omega-3 and less omeg-6 fatty acids and decreased intake of SFAs (via less consuming of processed foods).

Keywords:
Cancer, Fatty Acids, Ketogenic Diet

1. INTRODUCTION

Cancer, acknowledged as a primary global factor in mortality, has the capacity to influence a wide array of body parts and organs. This generic term for a vast range of diseases, characterized as the rapid creation of abnormal cells or as a transformation of cells into cancer cells via a multistage process (1). The transformation could be caused as a result of interactions of several factors such as dietary, genetics or environmental risk can lead to expand of the tumor cells. Thus, invasion of nearby cells and organs will be inevitable (2, 3). Metastases are responsible for the major causes of deaths. According to the World Health Organization (WHO), breast, lung, liver, colon, and rectum cancers are the leading cancers with high mortality, respectively (2).

Although we were just a little familiar with the concept of cancer, "the Warburg effect" was a turning point in cancer treatments. According to this phenomenon termed, most cancer cells prefer aerobic glycolysis to afford energy needed required for cellular processes, instead of relying on mitochondrial oxidative phosphorylation (4). As a feature, most cancer cells have a tendency to use

glucose through fermentation of glucose into lactate, even though lactate pathway provides less ATPs per glucose comparing to oxidative phosphorylation pathway (2 ATPs and 36 ATPs respectively). This process happens even in sufficient levels of oxygen to act as an aid for aerobic glycolysis which remains inefficient while generating ATP via mitochondrial oxidative phosphorylation pathway (5).

The inclusion of dietary fat, particularly when accounting for different cancer types and the quantity and nature of fatty acids, can be deemed a potential risk factor for cancer. Moreover, diets characterized by elevated meat and calorie intake, which are high in fat, primarily contribute to adverse health issues such as overweight, obesity, and the development of cancer (6).

1.1. Fatty Acids and Cancer

Lipids, regarded as one of the three primary macronutrients, predominantly comprise triglycerides in our diets, with phospholipids and cholesterol constituting the remaining components. Based on their chemical structures, fatty acids classified as saturated fatty acids and unsaturated fatty acids. unsaturated fatty acids subdivided into monounsaturated and polyunsaturated fatty acids (MUFAs and PUFAs) (7). In recent years among all fatty acids PUFAs have attracted researchers' attentions due to their associations with diseases (7-10). Besides these fatty acids which are found in nature or can be produced in body, there is another group of fatty acids entering our body as a result of industrial processing, called trans-fatty acids (TFAs). Vaccenic acid and elaidic acid known as primary TFAs that are followed by palmitelaidic acid and linoelaidic acid (6, 11).

Beyond supplying energy, maintaining membrane fluidity, fundamental structure of some hormones, fatty acids act as precursors substances of eicosanoids. The end stage production of eicosanoids are prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and lipoxins. Pro-inflammatory molecules which could be activated in stress conditions are cytokines (12).

As a lipid group, prostaglandins (PG) have effects on processes such as inflammation and the regulation of multiple functions of immune cells (13). Based on the organ or tissue, the binding receptors and the physiological situation can be different. PG contribute to the maintenance of homeostasis in both organs and tissues and participate in an alert system leading to responses such as pain and inflammatory symptoms. The target injured tissue, PG plasma concentrations and subtypes, genetic alterations, and the various intracellular signaling pathways are among the factors that have an impact on tumor regression or cancer expansion (14, 15). Thromboxanes (TX) are another type of cytokine that causes platelet aggregation as well as vaso- and bronchoconstriction in mammals (16). These physiologically active molecules derived from arachidonic acid (AA) and are effective in the cyclooxygenase pathway in human platelets. Moreover, TX plays a role in a variety of pathophysiologic events, including primary hemostasis, atherothrombosis, inflammation, and cancer (16, 17). LT are biologically active lipid mediators derived from the oxidative metabolism of the omega-6 polyunsaturated fatty acid arachidonic acid (18). Increased levels of leukotrienes have been linked to a variety of inflammatory diseases, because leukotrienes and their synthesis enzymes play an important role as immunological modulators (19). Leukotrienes may interact with a range of tissue cells, contributing to metabolic diseases, as well as cancer. Leukotriene signaling is involved in the active tumor microenvironment, which promotes tumor development and immunotherapy resistance (20, 21). Lipoxins can prevent new neutrophils from entering and encourage macrophages to remove apoptotic neutrophils (22).

