Omega-3 Fatty Acid and its Protective Effect against Cancer and Cancer-related Complication

Chandan Samanta a#, Souvik Tewari b†, Debnanda Chakraborty c‡ and Shraddha Vaishnav d†

a Department of Nutrition and Public Health, The University of Burdwan, West Bengal, India.  
b Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, West Bengal, India.  
c II(SACT-II) Department of Nutrition, Bajkul Milani Mahavidyalaya, West Bengal, India.  
d Department of Biotechnology, Bharti Vishwa Vidyalaya, Drug, Chhattisgarh, India.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

ABSTRACT

Cancer is a broad term for a group of diseases that begin when abnormal cells grow out of control in practically any organ or tissue of the body. A variety of nutrients are included in the diet of people with cancer but omega-3 polyunsaturated fatty acids are one of the most effective nutrients. Numerous clinical and epidemiological studies have shown that polyunsaturated omega-3 fatty acids play an important role in maintaining the health of people with cancer. Omega-3 polyunsaturated fatty acid, by their own antioxidant, antitumour, anticarcinogenic, and neuroprotective properties, help cancer patients to reduce their various physical complications. Fish oil contains omega-3 fatty acids mainly docosahexaenoic acid and eicosapentaenoic acid have antioxidant properties that help to increase antioxidant enzymes and remove the reactive oxygen species from cancer patient’s body and also reduce the oxidative stress. Now, omega-3 polyunsaturated fatty acid is considered as pharmaconutrient. As a pharmaconutrient, omega-3 fatty acid reduces the inflammatory response of cancer patients. The cyclooxygenase-2 expression is suppressed by the omega-3 fatty acid and reduce the growth of tumour cell. Mental wellness is a
significant lifestyle aspect that the cancer patient cannot maintain. As a result, they are suffering from major depression. Omega-3 fatty acids exhibit neuroprotective activity against various brain diseases. This review summarizes that the omega-3 polyunsaturated fatty acids have an antioxidant and anticarcinogenic function that can inhibit the cancer cell growth and maintain the health status and lifestyle behaviour of the cancer patients.

Keywords: Cancer; omega-3; docosahexaenoic acid; fish oil; oxidative stress; antioxidant; anticarcinogen; inflammatory response; pharmaconutrient; depression.

1. INTRODUCTION

Omega-3 fatty acid is the polyunsaturated fatty acids (PUFA) characterized by the presence of carbon-carbon double bond (C=C). The fatty acid has two specific terminations one is methyl (–CH₃) and the other is the acid group (–COOH) [1]. These are the unsaturated fatty acids which is also named omega-3 oil, or n-3 fatty acids. There are three forms of omega-3 fatty acid involvement in human health. These are alpha-linolenic acid (ALA) found in plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) both are found in cold-water marine fish [2]. Our body can’t synthesize omega-3 fatty acids, so they are taken through food. But eicosapentaenoic acid and docosahexaenoic acid are produced by the conversion of alpha-linolenic acid in the human body [3,4].

Oxidative damage of the cell due to the metabolism of primary and secondary environmental pollutants leads to the production of free radicals, which is heavy carcinogens. The natural and bio-chemical antioxidants are effective ingredients for neutralizing the removal of free radicals from the cells [5].

The omega-3 fatty acids play a vital role as an antioxidant [6]. It helps to reduce oxidative damage and remove the free radicals from our bodies. Dietary omega-3 fatty acids have a significant and active impact on degenerative diseases like cancer [7]. Some researchers have shown that eicosapentaenoic acid and docosahexaenoic acid have the ability to resist cancer proliferation, apoptosis, and differentiation [8]. They also inhibit angiogenesis, invasion of tumour cells [9,10], and metastasis. The most common occurrence of cancer is tumour cell development. The unsaturated omega-3 fatty acids mainly EPA and DHA have an antitumour function, so that they can obstacle the formation of tumour cells [11].

