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CLINICAL

Omega-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials

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Abstract Over the past decades, extensive studies have addressed the therapeutic effects of omega-3 polyunsaturated fatty acids (omega-3 FAs) against different human diseases such as cardiovascular and neurodegenerative diseases, cancer, *etc.* A growing body of scientific research shows the pharmacokinetic information and safety of these natural occurring substances. Moreover, during recent years, a plethora of studies has demonstrated that omega-3 FAs possess therapeutic role against certain types of cancer. It is also known that omega-3 FAs can improve efficacy and tolerability of chemotherapy. Previous reports showed that suppression of nuclear factor-κB, activation of AMPK/SIRT1, modulation of cyclooxygenase (COX) activity, and up-regulation of novel anti-inflammatory lipid mediators such as protectins, maresins, and resolvins, are the main mechanisms of antineoplastic effect of omega-3 FAs. In this review, we have collected the available clinical data on the therapeutic role of omega-3 FAs against breast cancer, colorectal cancer, leukemia, gastric cancer, pancreatic cancer, esophageal cancer, prostate cancer, lung cancer, head and neck cancer, as well as cancer cachexia. We also discussed the chemistry, dietary source, and bioavailability of omega-3 FAs, and the potential molecular mechanisms of anticancer and adverse effects.

Keywords Omega-3 FA · Cancer · Nuclear factor-κB · Clinical trials

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Abbreviations

FAs	Fatty acids
NF-κB	Nuclear factor-κB
COX	Cyclooxygenase
ALA	Alpha-linolenic acid
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
AA	Arachidonic acid
Bcl-2	B-cell lymphoma 2
LTA	Light transmission aggregometry
EQELS	Electrophoretic quasi-elastic light scattering technology

1 Introduction

Cancer is a global health problem which is defined as a large group of diseases involving uncontrolled growth of cells which can invade other parts and expand through the body [1]. It is classified according to the types of tumor cells into

five major groups including carcinoma (derived from epithelial cells), sarcoma (derived from connective tissue), lymphoma and leukemia (derived from hematopoietic cells), germ cell tumor (derived from pluripotent cells), and blastoma (derived from precursor cells) [2, 3]. Cancer is caused by both genetic and epigenetic alterations [4]. In other words, several factors influence the occurrence and progression of cancers, including inherited mutation, hormonal changes, alcohol consumption, smoking concomitant diseases, pollution, *etc.* [5–7]. A recent statistical report from the USA in 2014 shows that there are nearly 1,655,540 new cancer cases and the disease is responsible for about 585,720 deaths per year. Sex, age, and race can affect cancer incidence rate [8]. Due to unavailability and poor cost-effectiveness of cancer treatment strategies including surgery, chemotherapy, phototherapy, and radiotherapy, nowadays much attention has been paid to preventive strategies and the promising role of diet [9–12]. Furthermore, a plethora of adverse effects has been reported from chemotherapeutic drugs [13–17]. Several epidemiological studies indicated that high fish consumption is inversely correlated with incidence of certain types of cancer [18–22]. The therapeutic role of marine-based foods on cancer is approved by several experimental studies, which are performed on fish oil or its major active constituents omega-3 FAs [23, 18, 24–26].

The term "omega-3 FAs" refers to a group of polyunsaturated fatty acids which contain a double carbon–carbon bond at the third carbon atom (n-3 position) from the methyl end of the carbon chain [27]. Alpha-linolenic acid (ALA, 18-carbon unsaturated fatty acid obtained from plant sources), eicosapentaenoic acid (EPA, 20-carbon unsaturated fatty acid obtained from marine source), and docosahexaenoic acid (DHA, 22-carbon unsaturated fatty acid obtained from marine source) are well-known omega-3 FAs which play an important role in human physiology [28–30]. Our body has a limited ability to form EPA and DHA from ALA [31, 32]. This limited ability, however, may even become less efficient with age [33, 34]. Thus, omega-3 FAs must be primarily obtained from dietary sources [35–37].

The aim of this review article is to assess the most recent works on chemistry, dietary source, bioavailability, and available clinical data on the therapeutic role against certain types of cancer, molecular mechanisms underlying anticancer effects, ongoing and recruited clinical trials, and adverse effects of omega-3 FAs. It also discusses future directions on the applications of these interesting fatty acids.

2 Chemistry

Fatty acids (FAs) are the major group of primary metabolites that are synthesized from a two-carbon precursor, acetyl coenzyme A. The common feature of all FAs is that they possess a hydrophilic carboxylic acid group in one end and a long hydrophobic hydrocarbon-chain that ends with a methyl group. In their nomenclature, the methylene carbon next to the carboxyl is termed as the alpha (α) carbon while the methyl tail end is called the omega (ω) or n carbon (Fig. 1).

Depending on the presence and number of double bonds, fatty acids may be classified as saturated, unsaturated, or polyunsaturated. Saturated fatty acids such as butyric, lauric, myristic, palmitic, and stearic acids are common ingredients of foods and possess no double bond in their structure. Some FAs such as oleic acid have one double bond and, hence, are called monounsaturated, while those with more than one double bond are called polyunsatured FAs (PUFAs). Based on the number and location of the double bond with respect to either the ω-tail (n-tail) or the carboxyl head ends, unsaturated FAs can be described in two ways [38]. For FAs nomenclature based on the ω-end, the number of carbons in the FA is described first followed by the number of double bonds and then the position of the double bonds. For example, stearic acid with 18-carbon skeleton and no double bond is described as 18:0, while oleic acid with one double bond at position 9 is written as 18:1n-9. In an alternative FAs nomenclature, the carbon count starts from the carbonyl end and oleic acid can be presented as 18:1Δ9. The representation of some common FAs through these two nomenclatures are shown in Table 1. As shown in Table 1, omega-3 (ω-3, n-3) FAs are long-chain polyunsaturated FAs such as EPA, DHA, and ALA with the first of many double bonds begins at position 3 from the terminal methyl (ω or n) position. In contrast to omega-3 FAs, the other major group of PUFAs is the omega-6 (n-6) groups, such as linoleic (LA) and arachidonic acid (AA) (Table 1). In humans, LA is an essential FA and hence need to be taken from dietary sources such as vegetable and fruit/seed oil, animal fat, and dairy products. In contrast to LA, AA is not an essential FA in mammals and readily synthesized from LA and stored in large amount within the phospholipid layer of cell membranes. It is worth noting that AA is involved in various cellular functions including signaling processes and the immune response to a variety of stimuli [39, 40].

To date, the three most important omega-3 FAs are ALA, EPA, and DHA. The major sources of ALA are plant oils, while EPA and DHA are predominantly available in marine animals such as fish oils and other marine animal fats. The primary source of EPA and DHA, however, are marine algae

