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Role of polyunsaturated fatty acids in cancer prevention

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ABSTRACT

Polyunsaturated fatty acid omega-3 intake from fish or supplements has been studied related to reducing the risk of cancer (especially breast, colon, and prostate cancer) and other conditions with an inflammatory component. The beneficial action of eicosapentaenoic acid and docosahexaenoic acid has been attributed to the displacement of arachidonic acid from the cell membrane phospholipid and to the formation of less proinflammatory prostaglandins and leukotrienes from them. It is important to note that arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid could raise anti-inflammatory molecules such as lipoxins and resolvins. This suggests that polyunsaturated fatty acids form precursors to both pro- and anti-inflammatory molecules, and the balance between these mutually antagonistic compounds could determine the final outcome of the disease process. As a higher ratio of omega3/omega6 is desirable in reducing the risk of cancer and other chronic diseases, we believe that each population should be evaluated for the optimal omega3/omega6 ratio, taking into

RESUMEN

El consumo de ácidos grasos poliinsaturados (AGPI) ω3 proveniente del pescado o de suplementos ha sido estudiado por su relación con un menor riesgo de cáncer (especialmente de mama, colon y próstata) y otras condiciones con componentes inflamatorios. La acción benéfica del ácido eicosapentaenoico (EPA) y el ácido docosahexaenoico (DHA) ha sido atribuida al desplazamiento del ácido araquidónico (AA) de la membrana fosfolipídica y a la formación de prostaglandinas (PG) y leucotrienos (LT) con menor actividad proinflamatoria. Es importante resaltar que el AA, EPA y DHA pueden incrementar moléculas antiinflamatorias como lipoxinas y resolvinas. Esto sugiere que los AGPI forman moléculas tanto proinflamatorias como antiinflamatorias, y el balance entre estas moléculas antagoniza componentes que pueden determinar el resultado final de los procesos relacionados con la enfermedad. Una relación de ω3/ω6 es óptima para reducir el riesgo de cáncer y otras enfermedades crónicas. Nosotros consideramos que cada población debe evaluar la relación óptima de ω3/ω6 tomando en

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account the importance of obtaining them from secure sources and having a healthy lifestyle. Further research in this area is needed to assess the impact of nutritional factors for the development of cancer and other chronic diseases.
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cuenta la importancia de obtenerlos de fuentes seguras y tener un estilo de vida saludable. Sin embargo, son necesarios más estudios en esta área para medir el impacto de los factores nutricionales en el desarrollo del cáncer y otras enfermedades crónicas.

Palabras clave: Ácidos grasos poliinsaturados. Cáncer. Ácido eicosapentaenoico. Ácido docosahexaenoico. Ácido araquidónico.

BACKGROUND

The interaction of genetics and environment is the foundation for all health and disease. In the last two decades, using the techniques of molecular biology, it has been shown that genetic factors determine susceptibility to disease, and environmental factors determine which genetically susceptible individuals will be affected. It is already known that nutrition is an environmental factor of major importance. Using the tools of molecular biology and genetics, research is defining the mechanisms by which genes influence nutrient absorption, metabolism and excretion, taste perception, and degree of satiation, and the mechanisms by which nutrients influence gene expression[1].

One of the diseases caused by the interaction of environment and genetic factors is cancer, characterized by the increased proliferation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs (metastasis)[2].

Cancers count among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012[3], and the number of new cases is expected to rise by about 70% over the next two decades. In men, the five most common types of cancer diagnosed in 2012 were lung, prostate, colorectal, stomach, and liver cancer; while in women the most common types diagnosed were breast, colorectal, lung, cervix, and stomach cancer[2].

About 30% of cancer deaths are due to the five leading behavioral and dietary risks: high body mass index (BMI), low fruit and vegetable intake, lack of physical activity, and tobacco and alcohol use[2].