1.1 Major Sources of Omega-3 Fatty Acid

Table 1. Major sources of omega-3 fatty acid

| Species                  | LNA | Total EPA + DHA |
|-------------------------|-----|-----------------|
| Lake Trout, Siscowet    | 1.6 | 3.0             |
| Mackerel, Atlantic      | 0.1 | 2.5             |
| Mackerel, King          | 0.0 | 2.2             |
| Dogfish, spiny          | 0.1 | 1.9             |
| Mackerel, Chub          | 0.3 | 1.9             |
| Salmon, Atlantic, farmed| 0.1 | 1.8             |
| Herring, Pacific        | 0.1 | 1.7             |
| Herring, Atlantic       | 0.1 | 1.6             |
| Lake Trout              | 0.4 | 1.6             |
| Tuna, Bluefin           | 0.0 | 1.6             |
| Sturgeon, Atlantic      | 0.1 | 1.5             |
| Chub                    | 1.1 | 1.5             |
| Salmon, Chinook         | 0.1 | 1.4             |
| Sablefish               | 0.1 | 1.4             |
| Anchovy, European       | 0.0 | 1.4             |
| Tuna, Albacore          | 0.1 | 1.3             |
| Lake Whitefish          | 0.2 | 1.3             |
| Sprat                   | 0.0 | 1.3             |
| Trout, Lean Lake        | 0.0 | 1.2             |
| Salmon, Coho, farmed    | 0.1 | 1.2             |
| Bluefish, Atlantic      | 0.0 | 1.2             |
| Herring, Round          | 0.1 | 1.2             |
| Salmon, Sockeye         | 0.1 | 1.2             |
| Herring                 | 1.4 | 1.1             |
| Capelin                 | 0.1 | 1.1             |
| Whitefish               | 0.8 | 1.0             |
| Salmon, Pink            | 0.01| 1.0             |
| Sardines, canned        | 0.5 | 1.0             |
| Salmon, Chum            | 0.1 | 1.0             |
| Halibut, Greenland      | 0.01| 0.9             |
| Bass, Striped           | 0.01| 0.8             |
| Pompano, Florida        | 0.0 | 0.6             |
| Smelt                   | 0.5 | 0.5             |
| Mullet, Striped         | 0.1 | 0.5             |
| Pollock                 | 0.0 | 0.5             |
| Trout, Rainbow (Steelhead)| 0.1| 0.5             |
| Tuna, unspecified       | 0.01| 0.5             |

grams fatty acid per 100 gram edible fish tissue or edible food

*EPA and DHA are omega-3 fatty acids*

(Exler, 1987; Nettleton, 1995; Spiller, 1996; Wang, 1990)
1.2 Antioxidant Activity of Omega-3 Fatty Acid against Cancer

In human living cells, due to metabolism and other biochemical reaction, reactive oxygen species (ROS) are continuously formed. By the regular cellular metabolism, reactive oxygen species (ROS) are normally formed but during inflammation and exposure to certain exogenous factors such as ionizing radiation, nitrogen oxide pollutants, and some chemical carcinogens effects, the ROS formation can increase [12].

Antioxidants build up a defence against reactive oxygen species in our body but when ROS is
greater available over antioxidants than it leads to oxidative stress [13-15]. Oxidative damage in the cell due to ROS activity can change the metabolic pathway and it leads to DNA mutation. This cause increases the chance of cancer [16,17]. The in-vitro and animal experiments suggest that dietary antioxidant availability can reduce the growth of neoplastic cells [17,12].

Various numerous studies have shown that fish oil contains omega-3 fatty acids mainly EPA and DHA which have anticarcinogenic and antioxidant properties [18,19]. Li et al. [20] suggest that omega-3 therapy regulates the superoxide dismutase (SOD), glutathione peroxidase (Gpx) activity in the serum and it increases the ability to form antioxidant enzyme SOD 1, and catalase (CAT). The antioxidant enzymes SOD 1, Gpx, and CAT helps to remove the toxic ROS from the cell. Mansara et al. [21] suggest in their study that fish oil which contains more omega-3 fatty acids can improve the antioxidant status in RBC and plasma. Higher supplementation of EPA and DHA decreases the risk of cancer-related mortality [22]. Another study has evaluated that omega-3 fatty acids from fish oil could minimize the risk of breast cancer [23].