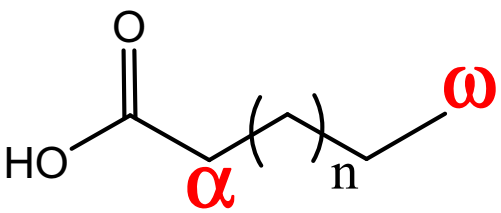
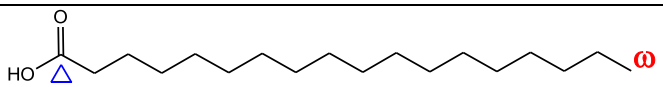
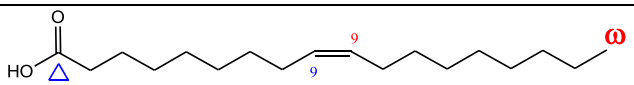
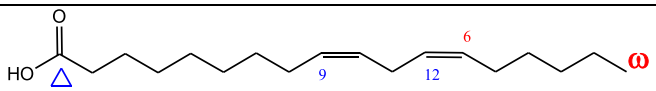
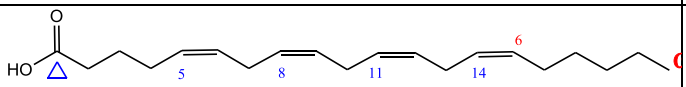
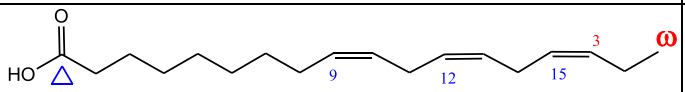
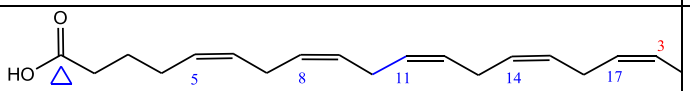
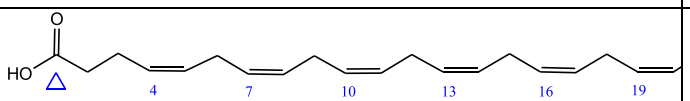
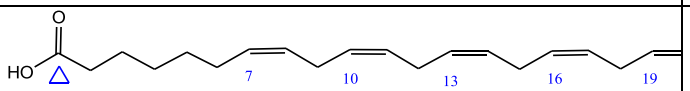


Fig. 1 General structure of FAs

Table 1 Structures of some common FAs and their nomenclatures

Nomenclature - Δ (carbonyl)-based	**Structure/Name**	**Nomenclature - ω-tail based**
18:0	 Stearic acid	18:0
18:1Δ9	 Oleic acid	18:1n-9
18:2Δ9,12	 Linoleic acid	18:2n-6
20:4Δ5,8,11,14	 Arachidonic acid	18:4n-3
18:3Δ9,12,15	 α-Linolenic acid	18:3n-3
20:5Δ5,8,11,14,17	 Eicosapentaenoic acid	20:5n-3
22:Δ4,7,10,13,16,19	 Docosahexaenoic acid	22:6n-3
22:Δ7,10,13,16,19	 Docosapentaenoic acid	22:5n-3

and the FAs appear to be accumulated in marine animals in higher trophic levels through the food chain [41]. The fourth omega-3 FA known as docosapentaenoic acid (DPA) is by far the least common constituent of the human diet and is known to be abundant in higher trophic marine animals, such as seals. Although the main commercial sources of omega-3 FAs are fish products, other sources including microalgae as the primary producers of EPA and DHA have been recognized only in recent years. A number of marine planktons with a promise of high omega-3 FAs yield have also been identified [42]. The production of omega-3 FAs in transgenic plants has further been described [43] suggesting that diversified sources of omega-3 FAs will be developed in the future.

3 Food sources

In human diets, omega-3 FAs are commonly bonded to fat structures and found as triglycerides [44–46]. These triglycerides contain a three-carbon glycerol structure esterified with three long-chain FAs [47, 38, 48]. Plant oils and fish are known as the main sources of omega-3 FAs in nature [49–51, 36]. It has been reported that plant oils are highly rich sources of ALA, whereas fish are known as highly copious sources of EPA and DHA. Among the plant oils, soybean oil (7.8 %), canola oil (9.2 %), and hemp oil (20 %) are known as the main herbal sources of ALA. In addition, flax, perilla, and chia are famed as other sources of ALA [52, 53]. Among the different species of fatty fish, mackerel (1.8–5.3 % weight), herring (1.2-3.1 % weight), and salmon (1.0–1.4 % weight) are known to contain EPA and DHA in large amounts [54, 52]. Pacetti *et al.* [54] found that the levels of fatty acids in the freshwater fish are higher than those of marine fish. This seems to be due to the different fatty acid composition of phytoplanktons in the freshwater and marine ecosystems. Moreover, the levels of EPA and DHA in marine phytoplankton are higher than those found in freshwater phytoplankton, but marine phytoplankton has lower levels of omega-6 FA. In addition to these findings, microalgae are known to be the other main source of omega-3 FAs. Currently, *Crypthecodinium cohnii* Javornicky and *Mortierella alpine* Peyronel are well-known microalga with DHA-rich oils [55]. It has also been reported that among the brown algae, the genus *Nannochloropsis* has higher levels of EPA [56].

Other dietary sources of omega-3 FAs such as nuts, seeds, vegetables, and some fruit, egg yolk, white and red meats contain minor quantities of omega-3 FAs [57, 58]. For example, among nuts, beechnuts (1.7 g ALA), butternuts (8.7 g ALA), and walnuts (3.3-6.8 g ALA) are the most common sources of ALA [59]. Moreover, fungi are other possible sources of omega-3 FAs [60]. Ribeiro *et al.* [60] found that some wild edible mushrooms from the genus *Suillus*, *Hygrophorus*, *Amanita, Russula, Boletus*, *Tricholoma*, *Fistulina*, *Cantharellus*, and *Hydnum* contain FA composition such as butyric acid, caproic acid, linoleic acid, myristoleic acid, oleic acid, palmitoleic acid, stearic acid, *etc.* They found that mushroom species contain both polyunsaturated and monounsaturated fatty acids [60].

Nowadays, eggs are used as valuable target for omega-3 FAs and, therefore, eggs fortification with omega-3 FAs are known as novel strategy for increasing the levels of these FAs in human diets [61, 62]. For this aim, hens were fed a diet containing fish oil and/or a mixture of fish oil and seed oil rich in ALA [63, 64]. In addition, feeding of hens with microalgae (as a rich source of EPA and/or DHA) increased the level of omega-3 FAs in the eggs [65–67].

In addition to this, it has been reported that n-6 to n-3 ratio for grass-fed beef and grain-fed beef is 2:1 and 4:1, respectively, and, consequently, grass-fed beef represents better source of omega-3 FAs [68–73]. In accordance with this data, it has been reported that grass-fed lamb has higher level of omega-3 FAs than grain-fed lamb [74, 75]. However, chickens which are fed with omega-3 FA-rich grains such as flax, chia, and canola, contain higher level of omega-3 FAs [76–78]. Furthermore, kangaroo fillet and steak meat contain 74 mg omega-3 FAs per 100 g [79].

4 Bioavailability

Until now, there are some clinical and animal studies about bioavailability of omega-3 FAs after consumption of fish and vegetable oils [80–82]. It has been reported that fish consumption can significantly increase the serum levels of EPA and DHA in humans compared to fish oil supplementation [83–87]. It has also been reported that randomization of EPA and DHA within fish oil triglycerides cause no effects on digestibility of each individual fatty acids [88, 86]. Besides, some studies examined the bioavailability and incorporation of EPA and DHA into the lipids of adipose tissue, as well as brain phospholipids [80, 89–91, 34]. It has been reported that 9-weeks consumption of corn oil-based high-fat diet at doses of 5 or 15 % (*w*/*w*) increased the levels of DHA and EPA in the plasma and tissue lipids of experimental mice, which is explained by increased levels of omega-3 long-chain PUFA [80, 92, 93].

In addition, omega-3 FA liposomal delivery system increased the bioavailability of omega-3 FAs in comparison with standard fish oil [94]. Dietary consumption of fish oil containing EPA and DHA can also increase the incorporation of these fatty acids into plasma lipids [95]. It has also been reported that after 1-month consumption, the amount of omega-3 FAs measured in plasma lipids reached to its steady-state levels [32, 90]. The incorporation of omega-3 FAs into human erythrocyte follows slow kinetics [80, 90]. However, one of the most important limitation for animal to human translational study is

the significant difference between metabolic rate of human and mice, which leads to the various effects of omega-3 FAs [80].