In Mexico, about 12% of the deaths per year are due to cancer[4], representing one third of the death causes[5], and it has been estimated that each year 128,000 new cases will be detected[6]. On the other hand, Mexico is one of the countries with the highest prevalence of obesity (37.5% of women and 26.8% of men), which has been considered as one of the major risk factors for cancer development[7], mainly esophageal, colorectal, breast, endometrium, and kidney[8].

Another risk factor closely related with obesity is diet. It has been estimated that 30-40% of all cancers can be prevented by appropriate diet, physical activity, and maintenance of appropriate body weight[9], but for some individual cancers, the percentage could rise[10].

Unraveling the linkage between diet and cancer is complex because thousands of dietary components are consumed each day. A typical diet may provide more than 25,000 bioactive food constituents and assessing intakes of some constituents is difficult due to wide variations in the amounts of bioactive components within a particular food. Moreover, dietary constituents are able to modify multiple processes in both normal and cancer cells[11], for example: diets high in vegetables, fruits, and omega-3 (ω3) fatty acids may have a protective effect against different types cancers; conversely, excess consumption of red and processed meat may be associated with an increased risk[8].

Some fundamental cell processes attached to diet, such as DNA repair, carcinogen metabolism, cell

proliferation, cell cycle, hormonal regulation, apoptosis, inflammation and immunity, and cell differentiation, among others, may promote or inhibit cancer development and progression, supporting the relation between nutrition and cancer[11].

Leading the inflammation process (also present chronically in obesity), it is well known that the functions of the cells involved are dependent on nutrition and diet, with the polyunsaturated fatty acids ω6 and ω3 being those which most determine their functions.

Omega-3 fatty acids, such as α-linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), have been shown in animal studies to protect from cancer, while omega-6 (ω6) fatty acids, such as linoleic acid (LA) and arachidonic acid (AA), have been found to be cancer-promoting fats[10].

POLYUNSATURATED FATTY ACIDS IN DIET

In dietary terms, problems began since industrialized societies were characterized by an increase in energy intake and decreased energy expenditure, and also increased intake of saturated fat, ω6 fatty acids, and *trans* fatty acids and decreased ω3 fatty acids, fruits, vegetables, complex carbohydrates, fiber, and antioxidants[1].

The increase in *trans* fatty acids is detrimental to health; they can interfere with the desaturation and elongation of both ω6 and ω3 fatty acids, thus further decreasing the amount of AA, EPA, and DHA availability for human metabolism[1]. The beneficial health effects of ω3 fatty acids, EPA and DHA, were described first in the Greenland Eskimos who consumed a high seafood diet and had low rates of coronary heart disease, asthma, type 1 diabetes mellitus, and multiple sclerosis. Since that observation, the beneficial health effects of ω3 fatty acids have been extended to include benefits related to cancer prevention and treatment, inflammatory bowel disease, rheumatoid arthritis, and psoriasis[12].

It has been argued that the fall in the intake of biologically active ω3 fatty acids, especially that of EPA and DHA, has been one of the major changes in Western diet in the last 50 years, and it has contributed to the increasing incidence of cancer[13].

Pre-civilized man is estimated to have had a ω3/ω6 intake ratio of 1/1. The average Japanese diet has a ω3/ω6 ratio of 1/4[14]. By contrast, Americans consume a daily average of 13-15 g of ω6 for a ω3/ω6 intake ratio of approximately 1/10[15], but it has been estimated that Western diet has a ratio of 1/15-1/20[1].

Omega-3 intake from fish or supplements has been studied related to reducing the risk of cancer (especially breast, colon, and prostate cancers) and other conditions with an inflammatory component[15-18].