1.3 Protective Effects of Omega-3 Fatty Acids on Suppression of Tumour Cell

Numerous research study has found that the suppression of tumour cell invasion is the functional properties of DHA. In a study on the effects of DHA on tumour cell invasion, Connolly and Rose, by using an in vitro invasion test, assessed the impact of linoleic acid, EPA, and DHA on the invasion efficiency of the MDA-MB-435 human breast cancer cell line. This shows that all fatty acids do not support tumour cell migration. DHA and EPA resist tumour cell growth but linoleic acid does not work on the tumour cell. [24]. Another research study indicates that the combination of DHA with nutritional component genistein, collectively increase the anti-invasion impact of tumour cell [11]. Genistein is an anticancer agent which is isolated from the soybean.

Due to obstruction of prostaglandin E2 (PGE2), production and cyclooxygenase-2 (COX-2) expression cell invasiveness is developed. Many researchers noted that combination therapy of DHA and genistein can improve the production of PGE 2 and the expression of COX 2 [11]. Sun et al. [25], reported that human hepatocyte carcinoma cell line migration and invasion are prevented by the DHA. Increased acceptance of dietary omega-3 fatty acids mainly docosahexaenoic acid impedes the initiation and formation of tumour cells.

1.4 Role of Omega-3 Fatty Acid on Different Cancers

Malnutrition of cancer patients reduces their responses to cancer therapy and prolongs other infections. That’s because they have to stay in hospital for a long-time treatment. This progresses the post-operative complications and increases the risk of death [26,27]. The patient may feel functionally and mechanically alteration when their tumour is developed in the gastrointestinal tract. Some of the adverse symptoms like nausea, vomiting, dysphagia, and mucositis are noticeable in this condition [28]. High inflammatory conditions of cancer patients contribute to various physical complexity like depression, cachexia, pain, and paraneoplastic syndromes [29, 30]. For maintaining immunocompetence during cancer treatment, immune-nutrition with omega-3 fatty acid is mostly prescribed [31, 32].

Clinical nutrition therapy which depends on functional nutrients is called Pharmaconutrition. Pharmaconutrition is commonly used in supporting medical care treatment through the enteral, internal, or parenteral route. To diminish cancer-related complications, the most employed nutrient supplementation are pharmaconutrients. Currently in modern times, omega-3 fats are considered as key pharmaconutrient. Pharmaconutrient omega-3 polyunsaturated fatty acid acts as a receptor agonist, molecular pathway modulator, inflammatory response reducer, efficiency developer of chemotherapy, and overall increase the relieving of cancer patients [13,33,34]. Sometimes breast cancer multifocality is seen when the omega-3 fatty acids level is lower in the mammary region. The pharmaconutrient omega-3 PUFAs are much effective for curing and handling cancer-related complications and also important for cancer management and prevention [35,36].

1.5 Omega-3 Fatty Acids and Cancer-Induced Pain

Maximum cancer patients feel various types of inflammation that are related to this disease. Different types of pain are reported by the
patient, this causes decreases the performance activity when cancer treatment was continued [37]. Pain is mainly related to the localization and presence of tumour cells but these also happen by treatment of chemotherapy and cancer surgery [38]. Various pain of cancer causes an inflammatory and neuropathic condition that is associated with tumour mass increment [39]. Chemotherapy and radiotherapy dependant toxicity and inflammation develop inflammatory symptoms, decrease the quality of life, and demonize the medicare success of cancer patients [40]. The nutritional enriched supplement with fish oil which contains omega-3 PUFA collectively decreases the fatigue and pain symptoms of the cancer patients during chemotherapy and radiotherapy [41,42].

Harshman et al. [43] suggest that using 3.3 g of fish oil which contains 560 mg of EPA and DHA with a ratio of 40:20 decreases the pain of human breast cancer. The numerous studies of Maschio et al. [44], suggest that using 400 mg DHA and 600 mg ALA on humans with multiple myeloma, pain is failed to increase significantly. In another study by Shan et al. [45], 3.3 grams of fish oil which are enriched with 560 mg eicosapentaenoic acid and docosahexaenoic acid with a ratio of 40:20, reduce the obese human’s breast cancer pain.