5 Cancer therapy

A large number of publications support the efficacy of omega-3 FAs in cancer therapy, mainly if they are administered in combination with traditional treatments. Their biological and molecular characteristics as well as the ability to interact with other nutrients, such as omega-6 FAs and antioxidants [96], lead to the speculation that omega-3 FAs can significantly inhibit the onset of some forms of cancer. It is known that omega-3 FAs competes with LA, also known as a key nutrient in cancer. The ratio of the two classes of FAs is important, since omega-3 and omega-6 share the same biochemical pathways and can compete between them to generate imbalances [97]. The precursor of the omega-3 FA, ALA, represents a key molecule linked to anti-inflammatory response. The precursor of the omega-6 FA, LA, is associated to pro-inflammatory response. Cancer progression seems to be influenced by the ratio omega-3/omega-6 FA in the diet, rather than by their singular intake. The high intake of omega-6 FA in Western countries has been correlated with the incidence of several types of cancers [98].

Omega-3 and omega-6 FAs compete at the level of the activity of enzymes which promote the formation of cancer-promoting factors [99]. In addition, omega-3 FAs make cancer cells more sensitive to the action of free radicals especially when the membranes of tumor cells are richer in unsaturated FAs, and lower in saturated FAs, because it makes the membrane less rigid and more vulnerable. Finally, while LA promotes the survival of tumor cells preventing their death, omega-3 FAs promote the self-destruction of the tumor cells, thus limiting the expansion of cancer. Suppressive effect on the production of prostaglandin E2 (PGE2 AA-derived) has been implicated in the immune response to inflammation, cell proliferation, differentiation apoptosis, angiogenesis and metastasis [100].

It has been demonstrated that omega-3 FAs, especially EPA and DHA, affect cancer cell replication, cell cycle, and cell death. In this context, *in vitro* and *in vivo* studies have shown that omega-3 FAs sensitize tumor cells to anticancer drugs. The growth of various types of cancers, such as prostate, lung, colon, and breast cancer has slowed down by supplementing the diet of tumor-bearing mice with oils containing omega-3 FAs. In addition, omega-3 FAs are recognized as safe molecules and for this reason they are used as adjuvants in anti-cancer therapy.

Membrane lipid rafts are lipidic microdomains consisting mainly of sphingomyelin, cholesterol, and glycerophospholipids that hold many signaling proteins. These microdomains are involved in a myriad of cellular functions, such as signal transduction, membrane trafficking, neuronal differentiation, entry of pathogens and toxins into the cell. Their structure and function are sensitive to alteration by dietary fats, such as omega-3 FAs. In recent years, modulation of lipid rafts by omega-3 FAs is emerging as a new field to better understand the mechanism of action of PUFAs as chemoprevention agents in cancer therapy. In particular, EPA changes lipid composition in lipid rafts resulting in an inhibitory effect on proliferation of several cancer cell types [101, 102]. A strategy to reinforce the efficacy of chemotherapeutic drugs is to increase their cellular uptake linking them to lipophilic carriers. To this aim, dietary supplementation to patients affected by various types of cancers with omega-3 FAs improved the efficacy of chemotherapy drugs, such as doxorubicin, epirubicin, CPT-11, 5-fluorouracil, and tamoxifen, and radiation therapy [103]. However, how omega-3 FAs can affect physiological processes remains a question to be answered, although the potential mechanisms have been hypothesized. The major pathways involved in response to omega-3 FAs in cancer therapy are: (1) alteration of membrane-associated signal transduction, such as the modification of lipid composition of membrane rafts: *i.e.*, alteration in EGFR signaling [104, 105]; (2) increase of lipid peroxidation which causes irreversible cell damage [106, 107] enhancing drug sensitivity and inducing apoptosis [108, 109], or modulating gene expression involved in multiple signaling pathways including NF-κB [110], Notch, Hedgehog, Wnt [109] and mitogen-activated protein kinases (MAPKs) [111]. Dietary supplements enriched in omega-3 FAs have also been tested in clinical trials where their immunomodulatory properties have been analyzed as a possible explanation of the anti-carcinogenic effects owing the ability to reduce infection and inflammation [112].

5.1 Breast cancer

The data obtained from epidemiological studies, animal models, and cell culture suggested that omega-3 FAs are efficient inhibitors of breast cancer. The development of metastasis makes breast cancer a lethal disease. Several mechanisms have been hypothesized to explain the anticancer properties of omega-3 FAs. They suppress the formation of AA-derived prostanoids (prostaglandin E2), which are responsible for inflammatory response, cell growth, apoptosis, angiogenesis, and metastasis [113]. The same authors also reported that EPA and DHA induce apoptosis in two types of breast cancer cells MDA-MB-231 (ER-negative) and MCF-7 (ER-positive), by activation of Bcl2 expression and pro-caspase-8, together with reduction of EGFR activation [113]. In an *in vivo* and *in vitro* study, it has been reported that DHA inhibited breast cancer cells growth via down-regulation of Wnt/β-catenin signaling [114]. Dyari and colleagues, in a recent work [115], demonstrated that breast cancer cells (MDA-MB-231) are sensitive to a synthetic omega-3 FA (omega-3 epoxyfatty

acids). This compound was proved to act as an antiproliferative and pro-apoptotic agent, similarly to its natural counterpart. The authors concluded that the omega-3 monoepoxides enhance caspase-3 activity, and activate c-jun-N-terminal-kinase signaling, leading to cyclin D1 down-regulation and cell cycle arrest in G_1-phase, supporting their potential role of a new class of antitumor agents [115].

Following a relatively new view, it has been speculated that omega-3 FAs may regulate the expression of micro-RNA. This hypothesis has been confirmed after the demonstration that DHA inhibits the expression of micro-RNA, miR-21 in breast cancer cells. In this study, the authors reported that the growth and formation of metastases from breast cancer was associated with increased concentrations of miR-21. This, in turns, acts on a series of signaling molecules involved in tumor formation, such as colony stimulating factor-1 (CSF-1) gene, a potent activator of cancer proliferation and metastases formation. DHA reduced miR-21 levels and blocked the activity of CSF-1. The results obtained by administering DHA to the cells were confirmed in mice fed with fish oil [116]. In several epidemiological studies, it has been shown that a deficiency in omega-3 FAs increases the probability to develop metastases, while a diet rich in omega-3 FAs can reduce their size [117–119]. According to these results, women affected by metastatic breast cancer supplemented with 1.8 g of DHA during chemotherapy with antracyclins could increase their survival by 8 months. Probably, the enrichment of tumor cell membranes with this FA sensitizes them to chemotherapy. For these reasons, the authors concluded that this anticancer treatment could decrease symptoms and distancing the time of death without further toxic side effects to the patient [120].

5.2 Colorectal cancer

Colon rectal cancer (CRC) is the most common malignant disease and represents the third leading cause of cancer-related death in the Western countries [121]. The efficacy of omega-3 FA protection in colon cancer has been documented both in animal and cell culture models. At the time of this review, searching in PubMed for "omega-3 and colorectal cancer", 335 results were retrieved. In the last decade, excellent reviews have been published about omega-3 FAs as chemopreventive agents able to interfere with colon cancer pathways signaling. The etiology of CRC is a multifactorial process, which includes specific oncogene mutations, tumor suppressor genes, environmental factors and lifestyle, especially diet habits [122]. DHA suppresses the proliferation, induces apoptosis in colon cancer cells *in vitro* and decreases the formation and growth of induced tumors *in vivo.* In Apc(Min/+) mice omega-3 FAs (especially EPA) have been reported to significantly suppress polyps formation after 12 weeks of feeding with highly purified EPA as free FA [123]. In human colon metastatic (SW620) and primary adenocarcinoma (SW480, DLD-1) cell lines, DHA has been reported to act as a selective sensitizer to TRAIL-mediated apoptosis. In the same study, the authors also reported that TRAIL-mediated apoptosis induces changes at the levels of specific sphingolipids [124]. In a recent work, Cai and colleagues (2014) [125] analyzed the effect of radiation therapy in combination with DHA on two human colorectal cancer cell lines with different radio-sensitivity. They reported a synergistic cytotoxic effect in the radio-sensitive LS174T cells and additive effect in the radio-resistant HT-29 cells. Lipid peroxidation was partially involved in this mechanism, which also involved changes in the expression of NF-κB p65, COX-2, and Bcl-2 proteins [125].