METABOLISM OF POLYUNSATURATED FATTY ACIDS

Polyunsaturated fatty acids (PUFA) are fatty acids with at least two carbon-to-carbon double bonds in the hydrocarbon chain. There are at least four independent families of PUFAs, depending on the fatty acid from which they are synthesized. They include: the ω3 series derived from ALA (18:3, ω3); the ω6 series derived from *cis*-LA (18:2, ω-6); the ω9 series derived from oleic acid (18:1, ω-9); and the ω7 series derived from palmitoleic acid (16:1, ω7)[13]. The PUFAs ω3 and ω6 are considered as essential fatty acids because humans, like all mammals, cannot synthetize them and must obtain them from diet[1].

Linoleic acid is converted to γ-linoleic acid (GLA, 18:3, ω6) by the action of the enzyme Δ6 desaturase (d-6-d). Then GLA is elongated to form dihomo-GLA (DGLA, 20:3, ω6), the precursor of the series-1 of prostaglandins (PG). Dihomo-GLA can also be converted to AA (20:4, n-6) by the action of the enzyme Δ5 desaturase (d-5-d). Arachidonic acid forms the precursor of series-2 of PGs, thromboxanes (TXA) and the series-4 of leukotrienes (LT). Related to ω3 metabolism, ALA is converted to EPA (20:5, n-3) by d-6-d and d-5-d. Eicosapentaenoic acid forms the precursor of the series-3 of PGs and the series-5 of LTs (Fig. 1). The LA, GLA, DGLA, AA, ALA, EPA, and DHA (22:6, ω3) are all PUFAs, but only LA and ALA are essential fatty acids. Both AA and EPA also give