Along with immune system activation, these mediators engage in with a positive feedback cycle. Under hypercytokinemia phases, body tissues and organ damages caused by cytokines will be unavoidable (19). In these circumstances Eicosapentaenoic acid (EPA) fatty acids have

significant effect on reducing cytokines levels and repressing ubiquitin-proteasome pathway - the primary mechanism in which protein catabolism occurs in cytosol and nucleus (23). Activating the production of reactive oxygen species (ROS) and other toxic supplies of lipid peroxidation is another effect of PUFAs documented as a cytotoxic effect of PUFAs (24). Responding to the different situations, inflammatory or anti-inflammatory mediators can be produced by various pathways (25).

Among these mediators anti-inflammatory ones are derived from omega-3 fatty acids such as α-linoleic acid (ALA) and EPA. In contrast to anti-inflammatory mediators, pro-inflammatory substances are generated from omega-6 fatty acids, including AA. Since many enzymes (e.g. desaturase and elongase enzymes) are common between omega-3 and omega-6 fatty acids, plasma levels of these fatty acids have a significant role in leading metabolism to an inflammation status or protect body via anti-inflammatory mediators (6).

Cancer cachexia is a main outcome which should be taken serious throughout the treatment. This syndrome qualifies by an ongoing weight loss and anorexia, feeling of weakness in many cases, suppressions in immune system and imbalances in fluid and energy (26).

Along with these events, as a result of enhancement in the rate of lipolysis, mass of adipose tissue decreases. The mechanism underlying this can be described as the rises in the levels of lipid-mobilizing factor (LMF) and proteolysis-inducing factor (PIF). Cancer tumor cells secrete these factors resulting in wastages of fat and muscle masses; LMF can cause this effect by directly stimulating lipolysis in adipocytes, the same process of lipolytic hormones. On the other hand, PIF activation lessens protein synthesis and promotes protein degradation, as well, which these two develop muscle atrophy (6, 27, 28).

However along with decreases in lipoprotein lipase (LPL) activation, browning of white adipose cells has been suggested to be another possible mechanism responsible for cancer cachexia complications. An event in which by expressing of the uncoupling protein 1 (UCP1), energy expenditure promotes and weight loss appears as a sequence. According to some of recent research (27, 29, 30), UCP1 can be effected by environmental factors (e.g. medicines) and inflammatory mediators (e.g. interleukin-6 (IL-6)).

Nutritional habits and constituents are among the most important factors related to a broad range of noncommunicable diseases such as cardiovascular disease (CVD) and cancer. Thus, as it has been shown in multiple studies, food habits and choices play a crucial role in prevention or deteriorating these conditions (31-34). Progressing of cancer is a multistage process effected by many factors such as our daily intakes. Moreover, scholarly works have demonstrated the correlation between dietary fatty acids and several forms of cancer. Based on the WHO latest guidelines, in order to prevent chronic diseases such as cancer, intakes of saturated fatty acids should be limited and substituted with unsaturated fats. In order to reach this aim, consumption of animal proteins especially red meat and high fat dairy products should be limited (35).

However, in 2015, Hodge and colleagues (36) demonstrated a positive association between the risk of colorectal cancer (CRC) and SFA intakes. Furthermore, the risk of rectal cancer remains stronger comparing to cancers in the colon by high consumptions of MUFAs and SFAs. Approving these data, Jackson et al. (37) indicated an inverse relation between plasma levels of palmitic acid and the risk of prostate cancer in 435 participants (209 cases vs. 226 controls). Although due to this study consumption of SFAs can increase the risk of cancer, the direct effect of SFAs on cancer still is unknown.