Omega-3 FAs can block the activity of undifferentiated self-renewing colon cancer stem (CSC)-like cells (CSLCs), responsible for tumor formation, maintenance and chemotherapy-resistance. FuOx (5-Fluorouracil) (5-FU+Oxaliplatin) is the elective drug combination applied in colon cancer chemotherapy. FuOx-resistant CRC contains many CSCs. Vasudevan and co-workers [126] in a recent paper demonstrated the efficacy of EPA in inhibiting cell growth, colonosphere formation and sphere-forming frequency and in increasing sphere disintegration when combined with FuOx. In the same context, De Carlo *et al.* reported that EPA increases the sensitivity of COLO 320 DM cells to both drugs 5-FU+Oxaliplatin. EPA also increased the sensitivity of the CSLCs-bearing colon cancer marker CD133 to 5-FU [127].

Often, tumors are associated with the presence of inflammation. Changes in the genes encoding for enzymes involved in this pathway such as prostaglandin H synthase, COX-1 and COX-2 may be associated with CRC [128]. In the advanced stages of cancer progression, the activity of pro-inflammatory molecules is precisely controlled by the tumor mass: it stimulates the formation of new blood vessels and promotes the generation of metastases. Habermann and colleagues hypothesized that consuming high amounts of fish rich in omega-3 FAs may reduce the risk of colorectal cancer in those patients bearing genes whose activity increases the levels of pro-inflammatory molecules. In their study, the researchers compared genes in 1,574 individuals affected by colon cancer and 791 patients affected by rectal cancer with healthy patients. Consumption of low levels of omega-3 FAs increased cancer risk if variants of PTGS1, PTGS2 and ALOX15 genes were present, leading to the production of higher levels of prostaglandins and leukotrienes. In particular, CRC risk was greater for bearers of PTGS1 who assumed low levels of DHA. In a similar way, tumor incidence was higher in those carrying ALOX15 gene variant (which increases inflammation) and consumed little quantity of EPA. On the basis of these results, the authors concluded that the combination of omega-3 FAs and genes variants present in the organism can result in the a

higher risk of developing colon cancer [129]. In a Japanese study, the efficacy on omega-3 FAs was also tested in humans in a double-blind randomized controlled trial in patients with both colorectal ACF and colorectal polyps planned polypectomy. Here, EPA (2.7 g per day) has been reported to be able to inhibit colorectal aberrant crypt foci, compared to placebo control group after one month of supplementation [130].

5.3 Leukemia

The tumors against which omega-3 FAs resulted to be useful to date, are primarily colon, prostate and breast cancers, but relatively few papers have reported the ability of these nutrients to inhibit growth and induce differentiation in leukemia cells. In the promonocytic leukemia cell line U937, EPA and DHA have been shown to inhibit DNA synthesis and cell cycle progression. After treatment of U937 with EPA, an enhanced expression of C/EBPβ, a tumor suppressor gene silenced by promoter hypermethylation in U937 cells, was observed. These data confirmed the role of PUFA in the regulation of gene expression [131]. More recently, the same authors reported that the activation of C/EBPβ tumor suppressor gene by EPA involves Ras/MEK/ERK pathway [132]. Down-regulation of cyclin expression and cell cycle arrest are two mechanisms through which EPA exerts its anti-proliferation activity in K-562, a human erythromyeloblastoid leukemia cell line [133]. In human promyelocytic leukemia cells HL-60, treatment with EPA increased apoptosis and necrosis in a dose and time-dependent manner. In this model, EPA-induced cell death was related to the inhibition of lipoxygenase [134]. Another study extends the efficacy of an EPA derivative, the Δ12-prostaglandin J3, to chronic myeloid leukemia. In mice, this compound was able to selectively kill cancer stem cells present in the spleen and bone marrow. Each mouse was injected with 600 ng/day of Δ12-prostaglandin J3 for a week while the cells were observed for p53-mediated apoptosis. Transplantation of cells isolated from mice treated with Δ12-prostaglandin J3 to other animals resulted in the inability to develop a new cancer, indicating that the treatment completely eliminated all cancer stem cells [135]. In a similar study, Altenburg and co-workers reported the ability of DHA conjugated with 2,6-diisopropylphenol (DIP-DHA) to affect cell viability of two types of T cell acute lymphoblastic leukemia (T-ALL) cell lines: Jurkat and CEM. Their data indicated that DIP-DHA acts a stronger anticancer molecule than DIP or DHA alone [136].

Acute myeloid leukemia (AML) is one of the most severe neoplastic forms. It is relatively rare, but its frequency increases with age [137]. A study conducted in 2009 at the University of Nevada highlighted the benefits of omega-3 FAs in AML treatment. In this case, DHA was effective on the primitive and undifferentiated AML cell line KG1a. In this model, DHA induced DNA fragmentation with an increase in the expression of the pro-apoptotic protein Bax [138].

5.4 Gastric cancer

In the USA, in 2014, 22,220 estimated new cases and 10,990 deaths due to gastric cancer were expected (http://www.cancer.gov/). Gastric cancer (GC) is the fourth most common cancer worldwide with a scarce survival rate. Omega-3 FAs has been also tested on gastric cancer cells, showing the capacity to inhibit their proliferation. In most papers published on this topic, the antiproliferative effects of omega-3 FAs seem to be exerted through apoptosis activation. In this respect, Sheng and co-workers (2014) [139] reported that in a human gastric cancer cell line, MKN-45, EPA and DHA induced apoptosis by activating ADORA1, a subtype of adenosine receptor functionally involved in cell death that resulted up-regulated after treatment with omega-3 Fas. In another cell model, SGC7901 cell line, DHA inhibited cell growth at different concentrations in a dose- and time-dependent manner. This antineoplastic effect was enhanced in association with 5-FU. In particular, combination treatment with DHA and 5-FU increased the mRNA level of apoptosis-related genes, including Bax, and decreased the mRNA expression of Bcl-2 [139].

Cancer cells are generally characterized by an increase of glucose consumption. Glucose is converted into lactic acid in the absence of oxygen. The impairment of the metabolism of cancer cells may represent a strategy to inhibit their proliferation. In a mouse xenograft model, it has been reported that the growth of human gastric cancer cells can be delayed by feeding mice with a ketogenic diet low in carbohydrates and supplemented with omega-3 FAs and medium-chain triglycerides [140]. Finally, in humans, omega-3 FA supplementation can help to recover a good state of health after surgery. Demonstration of this effect comes from a study conducted by González's group where patients with GC who underwent a total gastroectomy remitted faster when diet included supplements enriched in omega-3 FAs [141].