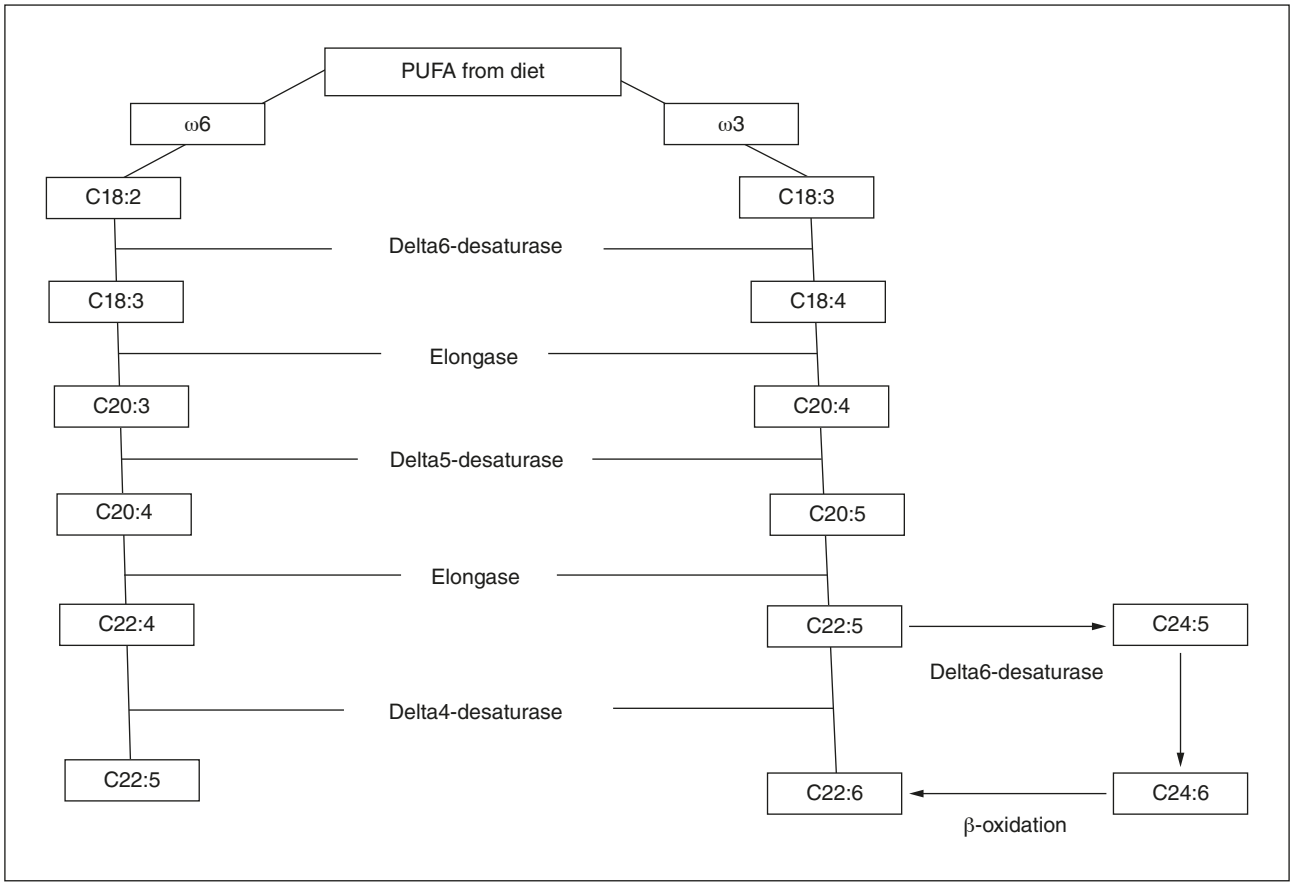

Figure 1. Metabolism of ω6 and ω3 polyunsaturated fatty acids (elongation and desaturation). Metabolism of ω6 and ω3 polyunsaturated fatty acids (elongation and desaturation). PUFA: polyunsaturated fatty acid; C18:2: linoleic acid; C18:3: γ-linoleic acid; C20:3: dihomo-γ-linoleic acid; C20:4: arachidonic acid; C22:4: docosatetraenoic acid; C22:5: docosapentaenoic acid; C18:3: α-linoleic acid; C18:4: stearidonic acid; C20:4: arachidonic acid; C20:5: eicosapentaenoic acid; C22:5: docosapentaenoic acid; C22:6: docosahexaenoic acid; C24:5: pentaenoic fatty acid; C24:6: pentaenoic fatty acid[39].

rise to their respective hydroxy acids, which in turn are converted to their respective LTs. Both PGs and LTs have proinflammatory action, and are known to be involved in various pathological processes, such as atherosclerosis, bronchial asthma, inflammatory bowel disease, and cancer, among others[19-24].

The beneficial action of EPA and DHA when supplemented from external sources has been attributed to the displacement of AA from the cell membrane phospholipid and to the formation of less proinflammatory PGs (such as PGE3 and PGF3α), TXA3, and LTs (such as LTB5, LTC5, and LTD5) from them, and hence a favorable response. It is interesting to note that AA, EPA, and DHA could give rise to anti-inflammatory molecules such as lipoxins and resolvins. Both lipoxins and resolvins suppress inflammation and help in the resolution of inflammatory events, including leukocyte infiltration and clearance of the cellular debris from the site of inflammation. This suggests that PUFAs form precursors to both pro- and anti-inflammatory molecules, and the balance between these mutually antagonistic compounds could determine the final outcome of the disease processes[13].

FOOD SOURCES OF POLYUNSATURATED FATTY ACIDS

The main food sources of essential fatty acids are: for LA, cereals, eggs, poultry, most vegetable oils, whole-grain breads, baked goods, margarine,