Including in a variety animal oils, vegetable oils, and marine oils, recent data suggested controversial effects of palmitoleic acid (omega-7 MUFA). Although anti-inflammatory, lipid-modulating and improving insulin sensitivity effects were shown in some studies (38-40), the relation between palmitoleic acid and cancer remains unclear. In a case-control study conducted with 426 cases and controls, a positive

association between higher concentrations of palmitoleic acid in subcutaneous adipose tissue and risk of colorectal cancer (CRC) was indicated (41). However, considering avocado as the leading dietary source of this fatty acid in some populations, data could be different. In the case-control study performing in Jamaica, there was not a relation between palmitoleic acid and prostate cancer (37).

As the PUFAs follow different pathways and result in the two main inflammatory and anti-inflammatory mediators, the effect of them will be opposite. While omega-3 FAs have protective influences against cancer, omega-6 FAs increase inflammatory mediators (42).

Omega-6 FAs are one of the main groups of PUFAs which first convert to AA, and then end up with mostly pro-inflammatory metabolites (e.g. PGE2) (19). All these pathways and reactions can deteriorate patient's condition. Higher concentrations of dihomo-γ-linolenic acid in tissues were illustrated to be related with increased risk of cancer. The reverse impact of omega-6 fatty acids on individuals with advanced prostate cancer, gastric adenocarcinoma, colorectal cancer (CRC), and colorectal adenoma (41).

In addition, considering AA and other omega-6 FAs such as adrenic acid as the precursor for following pro-inflammatory mediators or accelerating tumor boosting, the low levels of these FAs could be explained. Schumacher et al. displayed a significant decreased levels of omega-6 FAs (AA and adrenic acid) in prostate cancer tissues (43).

Omega-3 FAs have opposite effect of omega-6 FAs with both providing anti-inflammatory metabolites, and reducing pro-inflammatory mediators via preventing pathways such as AA conversion to leukotrienes (6). Investigations on omega-3 FAs and risk of different types of cancer show these protective characteristics (42).

Dietary intakes of omega-3 FAs via consuming fish or taken as supplements may have the same effect over an extensive diseases including cancer. Intakes of EPA and Docosahexaenoic acid (DHA) are in an inverse relation with endometrial (44), CRC (36), breast (45) and liver (46) cancers. The enzymes responsible for transforming ALA into EPA and DHA overlap with the metabolic pathways of arachidonic acid and linoleic acid. This implies that these pathways compete with each other, as discussed in earlier sections. Phospholipase A2 cleaves membrane phospholipids in inflammatory processes, releasing AA into the cytoplasm and triggering the formation of highly inflammatory eicosanoids by cyclooxygenases and lipoxygenases. The switch from an omega-6 to an omega-3 PUFA profile in the membrane lipid composition is critical because it boosts the generation of omega-3-derived mediators like thromboxane A3 and prostacyclin I3, which are weaker inflammatory inducers (47). Moreover, EPA and DHA supplementation are frequently used in the nutritional therapy of cancer patients, and they produce favorable effects during cancer treatment due to membrane regulation, according to a review article (48).

In order to decrease the risk of cancer many guidelines suggest to reduce the intake of processed products of red meat which contain saturated and monounsaturated fatty acids and add fish and marine products to improve the intake of omega-3 FAs. This changes in meal plan can diminish the risk of CRC cancer (36). The protective effects of omega-3 FAs have been demonstrated in breast cancer (49). Moreover, EPA reduced the risk of NPFCs (nonproliferative fibrocystic conditions) and risk of breast cancer (45). Some studies suggest the beneficial effects of fish oil supplementations (> 3 g per day) or EPA/DHA (> 1 g EPA and > 0.8 g DHA per day) as a contributory support along with chemotherapy treatment (50).

Reduced levels of the omega-3: omega-6 fatty acid ratio have been linked to an elevated risk of liver cancer. The balance can be adjusted by enhancing the consumption of foods abundant in omega-3 fatty acids, a pattern observed in populations with high fish intake, such as Japan (46). Similar to the ratio of serum levels of these fatty acids, the ratio driven from subcutaneous adipose tissue concentrations can be

used to assess the risk of cancers (41). The same results were found in other case-control studies, indicating that high erythrocyte membrane levels of AA and EPA have a significant positive and inverse (respectively) relation with the risk of colorectal adenomas (51).