5.5 Pancreatic cancer

The first appearance of omega-3 FAs associated to pancreatic cancer is dated to early nineties, when several groups noted that the addition of omega-3 FAs in enteral feeding, together with other supplements (RNA, arginine), improved postoperative outcomes in surgical patients with upper gastrointestinal malignancies. The beneficial effects of omega-3 FAs resulted in a significant decrease of PGE2 production and reduction of postoperative infectious/wound [142, 143]. This approach was renewed in a series of more recent studies demonstrating that prolonged and regular parenteral omega-3 FA administration results in rapid and sustained cellular uptake of EPA and

DHA methyl esters in erythrocyte cell membranes of patients with advanced pancreatic cancer [144]. When the treatment included administration of gemcitabine and intravenous omega-3 FA-rich lipid emulsion, pro-inflammatory circulating cytokines, and growth factors were significantly reduced with improved outcomes [145]. On the other hand, the existence of an inverse associations between intake of omega-3 FAs and risk of pancreatic cancer was reported in a large population-based case-control study [146] and confirmed in an animal model represented by EL-K-*ras* mice fed with a high omega-3 FA diet (23 % menhaden oil) compared with age-matched EL-K*ras* mice fed standard chow (5 % fat). In the first group, the incidence, frequency, and proliferative index of pancreatic pre-cancer EL-K*ras* mice were reduced compared to the control group [147]. However, a systematic review previously published on the effect of omega-3 FAs on cancer risk in prospective cohort studies, denied the existence of convincing evidence about the association between omega-3 FAs and cancer incidence. Moreover, the dietary supplementation with omega-3 FAs was unlikely to prevent cancer, including aerodigestive, bladder, lymphoma, ovarian, pancreatic, or stomach cancers [148]. These contradictory studies may suggest that omega-3 FA administration may play a role in the therapy, more than prevention of pancreatic cancer. In fact, in addition to the human trials cited above where omega-3 FAs were employed in parenteral nutrition, several studies in preclinical models support their therapeutic potential in pancreatic cancer. In four pancreatic chemo-resistant cancer cell lines the administration of 100 μM omega-3 FAs in combination with gemcitabine resulted in a time/dose-dependent inhibition of proliferation and reduction of I-kB phosphorylation and NF-κB activation when compared with omega-6 FA control. In addition, omega-3 FAs when associated with gemcitabine also significantly decreased Stat3 phosphorylation, whereas gemcitabine alone had no effect [149]. DHA and EPA significantly inhibited cell growth and increased apoptosis in SW1990 and PANC-1 pancreatic cancer cells. DHA administration diminishes β-catenin expression and induced β-catenin/Axin/GSK-3β complex formation which is known as a precursor to β-catenin degradation [150]. In addition, when mouse pancreatic cancer cells (PANC02) were implanted into fat-1 transgenic mice, which express omega-3 FA desaturases, resulting in elevated endogenous levels of omega-3 FAs, β-catenin levels were reduced with a significant increase in apoptosis compared with control mice [150]. A link between omega-3 FAs and oxidative stress was also evidenced. EPA and DHA were able to induce ROS accumulation and caspase-8-dependent cell death in MIA-PaCa-2 and Capan-2 pancreatic cell lines [151]. In addition, considering that the pancreas has a high capacity to accumulate EPA at a level markedly higher than several other tissues, a study was designed where athymic nude mice fed with a diet supplemented with 5 % fish oil, which contained high levels of EPA and DHA, strongly suppressed the growth of MIA-PaCa-2 human pancreatic cancer xenografts. In this model, EPA also induced autophagy in these cancer cells suggesting that combination of EPA with an autophagy inhibitor may be a useful strategy in increasing the therapeutic effectiveness in pancreatic cancer [151].

5.6 Prostate cancer

Preclinical studies suggest lowering dietary fat and decreasing the ratio of omega-6 to omega-3 FA decrease the risk of prostate cancer development and progression. However, the story of clinical trials regarding the association between omega-3 FA consumption and risk of prostate cancer is studded of controversial results. Early epidemiological studies suggested that low-fat diets rich in omega-3 FAs prevented the development and progression of prostate cancer, while a high-fat diets rich in omega-6 FAs promoted prostate cancer [152–154]. These data were indirectly confirmed by a work where a different approach was used. Men with prostate cancer who did not receive prior therapy were treated with a diet low in fat (15 % kcal) compared to a Western diet (40 % kcal fat). Serum from patients in the low-fat group significantly decreased the growth of LNCaP prostate cell line relative to Western diet serum. Correlation analysis revealed that decreased omega-6 and increased omega-3 FAs correlated with decreased serum stimulated LNCaP cell growth [155]. Later, two important case-control analyses reached the conclusion that omega-3 FAs may be associated with increased risk of prostate cancer. In the first work (1658 cases and 1803 controls), no FAs were associated with low-grade prostate cancer risk and DHA was positively associated with high-grade disease [156]. The second case-cohort study examines the associations between plasma phospholipid FAs and prostate cancer risk among participants in the SELECT (Selenium and Vitamin E Cancer Prevention) trial. Men in the highest quartile of omega-3 FA consumption had increased risks for low-grade, high-grade and total prostate cancer compared with men in the lowest quartiles. The conclusion of the authors was to cautiously consider increasing omega-3 FA consumption at the light of their potential risk [157]. To further confirm this observation, very recently, the Alpha Omega Trial, a double-blind, placebo-controlled trial designed to determine the of recurrence of cardiovascular disease in relation to supplementation with ALA, EPA and DHA, indicated that 2 g of ALA per day increased PSA (prostate-specific antigen) by 0.10 ng/mL, although no effect was measured. It is not clear if ALA intake has a clinically significant effect on PSA or prostate cancer [158]. The state of art remains confused and more studies are certainly needed to establish whether or not omega-3 FA intake really

increases the risk of prostate cancer. These studies generated doubts and contradictions. As an example, it is not clear why the Japanese who have an intake of omega-3 FAs about 8-fold higher than that of Americans and with a blood level twice as high, show an incidence of prostate cancer dramatically lower than the Americans (22.7 per 100,000 in 2008 *versus* 83.8 per 100,000) [159]. To confirm this paradox, in a prospective study performed predominantly on American men who were screened annually for newly incident of prostate cancer, dietary intake of total ALA was not associated with risk of total prostate cancer or prostate tumors [160]. Moving to preclinical studies, the view totally changes in favor of a protective role of omega-3 FAs against prostate cancer. Using the prostate-specific PTEN-knockout mice, an immune-competent, orthotopic prostate cancer model, it was found that omega-3 FAs reduced prostate tumor growth, slowed histopathological progression, and increased survival, whereas omega-6 FAs had opposite effects. Since tumors from mice on the omega-3 FA diet had lower proportions of phosphorylated Bad and higher apoptotic indexes compared with those from mice on omega-6 FA diet, it was suggested that modulation of prostate cancer development by PUFA is mediated in part through Bad-dependent apoptosis [161]. Similarly, changing from a diet rich in omega-6 FAs, typical of the Western diet, to a high omega-3 FA diet at adulthood reduced prostate cancer risk in the male offspring born from female SV 129 mice that had consumed a high omega-6 diet and were bred with homozygous C3(1)Tag transgenic male mice [162]. In LNCaP and PacMetUT1 human prostate adenocarcinoma cells, exposure to physiologically achievable levels of DHA prior to treatment with hydrogen peroxide results in decreased cancer cell survival which was associated with nuclear exclusion of NF-κB, suggesting that DHA attenuates the NF-κB survival pathway [163]. In two different prostate cancer cell lines, namely PC3 and DU145 expressing mutant p53, DHA increased both autophagy and apoptosis leading to the generation of mitochondrial ROS. Pre-treatment with the antioxidant N-acetyl-cysteine (NAC) markedly inhibited both the autophagy and the apoptosis triggered by DHA, indicating that mitochondrial ROS mediate the cytotoxicity of DHA [164]. This mechanism, in some ways, interferes with Akt and mTOR phosphorylation, whose levels resulted diminished following DHA treatment in a concentration-dependent manner, while NAC almost completely blocked that effect [164]. Other mechanisms of action triggered by omega-3 FAs on cellular models have been recently reviewed elsewhere [165]. The correlation between omega-3 FA supplementation and prostate cancer was treated also in the paragraph relative the adverse effects of omega-3 FAs.