sunflower, saffola, and corn oils; and for ALA, canola oil, flaxseed oil, linseed and rapeseed oils, walnuts, and leafy green vegetables such as purslane[25] (Table 1). The average daily intake of PUFAs varies from country to country; however, in general, the intake is around 7-15 g/day in Europe and USA[20,22]. Fresh cow's milk contains small amounts of GLA (0.25% of the total fats). Evening primrose oil, borage oil, black currant oil, and hemp seed oil contain substantial amounts of GLA. GLA is present in evening primrose oil at concentrations of 7-14% of total fatty acids; in borage seed oil it is 20-27%, and in black currant seed oil at 15-20%. Gamma-linoleic acid is also found in some fungal sources[26,27]. Meat, egg yolks, some seaweeds, and some shrimps contain substantial amounts of AA[28]. The average daily intake of AA is estimated to be about 100-200 mg/day[29], more than enough to account for the total daily production of various PGs, which is estimated to be about 1 mg/day. The major source of EPA and DHA in the diet is from marine fish such as tuna, trout, and salmon. Fresh water fish are unlikely to contain substantial amounts of EPA and DHA. It is important to note that because of their instability, substantial loss of PUFAs occurs during food processing and hydrogenation[30,31].

Table 1. Food sources of essential fatty acids

Food sources of EFA	
ω6 Fatty acids	ω3 Fatty acids
Cereals	Canola oil
Eggs	Flaxseed oil
Poultry	Linseed oil
Vegetable oils	Rapeseed oil
Whole-grain breads	Walnuts
Baked goods	Purslane
Margarine	Marine fish (main source of EPA and DHA)
Sunflower oil	
Saffola oil	
Corn oil	

EFA: essential fatty acids; ω6: omega-6; ω3: omega-3; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

MECHANISM OF ACTION OF POLYUNSATURATED FATTY ACIDS IN CANCER

Although fatty acids are consumed at high levels in typical Western diets, tumor cells display a strong dependence on *de novo* fatty acid synthesis. The increased proliferation and metabolism of cancer cells could be the trigger for the abnormal requirement for fatty acids compared to normal cells. Data from several preclinical studies suggest that ω3 PUFAs can exert an antitumor effect through various molecular interactions that inhibit cellular proliferation and promote cell death. Dietary PUFA can influence the fatty acid composition of glycerophospholipids in cell membranes; DHA, for example, inserts into the phospholipid cell membrane, thereby altering permeability, cell elasticity, and the function of many membrane embedded receptors and proteins. Additionally, attenuation of inflammatory pathways and activation of the peroxisome proliferator-activated receptor γ (PPARγ) have recently been implicated[32,33].

It has been established that ω3 can suppress the development of cancer by inhibiting cellular proliferation and inducing cell death[34]. *In vitro* studies that elucidate the effects of ω3 on murine and human breast cancer cells provide important insights into the mechanisms underlying the inhibition of tumorigenesis. Alteration of the lipid membrane by ω3 and the related disruption of proinflammatory eicosanoid synthesis by the cyclooxygenase 2 and lipoxygenase enzymes has recently been demonstrated in mouse and human breast cancer cell lines[35-38].

Biologic effects of ω3 also include decreased production of prostaglandin E2 metabolites, thromboxane A2 (platelet aggregation), leukotriene B4 (leukocyte chemotaxis and adherence), and decreased release of inflammatory cytokines, including interleukin B1 and platelet-derived growth factor[39]. By reducing prostaglandin synthesis, EPA and DHA may reduce aromatase activity, local estrogen synthesis, and estrogen-related signaling[40]. Both EPA and DHA have PPARγ agonist activity and promote differentiation and apoptosis through enhanced lipid peroxidation, mitochondrial calcium homeostasis, and increased p53 expression, and through enhancing the downregulating activation of nuclear factor kappa B (NF-κB), and repressing the expression of NF-κB-targeted genes[41]. They also increase adiponectin secretion (at least in obese animal

models) and reduce proliferation and signaling through the extracellular signal regulated kinases (ERK) as well as phosphatidylinositol 3 kinase (PI3K) pathways[42,43]. Insulin resistance in obese animal models is reduced through attenuation of NF-κB signaling and upregulation of insulin sensitivity related genes GLUT 4 and IRS-1[44]. Looking at the biologic pathway modulation observed in predominately preclinical studies, one would expect to see prevention of tumors where inflammation plays a role in promotion or progression.