1.6 The Preventive Activity of Omega-3 Fatty Acids on Anorexia Cachexia Syndrome

Cancer anorexia cachexia syndrome (CACS) is a wasting and impairing aspect at all stages of malignancy. Primarily it represents, anorexia, weight loss, muscle wasting, and secondarily it represents the metabolic changes of cancer patients [46]. Omega-3 fatty acid supplementation is currently used to protect against various complications such as cancer anorexia-cachexia syndrome. But, the efficacy of this molecule for these complications is still questionable [47].

Depending on various clinical data, fish oil which is the main source of omega-3 fatty acids has an active and effective response to cancer cachexia [48]. However, the omega-3 supplement is important for the recovery of postoperative conditions and decreases the complications like infection and wound in cancer patients [49]. Fish oil supplements stabilize the gastrointestinal cancer patient’s body weight [50,51].

According to the study of Solis-Martinez et al. [52], 2 g pf EPA supplementation maintains the weight and lean body mass (LBM) of human head and neck squamous cell carcinoma with the complication of cachexia-anorexia syndrome. Other numerous studies evaluate that, the use of 53.6% of eicosapentaenoic acid and docosahexaenoic acid or 54.4% ALA supplementation improves weight gain of rat’s breast carcinoma with the complication of cancer-associated cachexia [53].

1.7 Omega-3 Fatty Acid as a Crucial Component of Maintaining Major Depression Disorder (MDD) of Cancer Patient

About 5% to 60% of oncological patients commonly suffer from depression [54]. Tumour necrosis factor (TNF), interleukin 1 beta (IL-1β), and interferon lambda (IFN-λ) are known as pro-inflammatory cytokines. They are formed by the interaction between tumour-host interaction and can reach the hypothalamus, which initiates a depression behaviour. The manifestation of serotonin and noradrenaline uptake transporters is also stimulated by cytokines that can diminish the number of neurotransmitters in the central nervous system (CNS) [55]. The hormone leptin is observed in the gastric tissue, which may be involved in gastrointestinal carcinoma-associated depression [56].

Bigornia et al. [57] suggest that omega-3 supplements are most important and beneficial for a person who is suffering from depression [57]. A lack quantity of omega-3 fatty acids in the brain can increase the probability of depression and anxiety disorder [58]. The omega-3 fatty acids show neuroprotective activity which suppresses the occurrence of brain diseases such as depression and anxiety [59]. Numerous research study suggests that 1.5 g/kg omega-3 polyunsaturated fatty acid (34% EPA + 24% DHA) supplementation decrease the depressive behaviour on LPS (lipopolysaccharide) induced depression of rat [60].

1.8 Paraneoplastic Syndrome of Cancer and Omega-3 Fatty Acid

The multiple clinical complications of cancer patients with tumour metabolites are called paraneoplastic syndrome. These disorders are
classified as neurological, haematological, dermatological, rheumatological, and endocrinological complications [61].

The paraneoplastic syndrome of endocrine happens through the interaction of endocrine and neuroendocrine cells tumour release substances which is spread out all parts of the human body [62]. The complications such as gynecomastia, acromegaly, hypertension, ovarian hyperstimulation, non-islet cell tumour hypoglycaemia, hypercalcemia, and hyperthyroidism are considered a rare paraneoplastic syndrome [63]. The animal model studies of Azuma et al. [64] suggested that the omega-3 supplements can reduce bone resorption by the influx down-regulation of the inflammatory cell [64]. Postmenopausal women improve their skeletal health by lowering parathyroid hormone (PTH) levels which is happen due to exercise and the use of omega-3 fatty acid supplementation [65].

Production of onconeural antibody or tumour antibody which reacts on the nervous systems and promotes nerve damage. This complication is known as a neurological paraneoplastic syndrome [66]. Neuropathies, cerebellar degeneration, encephalomyelitis, myelitis, neuromyotonia, myasthenic syndrome, and dermatomyositis are the most common neurological paraneoplastic syndromes [66,67]. The omega-3 fatty acid supplementation contributes to neuroprotective activity against traumatic injury. Yorek et al. [68] find that fish oil and resolin D1 (RvD1) promote beneficial activity on neuropathy [68].