Furthermore, beyond demonstrated beneficial outcomes such as protective effects, dietary intakes of omega-3 FAs improve the quality of life in many patients. For most patients, cancer cachexia, excessive weight loss along with chemotherapy reduce quality of life. Thus, enhancing these symptoms can be so effective as well (52).

Other group of fatty acids in our diets basically are came from industrial sources, called as trans-fatty acids (TFAs). High consumption of processed foods increases the intake of TFAs, and increased intake of TFAs leads to health complications (e.g., CVDs, cancer, obesity) or even interference with essential fatty acids (competing with EFAs for the reaction enzymes, which results in less conversion of EFAs to needed metabolites) (11). One of the most common outcomes of TFAs is gaining weight and cause overweight or obesity especially among women (53, 54) which indirectly increases the risk of cancer. In addition, studies observed a positive relation between TFAs and cancer mortality which the possible mechanism could be via raising colonic mucosa irritation (55). However, the amount of intake influences the outcomes and makes the deductions contradictory. Although the positive association of high consumption of TFAs with colorectal cancer has been shown in many studies (56-58), according to study of Vinikoor et al. (59), intakes within energy limitations for FAs was not related to increased risk of colon cancer.

1.2. Ketogenic Diet

In recent years, beneficial effects of ketogenic diets (KD) have become one of the disputing subjects in oncology. The ketogenic diet (KD), which is characterized by high fat intake, very low carbohydrate consumption, and sufficient protein levels, has demonstrated antitumor effects by diminishing the energy supply to cells (60). This diet is contraindications for cancer patients with cardiomyopathy, liver diseases, kidney and pancreas complications. On the other hand, cancer patients mostly take multiple therapies which could interact with micronutrients intakes and KD can amplify this situation (e.g. long term KD has been correlated with calcium deficits) (61).

Beyond unwanted side effects of KD, this diet can be useful in many patients and increases their life quality. As one of the common points in many studies, KD can be well tolerate in cancer patients. At the same time, a ketogenic diet (KD) helps maintain a stable lipid serum profile, including total triglycerides, cholesterol, HDL, and LDL. Additionally, it enhances insulin requirements in patients while boosting the tumor response to chemotherapy (62, 63).

Most of studies applied an average carbohydrate restriction of 20 - 70 gr per day over a period of time between 12 and 16 weeks to assess the outcomes of KD (62, 63). Concluding from the studies the direct effect of KD still remains obscure based on the differences between cancer types and individuals. And in order to add the KD as a contributory treatment to protocols further studies are required (64).

2. CONCLUSION

In conclusion, this paper has highlighted the diverse roles of dietary fatty acids based on their chemical structures, including saturated fats (SFAs), monounsaturated fats (MUFAs), and polyunsaturated fats (PUFAs), in various pathways within the human body. Notably, their involvement in pathways associated with inflammation is of significant importance, particularly concerning chronic diseases such as cancer, as evidenced by numerous studies.

While previous guidelines have focused on establishing upper limits for fatty acid intake, recent evidence underscores the critical importance of considering the types and ratios of these fatty acids. Emphasizing an increased omega-3: omega-6 ratio, achieved through the consumption of omega-3 fatty acid-rich foods like fish, flaxseed oil, walnuts, and

certain algae, in comparison to omega-6 fatty acid sources such as safflower oil and sunflower oil, has shown promise. This approach is particularly relevant in assessing the risk of cancer, where modulation of inflammation pathways, cell proliferation, angiogenesis suppression, and increased apoptosis may play crucial roles.

Furthermore, leveraging the insights from the 'Warburg Effect' and implementing a balanced diet or a ketogenic diet (KD) for cancer patients can serve not only as a supplementary treatment alongside chemotherapy but also as a means to address cancer -related complications, notably cancer cachexia. This dual benefit has the potential to enhance the overall quality of life for cancer patients, impacting emotional well-being positively. Ultimately, such improvements in life quality can complement primary treatments, contributing to a more holistic approach to cancer care.

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