POLYUNSATURATED FATTY ACIDS AND BREAST CANCER

Breast cancer (BC) remains one of the commonest cancers (one in eight women will be diagnosed with BC in her lifetime[45]) and a leading cause of death from cancer. One of the crucial gaps identified is how to implement a sustainable and preventive lifestyle strategy[46]. Both risk factors and protective factors must be considered. Some risk factors, such as genetic predisposition, cannot be modified, whereas others (unhealthy diet, sedentary lifestyle) can be avoided[45].

There are strong links between environmental/lifestyle factors and BC, suggesting that modifying these factors may result in decreasing BC risk.

For instance, dietary fats have been extensively studied in the prevention of BC, where marine ω3 fatty acids may be protective[47].

Now there are several studies that have tested the relation between BC and PUFAs. Except for the study by London, et al.[48], all of these studies found an association between a higher ratio of ω3 to ω6 fats and reduced risk of BC. Long chain ω3 and ω6 have a different effect on the breast tumor suppressor genes *BRCA1* and *BRCA2*. Treatment of BC cell lines with ω3 (EPA or DHA) results in increased expression of *BRCA1* and *BRCA2* genes, while AA had no effect[49].

In another study included 35,000 postmenopausal women in the vital cohort, who completed a baseline food frequency questionnaire and questions on supplement use and risk factors for BC and were then followed for a median of six years. A 32% reduction in breast cancer risk was observed in current fish oil users after adjustment for other factors[50].

In a meta-analysis of 21 independent prospective cohort studies, Zheng, et al. found a significant reduction of BC risk with marine ω3[51]. However, this meta-analysis highlights the difficulties in assessing the effects of specific dietary fats on BC risk. In subgroup analyses, Zheng, et al. found that the inverse associations between marine ω3 and BC risk were significant only in postmenopausal women, were stronger in East Asian populations compared with western populations, and were more evident without adjustment for BMI. This suggests that marine ω3 may influence BC risk partly through an effect on BMI or related factors (insulin or adipokines), whereas the importance of BMI on BC risk during the premenopausal and postmenopausal periods is still a matter of controversy[6]. It has long been suspected that ω6 increases the risk of cancers, and this has been confirmed in controlled trials in which ω6 intakes were modified. In the Los Angeles Trial, there were more cancers in the experimental group with high ω6 intake, whereas in the Lyon Diet Heart Study, there were fewer cancers in the group with low ω6[52,53]. Thus, when analyzing the associations between ω3 and BC risk, it is crucial that ω6 is included in the analyses[54].

Yang, et al. used the ratio of ω3/ω6 in a meta-analysis comprising 274,135 women with a total of 8,331 BC events from 11 independent prospective studies[54]. Women with a higher ω3/ω6 ratio had a significantly lower risk of BC (relative risk: 0.90; 95% CI: 0.82-0.99). When the authors analyzed only dietary intake, they found a 6% reduction in BC risk per one tenth increment of the ω3/ω6 ratio.

Studies support an association between endogenous sex hormone levels and BC risk for postmenopausal women, whereas the association is less clear for premenopausal women[55]. One possible explanation is that the high estrogen levels present before menopause increase blood marine ω3[56], which in turn may partly counteract the effect of estrogens as marine ω3 are protective[51,54,57].

The accumulated evidence shows that in addition to genetic predisposition and estrogen exposure, a number of lifestyle, environmental, and pharmacological

factors play an important role in BC risk and BC survival. Optimal physical activity decreases insulin resistance, diabetes risk, and the risk and progression of BC[58]. To reduce insulin resistance and diabetes, which are associated with an increased BC risk, women should increase their consumption of ω3 and fiber and favor low glycemic index foods. In addition, organic foods have been shown to contain more polyphenols and have a higher ω3/ω6 ratio than non-organic foods. As a higher ω3/ω6 ratio has been associated with decreased BC risk, consumption of organic foods may be beneficial.