5.7 Lung cancer

In the above-cited paper regarding the systematic review on omega-3 FA uptake and cancer risk, the authors found that for lung cancer, one work indicated a significant association for increased risk (IRR, 3.0; 95 % CI, 1.2–7.3), one for decreased risk (RR, 0.32; 95 % CI, 0.13–0.76), and 4 other estimates were not significant [148]. An early work on a large cohort of Norwegian men (25,956) and women (25, 496), age 16–56, indicated a significant lower risk of lung cancer for cod liver oil supplement (incidence rate ratio, IRR=0.5, 95 % CI=0.3–1.0), after adjusting for smoking status, gender, age at screening, and attained age. However, confounding factors, such as the presence of vitamin A, together with omega-3 FAs, in cod liver oil could have interference with the protective effect of this supplement [166]. Several studies have been published in the last decade on the role of omega-3 FAs not directly on lung cancer prevention and therapy, but to the depression in patients with newly diagnosed lung cancer. Also in this case, no conclusive results have been obtained. A study performed on 771 Japanese patients concluded that EPA and DHA intake might not be associated with depression, but ALA intake and total omega-3 FA might be [167]. In a different work on two different groups of patients affected by minor or more severe depression, the minor depression group had higher mean levels of DHA, but there were no differences between the major depression group and non-depression ones in any FAs [168]. From a molecular point of view, different doses of DHA (40, 45-55 μg/ml) or EPA (45-60 μg/ml) significantly suppressed the proliferation and induced apoptosis of lung adenocarcinoma cell line A549 [169]. A recent work suggested that this antiproliferative effect can be due in part to selective alteration of arachidonate metabolism that involves COX enzymes. EPA inhibited 50 % of proliferation of A549 cells (COX-2 over-expressing) at 6.05 μM, while almost 80 μM was needed to reach similar levels of inhibition of H1299 cells (COX-2 null) [170]. Accordingly, the formation of prostaglandin (PG)E3 in A549 cells was almost 3-fold higher than that of H1299 cells when they were treated with EPA (25 μM). In addition, when COX-2 expression was reduced by siRNA or shRNA in A549 cells, the antiproliferative activity of EPA was also reduced. These results suggest that the ability of EPA to generate PGE3 through the COX-2 enzyme might be critical for EPA-mediated of lung cancer cells via down-regulation of Akt phosphorylation by PGE3 [170].

5.8 Head and neck and esophageal cancers

Similarly to the clinical studies cited above for pancreatic cancer, the significant malnutrition and immunosuppression existing in a high percentage of head and neck cancer make patients highly susceptible to postoperative infections and complications. Therefore, immune-enhanced enteral nutritions compared to control diets were tested in several intervention trials. The formula including arginine, RNA, and

omega-3 FAs was associated to lower wound infections and general infections in patients with oral and laryngeal cancer compared to control subjects [171, 172]. However, fistula rates, differences in the trend of plasma albumin, transferrin, lymphocytes, weight, and inflammatory markers were not significantly improved in the enhanced diet groups [171]. In a similar trial, an omega-3 FAs enhanced formula with different omega-3/omega-6 ratios improved serum protein concentrations in ambulatory postoperative head and neck cancer patients with good tolerance [173]. More recently, the same group published that 37 post-surgical head and neck cancer patients consuming two or three cans per day of a designed omega-3 FA and arginine enhanced supplement for a 12-week period showed improved albumin, prealbumin, transferrin and lymphocytes levels in both groups. Weight, fat mass and fat-free mass improved during supplementation only in the group taking three bricks per day [174]. The same beneficial effects of formulas containing omega-3 FAs were observed in head and neck and esophageal cancer patients undergoing radiochemotherapy (RCT). Here, the effect of immunonutrition consisting of an arginine, omega-3 FAs, nucleotides-enriched diet was tested in 37 patients undergoing RCT. The results indicated that in enteral nutrition patients a significant gain in total body weight, albuminemia and plasma antioxidant capacity was observed. Functional capacity measured by WHO Performance Status and Karnofsky index was maintained in this group, but was significantly reduced in patients receiving standard enteral nutrition [175]. A different oral supplementation containing amino acids, omega-3 FAs, ribonucleic acids, vitamins and antioxidants resulted less effective in ameliorating pro-inflammatory, pro-angiogenic, and pro-oxidative status in 31 patients with non-metastatic stage III or IV head and neck squamous cell carcinoma treated with concomitant radiochemotherapy [176].

Few studies regarded the application of omega-3 FAs as supplement in the enteral nutrition of esophageal cancer. Early enteral nutrition with a large amount of omega-3 FAs was effective in reducing platelet aggregation, coagulation activity, and cytokine production. The anti-inflammatory effects of omega-3 FAs were confirmed by the clinical findings of lower body temperature and by biochemical marker, such as plasma IL-8 levels which were decreased significantly [177]. When RNA and arginine were added to the formula, the above described responses were improved [178]. A more recent trial further investigated the anti-inflammatory effects of omega-3 FA in 60 patients with esophageal cancer. In the group that received omega-3 FA supplement, inflammation and immune function improved following surgery. Serum procalcitonin level was notably lower and the $CD4^+/CD8^+$ ratio was markedly higher in the omega-3 FA group on post-operative day 6, but not on post-operative days 1 and 3 [179]. In general, these formulae containing omega-3 FAs can be used safely in those patients who develop sepsis, but there is insufficient evidence to recommend routine use of immunonutrition in patients undergoing esophageal cancer surgery [180].

6 Cancer cachexia

Several diseases such as AIDS, COPD, as well as several types of cancer are associated with cachexia [181, 182]. Cachexia is defined as weight loss resulting from loss of skeletal muscle with or without loss of adipose tissue associated with progressive functional impairment, fatigue, weakness, and insulin resistance that is not due to malnutrition [183, 184]. It is believed that near four fifths of advanced stage cancer patients experience cancer-induced cachexia [185]. Cancer-induced cachexia is responsible of about one-fifth of cancer-related death especially in patients who suffer from head and neck, pancreatic, lung, colorectal, gastric, liver, esophageal, malignancies [186–188]. This condition has deleterious effects on patient quality of life; make them more susceptible to the toxic effects of radiotherapy and chemotherapy and consequently limits treatment outcome and elevates mortality rate [189–191]. After one-third weight loss, death became imminent due to respiratory failure caused by diaphragm muscle devastating [188, 192]. Cachexia-induced muscle loss is a result of decrease in synthesis/degradation ratio of protein through imbalance of ubiquitin-proteasome as well as dystrophin glycoprotein complex pathways [193–195]. Loss of adipose tissue is also a result of an imbalance in lipogenesis and lipolysis [183, 196]. Recent studies show the key role of tumor-induced systemic inflammation, neuroendocrine activation and tumor-related lipolytic factor in cachexia-induced muscle and adipose loss [197–200]. A plethora of reports shows pivotal role of pro-inflammatory cytokines such as interferon γ, interleukins 1β, 2, 6 and tumor necrosis factor-α, as well as activation of NF-κB signaling in pathogenesis of cachexia-induced muscle proteolysis and lipolysis [201–204]. Multi-target therapeutic strategy for treatment of cancer cachexia is needed including nutrition support, drug therapy and life style change [205, 206]. The promising role of nutritional intervention with omega-3 FAs in treatment of cancer cachexia is publicized [207, 208]. Several experimental studies in cancer cachectic animals including mice, rat and dog showed that fatty acid-enriched fish oil consumption lead to prolonging of animal survival, increasing of body weight, improving macrophage function, suppression of lipolysis by down-regulation of zinc-alpha(2)-glycoprotein mediating by glucocorticoid signaling pathways, preservation of tissue glycogen stores, suppression of hypertriacylglycerolemia and fall in glucose, decreasing serum lactate level, inhibition tumor-induced fatty acid transport, down-regulation proteasome expression as well as up regulation of myosin expression [209–219]. EPA and DHA administration down-regulated ubiquitination of muscle proteins in Lewis lung carcinoma

induced cachexia [213]. *In vitro* studies on MAC16 tumor cells showed EPA inhibits protein degradation through down-regulation of muscle prostaglandin E2 and suppress tumor-induced lipid mobilization through suppression of adenylate cyclase mediating by guanine nucleotide-binding protein and down-regulation of cyclic AMP in adipocytes [210, 216, 220, 212].