Regarding BC specifically, the Guidelines state, "the best advice to reduce the risk of breast cancer is to engage in regular, intentional physical activity; to minimize lifetime weight gain through the combination of caloric restriction (in part by consuming a diet rich in vegetables and fruits) and regular physical activity; and to avoid or limit intake of alcoholic beverages"[59].

Additionally, treatment of estrogen receptor (ER)-positive and ER-negative human BC cell lines with both EPA and DHA was found to induce apoptosis and decrease cell viability[60]. This was paralleled by decreased or absent expression of Bcl2 and increased procaspase 8 expression in the EPA and DHA treated versus control cells. Bcl2 is a key apoptosis regulator protein and its overexpression has been implicated in a number of cancers. Cleavage of procaspase 8 amplifies the caspase cascade thereby promoting apoptosis. Interestingly, Corsetto, et al. also demonstrated inhibition of epidermal growth factor receptor (EGFR) activation by DHA and EPA, as well as a slight reduction in EGFR expression as a result of DHA exposure. EGFR is overexpressed in a number of malignancies, including BC, and promotes cell growth and migration via several downstream signaling proteins. Adding to these findings, the treatment of ER-negative human BC cells with DHA was shown to induce apoptosis via increased caspase 3 activity[61]. Additionally, DHA attenuated the migratory ability of these cells, suggesting that DHA may also prevent tumor cell invasion.

Docosahexaenoic acid has also been shown to increase intracellular reactive oxygen species (ROS) in ER-positive BC cells[62]. Kang, et al. demonstrated DHA induced ROS accumulation, leading to caspase 8 activation and resultant apoptotic cell death. This cytotoxic effect was abrogated by pharmacologic inhibition of specific caspases and knockdown of caspase 8 by small interfering RNA transfection. Therefore, EPA and DHA appear to exert their antitumor effects via multiple mechanisms including disruption of the cell membrane and embedded receptors, alteration of signaling pathways that are involved in cellular proliferation and migration, dysregulation of apoptosis, and the production of cytotoxic oxidating molecules[62].

POLYUNSATURATED FATTY ACIDS AND COLON CANCER

Although data related to PUFAs and their role in colon cancer (as in the other types of cancer) seems to have inconsistent results, is has been reported that ω3 can inhibit the growth of primary tumors and could be an effective preventive strategy for recurring colorectal cancer[63]. Also, a study showed that EPA inhibits human HT-29 colon cancer cell growth by PPARγ activation[64], which induces apoptosis through its activation in these cells[65].

Chamberland and Moon evaluated in *in vitro* studies whether ALA may downregulate malignant potential in human (HT29 and HCT116) and mouse (MCA38) colon cancer cell lines and they observed that treatment with 1-5 mm of ALA inhibits cell proliferation, adhesion, and invasion in both human and mouse colon cancer cell lines. Also, they observed that ALA did not decrease total colony numbers when compared to control, but they found that size of colony was significantly changed by ALA treatment when compared to control in all colon cancer cell lines. They suggest that these data enhance the current knowledge of ALA's mechanism and provide crucial information to further the development of new therapies for the management or prevention of colon cancer[66].

In spite of contradictions in the literature[67], it is generally thought that high calorie and fat intake are risk factors, especially in colon, breast, or prostate cancer development, and that ω6 (from plant oils

rich in LA) can promote inflammation and carcinogenesis[68]. Supplementation of diet with PUFAs can substantially influence cell physiology and cell kinetics, mostly by the modulation of oxidative metabolism and biosynthesis of PUFA metabolites. The particular species of free radicals affects specific phases of carcinogenesis in different ways[69]. The effects of ω6 PUFAs are primarily mediated by AA-derived eicosanoids. The anti-inflammatory and anticancer effects of nonsteroidal anti-inflammatory drugs, which function as specific inhibitors of AA metabolism, confirmed the significance of eicosanoids in cancer development[70,71].