Data obtained from a randomized cross over on twenty normal subjects that consume 0.5-mL fish oil supplementation as a rich source of omega-3 FAs per day shows that marine omega-3 FAs may increase appetite [221]. Randomized placebo controlled cohort study show that 6-week receiving of fish oil plus celecoxib (COX-2 inhibitor) and fish oil plus placebo significantly increase appetite, muscle strength, and decrease fatigue and C-reactive protein level in comparison with their baseline in patient suffering from advanced lung cancer [222]. However, body weight, muscle strength and amelioration of C-reactive protein level was higher in patients receiving fish oil plus celecoxib [222]. This study shows that combination of omega-3 FAs and COX-2 inhibitor such as celecoxib can help in the management of systemic immune-metabolic syndromes. Other studies also show that EPA supplementation increase lean body mass, appetite, and quality of life in advanced cancer patients [223–228]. A case report showed that 1-year oral consumption of EPA increased body weight, promoted patient compliance and increased survival in 76-years old subjects who suffer from relapsed rectal cancer (IV stage) receiving chemotherapy [229].

Three arms randomized clinical trial shows that EPA and megesterol acetate significantly increase body weight, lean body mass, body mass index, quality of life, and decrease serum level of inflammatory cytokines in cachectic cancer patients more than each group alone [230]. The promising effect of omega-3 FA consumption in management of head and neck cancer induced weight loss is also reported [224, 231].

Three-month consumption of ethanwell/ethanzyme (EE) regimen (enriched with omega-3 FA-, micronutrient-, and probiotic) ameliorated body weight loss, albumin and prealbumin level decreasing in head and neck cancer cachectic patients [231]. Similarly, it has been demonstrated that EPA-containing diet increase pre-operative lean body mass in head and neck cancer patients [224]. In addition, in cachectic pancreatic cancer patient 8-week EPA supplementation increased physical activity and improve quality of life [224]. Another study on pancreatic cancer cachexia has shown that 3-weeks administration of fish oil (2 g EPA/day) significantly increased insulin and decreased interleukin-6, cortisol/insulin ratio, and proteolysis inducing factor and eventually a decrease in cachexia catabolism [228]. Another related study demonstrated that oral administration of EPA in pancreatic cancer cachexia can down-regulate C-reactive protein through suppression of interleukine-6 [232]. EPA administration also can stabilize resting energy expenditure [233]. A systematic review of clinical trials on the therapeutic role of omega-3 FA consumption (EPA and DHA) on cancer cachexia showed that at least 1.5 g per day for more than 8-weeks period improve appetite, body lean mass, functional status, quality of life and decrease inflammatory mediators [234]. However, the available clinical data about effect of single-agent EPA on cancer cachexia are controversial and, due to lack of sufficient evidence, it is not easy to make a clear decision about its application as single agent [235–238]. However, the promising role of omega-3 FAs on acute phase responses after surgery and inhibition of protein degradation is publicized [239, 233]. In addition, the anabolic properties of long chain omega-3 FAs in healthy young and middle age subjects have been reported previously [240]. A phase II clinical trial showed that nutritional support, containing omega-3 FAs (EPA and DHA), vitamins (E, A, and C), antioxidant associated with medroxyprogesterone acetate and selective COX-2 inhibitor, significantly improves lean body mass, appetite, Eastern Cooperative Oncology Group performance status, and normalizes biochemical markers such as proinflammatory cytokines and oxidative stress [241]. Similarly, five different arm phase III randomized clinical study in cancer cachexia showed that 4-month treatment of the combination of medroxyprogesterone or megestrol acetate, L-carnitine, thalidomide with EPA leads to better outcome than each group alone in improving the lean body mass, appetite, quality of life, Glasgow Prognostic Score, grip strength, fatigue and relevant secondary endpoints, as well as normalization of interluekine-6 level [242]. Results from experimental and clinical studies have revealed that the omega-3 FA ability to suppress inflammation, proteasome expression and tumor-derived factor are the main mechanisms of their promising effect on cancer cachexia [219, 210, 243, 228]. Although omega-3 FAs as single agents have no effect on protein synthesis, some reports have revealed that combination of EPA with proteins and amino acids attenuate protein degradation and stimulate protein synthesis [244]. Three-weeks omega-3 FA supplementation in cachectic cancer patients has been shown to stimulate anabolism through modulation of hepatic export protein synthesis response to feeding [245]. The maximum tolerated dose for omega-3 FAs obtained from phase I clinical study in leukemia cachectic cancer was found to be 0.3 g/kg/day [246]. Overall, it can be concluded that omega-3 FAs associated with other nutritional supports and COX-2 inhibitor can be used as effective medication for management of cancer cachexia. However, more clinical studies are needed.

7 Ongoing and recruited clinical trials

Due to low side effects, high efficacy, and tolerability against chemotherapy and radiotherapy, a plethora of clinical studies has been performed on these compounds. A search in http://

clinicaltrial.gov with these keywords "Omega-3 PUFA+ Cancer", "omega-3 polyunsaturated fatty acids+cancer", "omega-3 polyunsaturated fatty acids+cancer", "ω-3 fatty acids+cancer", "n-3 fatty acids+cancer" at 14 October 2014 found that 117 clinical trials are recorded for clinical application of omega-3 FAs in cancer patients. Among the results, 23 clinical studies are still ongoing. Details are summarized in Table 2.

8 Adverse effects of n-3 polyunsaturated fatty acids

The results obtained in the field of nutritional lipid research support the hypothesis that a high intake of omega-3 FAs from foods or dietary supplements might have protective effects on human health. In fact, growing evidence suggests that the intake of omega-3 FAs is associated with low chronic inflammation which plays an essential role in the initiation and progression of degenerative pathologies such as cardiovascular diseases, insulin resistance, obesity, *etc.* However, the safety of supplementation with high omega-3 FA doses is still unclear and therefore the adverse effects associated with high intake of omega-3 FAs should not be overlooked. The review of the existing scientific data has revealed that a high intake of omega-3 FAs could be associated with immune function impairment, altered glucose and lipid metabolism and platelet dysfunction.

With regard to immune function impairment, it is well-known that both immunosuppression and excessive inflammation can lead to serious pathological conditions, such as infections and chronic degenerative pathologies, respectively. Omega-3 FAs have been shown to possess anti-inflammatory activity, as they are able to decrease the production of inflammatory cytokines and eicosanoids through the replacement of AA and inhibition of its metabolism, or impairment of the expression of inflammatory genes promoting transcription factor activation. Omega-3 FAs have anti-inflammatory activity which can prevent or reduce chronic inflammation. On the other hand, they can be detrimental in the context of an acute infection as shown by Ghosh *et al.* (2003). In experimental animals, the addition of omega-3 FAs on a high omega-6 FA diet protected against severe colitis, since it reduced the inflammation through the decrease in pathogenic bacteria and increase of eubiotic bacteria, such as *Lactobacillus* and *Bifidobacteria*. Moreover, omega-3 FAs reduced immune cell infiltration and impaired cytokine induction during infection [247, 248]. A very recent research published in 2014 pointed out some alarming aspects which warrant great attention in the future. The immune system is aimed to detect and eliminate pathogens and acts against transformed cells that may lead to cancer. An alteration in immune system could lead to immunosuppression and a reduction of immunological defense against some types of cancer. Xia *et al.* (2014) showed that high dietary intake of fish oil induces the expression of immunosuppressive cytokine IL-10 and promotes myelopoiesis. The immature myeloid cells exhibit morphological and functional characteristics of myeloid-derived suppressor cells (MDSCs) with the capability to down-regulate CD8(+) T cells activation, which can kill the tumor target cell. The authors concluded that omega-3 FA-induced production of MDSCs maintains tumor growth and points to MDSCs as a possible mediator linking dietary fish oil intake and immunosuppression in cancer immunosurveillance [249]. This research provides the opportunity to report the potential association between fish oil and cancer, especially prostate cancer. In 2011, in a large prospective investigation, Brasky *et al.* (2011) examined the association between fatty acids and prostate cancer risk. DHA was positively associated with high-grade disease and therefore may increase high-grade prostate cancer risk. The authors concluded suggesting that before making recommendations for dietary changes or use of food supplements for prevention of diet-related pathologies, is necessary to map a complete picture of the effects of nutrients on many diseases [250]. Several investigations showed that dietary omega-3 FAs may affect glucose metabolism and plasma lipids both in healthy people and patients with metabolic syndrome [251–257]. Nevertheless, overall the most representative meta-analysis performed in the last decade showed that omega-3 FA supplementation up to 5 g/day consumed for 3 months do not significantly affect insulin sensitivity and glucose homeostasis both in healthy subjects and diabetic patients [258–262].

As far as platelet dysfunction is concerned, in 1995, Tremoli *et al.* studied the effect of a short-term loading treatment (6 weeks) with 6 g/die omega-3 FAs followed by 12 weeks with 3 g/die in healthy volunteers. The results showed that the intake of omega-3 FAs inhibited platelet aggregation in duration of treatment- and dose-dependent manner. In fact, at 12 weeks, platelet aggregation, thromboxane A2 formation and the excretion of thromboxane metabolites in urine were reduced. It is noteworthy that after treatment, triglycerides and thromboxane A2 biosynthesis returned to baseline values within 4 weeks, whereas platelet aggregation remained impaired for 14 weeks. The authors added that platelet aggregation inhibition might have been ascribed to the enhanced concentrations of DHA in platelet phospholipids [263].

Since then, many studies demonstrated that omega-3 FAs may affect the platelet aggregation and pointed out the potential antithrombotic effects without clinically significant bleeding risk [264–267]. Platelet impairment can induce blood clotting problems and multiple studies have reported increases in bleeding times [268–270]. So, particular attention was paid to the increase of bleeding time after vascular, cardiac, abdominal and spinal surgery. Nevertheless, none of the investigations showed significant increases in perioperative bleeding events [271–273].

Table 2 Ongoing clinical trials on promising effect of omega-3 FAs in cancer patients according to www.clinicaltrial.gov

Identifier	Study types and Phase	Title
NCT01869764	Randomized open labeled clinical trial phase II	Omega-3 FA in treating patients with stage I-III breast cancer
NCT00458549	Randomized double-blind clinical trial	Polyunsaturated FA in treating patients with prostate cancer undergoing prostate biopsy and/or surgery
NCT02101970	Randomized double-blind clinical trial phase II	Weight loss plus omega-3 FA or placebo in high risk women
NCT01821833	Randomized double-blind clinical trial	Omega-3 FA in treating pain in patients with breast or ovarian cancer receiving paclitaxel
NCT02134600	Randomized single blind clinical trial	OmegaChild - Omega-3 supplementation to children previously treated for cancer
NCT01049295	Randomized double-blind clinical trial Phase IV	Omega-3 FA and chemotherapy-induced neuropathy and inflammation in breast Cancer
NCT01823991	Randomized double-blind clinical trial	COGNUTRIN in breast cancer survivors
NCT02176902	Randomized open labeled clinical trial phase II	Low-fat diet and fish oil in men on active surveillance for prostate cancer
NCT01870791	Randomized open labeled clinical trial phase II	Study of additive omega-3 fish oil to palliative chemotherapy to treat oesophagogastric cancer
NCT01784042	Non-randomized open labeled clinical trial phase 0	Dietary energy restriction and omega-3 fatty acids on mammary tissue
NCT01803711	Randomized double-blind clinical trial phase II/phase III	Omega 3 FA supplements as augmentation in the treatment of depression (patients with cancer, cardiovascular diseases, and diabetes)
NCT02231203	Randomized double-blind clinical trial Phase IV	Effect of omega-3 FA on the perioperative immune response and erythrocyte function
NCT00455416	Non-randomized open labeled clinical trial phase II	Dietary intervention in follicular lymphoma
NCT01661764	Randomized double-blind clinical trial Phase II	Fish oil supplementation, nutrigenomics and colorectal cancer prevention
NCT01048970	Randomized single-blind clinical trial phase III	Effect on the nutritional and inflammatory status of DHA and EPA-containing supplement in patients with advanced lung cancer
NCT01653925	Randomized open labeled clinical trial	Molecular mechanisms of dutasteride and dietary interventions to prevent prostate cancer and reduce its progression
NCT01819961	Randomized double-blind clinical trial Phase IV	Parenteral fish oil in major laparoscopic abdominal surgery
NCT00790140	Randomized double-blind clinical trial phase IV	Trial of enteral nutrition enriched with EPA in upper gastrointestinal cancer surgery
NCT01902745	Randomized open labeled clinical trial phase II	Fatigue reduction diet
NCT02055833	Randomized open labeled clinical trial	Intensive nutritional counseling in head-neck cancer patients undergoing radiotherapy
NCT01778166	Randomized open labeled clinical trial phase IV	Gastrointestinal postoperative early enteral nutrition: immuno-enhanced versus standard early enteral nutrition
NCT01969110	Randomized open labeled clinical trial phase IV	Additional effects of perioperative immunonutrition in patients undergoing pancreaticoduodenectomy
NCT01256047	Randomized open labeled clinical trial phase IV	Effects of preoperative immunonutrition in patients undergoing hepatectomy

Moreover, caution was recommended when PUFAs supplementation was proposed in patients treated with antithrombotic and anti-coagulant therapies such as acetyl salicylic acid. A recent research performed by Cohen *et al.* (2011) aimed to study the effects of increasing doses of PUFAs on platelet function. In this investigation, 30 volunteers subdivided into three groups: group A, no antiplatelet agent; group B, daily aspirin only; group C, daily aspirin and clopidogrel, received increasing doses of omega-3 FAs from 1 to 8 g daily over 24 weeks. The effects of this supplementation were measured as bleeding time, light transmission aggregometry (LTA), and electrophoretic quasi-elastic light scattering technology (EQELS) at baseline and after 6, 12, 18 and 24 weeks of treatment. The bleeding time increased in a dose-dependent manner, but no bleeding episodes were observed. LTA showed that omega-3 FAs did not increase the antiplatelet effects of drugs and EQELS showed a significant increase in the negative resting platelet charge compared to baseline [274]. A very recent review published in 2014, examining the effects of omega-3 FAs (EPA and DHA, from fish oil), reached the same conclusions. Moreover, the authors added that there is no scientific support for discontinuing the use of omega-3 FA treatment before surgery or under the treatment with drugs that affect bleeding [275].

9 Conclusion and recommendations

In this paper, we critically reviewed the available scientific data about the beneficial effects of omega-3 FAs against breast, colorectal, leukemia, gastric, pancreatic, esophageal, prostate, lung, head and neck cancers, as well as cancer cachexia. The promising effect of omega-3 FAs on certain types of cancer is related to their ability to modulate membrane-associated signal transductions and genes expression involved in cancer pathogenesis and supress systemic inflammation. With respect to negligible adverse effects of a correct supplementation of omega-3 FAs, future clinical studies are needed to ascertain the possible therapeutic role of omega-3 FAs as adjuvant therapy against cancer. Finally, we recommend that future studies should be focused on:

- pharmacodynamic and pharmacokinetic of omega-3 FAs in humans;
- increasing the bioavailability of omega-3 FAs by employing microencapsulation, nanoencapsulation, solid lipid nanoparticle as well as liposomal delivery systems, *etc.*
- ascertain the most effective doses for beneficial role of omega-3 FAs on different types of cancer, as well as cancer cachexia.
- identification of possible effects of omega-3 FAs on new emerging therapies, such as microRNAs.
- examination of the possible interactions of omega-3 FAs with well-known anticancer drugs, as well as dietary supplements.

Conflicts of interest The authors declare that there are no conflicts of interest.

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