On the other hand, there is more evidence that ω3 exerts anti-inflammatory properties, thus suppressing colon cancer[72-75]. Over the last years, these ω3 properties were confirmed by experiments with cell cultures and laboratory animals, using the introduction of a newly discovered gene encoding ω3 fatty acid desaturase, which is not normally present in mammals[76].

Nutritionally induced changes in fatty acid composition may result in an increased sensitivity to chemo- and radiotherapy and decreased undesirable side effects[77-79]. There is also evidence suggesting that ω3 may uniquely regulate stem cell signaling pathways and the increased sensitivity of colon cancer cells to chemotherapy by upregulation of colonic differentiation markers[80].

POLYUNSATURATED FATTY ACIDS AND PROSTATE CANCER

Both EPA and DHA are the major ω3 PUFAs that decrease the risk of prostate cancer[41], and also they have been shown to downregulate cell proliferation of these cancer cells.

Epidemiological data showed that consumption of fish is inversely associated with the incidence and mortality rates from prostate cancer, especially metastatic cancer[81,82]. It has been reported that serum EPA and DHA levels in patients with prostate cancer were lower than those of patients with benign prostate hyperplasia[83].

Many scientific reports confirm the health benefits from the consumption of fish and protective properties of ω3 in relation to prostate cancer. However, there are reports that indicate a relationship of the high consumption of fish with the risk of prostate cancer because of its way of processing and preservation. High susceptibility of PUFAs to oxidation changes and the technological fish processing (smoking, high-temperature cooking methods) contribute to the formation of many compounds, such as polycyclic aromatic hydrocarbons and heterocyclic amines, which may influence the formation of cancers, including prostate cancer. It is necessary to ensure an adequate amount of PUFAs in the diet through the consumption of proper quality fish and fish oils[84].

CONCLUSIONS AND RECOMMENDATIONS

Cancer incidence and mortality are high in the Western world and a high ω6/ω3 PUFA ratio in the Western diet may be a risk factor; the balance of ω6/ω3 fatty acids is an important determinant in decreasing the risk for cancer.

Both ω6 and ω3 fatty acids influence gene expression. There is evidence to suggest that ω3 PUFA has antiproliferative effects in cancer cell lines, animal models, and humans. Omega-3 PUFA may also regulate other metabolic process, including β-oxidation, cellular signaling of membrane-bound proteins, eicosanoid synthesis, and direct activation of nuclear receptor and transcription factor, all of which may influence the development and progression to cancer. Overall, there seems to be a potential for the mechanism mediating cancer prevention by ω3 PUFA. However, more studies are necessary that will provide knowledge about dietary intake ω6/ω3 ratio, and plasma levels should be determined before and after intervention.

Particular attention should be paid to the high susceptibility of PUFAs to the oxidative processes, and to the method of processing, preservation, and storage of the food with them. Also, pollution from the environment can significantly reduce the impact of health benefits of PUFAs.

There are many ranges of intake of ω3/ω6 considered as adequate, based on the degree of severity of disease. Meanwhile, a higher ratio of ω3/ω6 is desirable in reducing the risk of cancer and other chronic diseases. Since the evidence that a ratio of 1/2 (ω3/ω6) reduced colorectal cell proliferation whereas a ratio of 1/4 had no effect and a higher ratio in breast cancer was associated with decreased risk[1], we believe that each population should evaluate the ω3/ω6 optimal ratio.

Besides the importance of maintaining a balance in the intake of ω3/ω6 from secure sources (such as organic food), it is also important to highlight a healthy lifestyle to prevent all types of cancer. A healthy lifestyle includes an adequate intake of calories, five or more servings of vegetables a day, three or more of fruits, high intake of fiber, avoiding refined sugar, saturated fatty acids and red meat, being more active, and also keeping an emotional equilibrium[84].

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