Rheumatologic paraneoplastic syndrome increases in the same way as an endocrine paraneoplastic syndrome [69]. It is a rare syndrome of cancer but it can arise mostly in two years before cancer diagnosis. The most common complications such as hypertrophic osteoarthritis, tumour-induced osteomalacia, polyarthritis, and cancer-related myositis belong to the rheumatological paraneoplastic syndrome [70]. The docosahexaenoic acid supplementation can decrease the clinical and biochemical symptoms of rheumatoid arthritis patients’ inflammation [71]. EPA/DHA supplementation intake can reduce the fibroblast growth factor-23 (FGF23) circulating level in renal transplant patients [72]. Thus, the tumour-associated hypophosphatemia and osteomalacia might be controlled by omega-3 supplementation.

1.9 Efficiency and Activity of Omega-3 Fatty Acids in Support of Cancer Patient Treatment

Omega-3 fatty acids demonstrate their effectiveness for supporting treatment of cancer patients in various ways.

1.9.1 By the suppress COX-2 expression

Omega-3 fatty acids suppress the effectiveness of COX-2 expression by the efficacy of inhibition of nuclear factor-kB (NF-kB). The transcription factor NF-kB initiates the development of inflammatory response cytokines, interleukin-1, and interleukin-6 including COX-2, interleukin-2, and tumour necrosis factor-alpha. Constitutive activation of NF-kB cells is associated with tumour cells growth and survival of cancer cells [73]. The production of interleukin-1, interleukin-6, and tumour necrosis factor-alpha may play an important role in happening cachexia which is mostly related to cancer. The resistance of the stimulation of NF-kB by the omega-3 fatty acid inhibits the making of NF-kB-dependent cytokines that helps to decrease the making of pro-proliferative eicosanoids. Dietary omega-3 fatty acids decrease the activity of NF-kB production that causes cancer cell growth is reduced [73,74].

1.9.2 Resistance of mitosis

Tumour cells enhance the multiplication of cancer cells. Protein kinase-C or PKC is a prototypical class of serine kinase that links multiple cellular processes to cancer [75]. Linoleic acid and arachidonic acid help inactivation of PKC and cause mitosis [76]. But, in colon carcinogenesis, DHA and EPA reverse the activity of PKC [77,78].

‘Ras’ and activator protein-1 (AP-1) is an oncogene that is repeatedly activated in the cancer cell and increases mitosis. Oncogene AP-1 and ras’s activity are decreased by the omega-3 fatty acid activation [79,80]. Eicosapentaenoic acid and docosahexaenoic acid resist mitosis and decrease the growth of colon and breast cancer [81,82].

1.9.3 Growth of cancer cells, controlled by restoring functional apoptotic pathway

Apoptosis is the process of programmed cell death. The apoptosis or apoptotic pathway is functional in our body. During cancer, the
apoptotic pathway is frequently inhibited or blocked by the increasing COX-2 expression [83]. NF-kB exhibits its activation in cancer cells and it blocks apoptosis [73]. Dietary omega-3 fatty acids block the activation of COX-2 and NF-kB. This mechanism is contributed to the remodelling of apoptosis. When the B-cell lymphoma 2 (bcl-2) family gene stops the apoptosis then docosahexaenoic acid inactivates the efficiency of bcl-2 family genes and increases the transcription of the gene that causes apoptosis tends to occur properly [84,85].

2. CONCLUSION

The omega-3 fatty acid is a crucial therapeutic supplement for cancer patients. The polyunsaturated omega-3 fatty acid is found in plant oil and various seeds but it is mostly present in cold-water marine fish's oil. This omega-3 fatty acid has neuroprotective, anticarcinogenic, and pain reductive activity. A cancer patient uses this polyunsaturated omega-3 fatty acid supplement as an anticarcinogen, immune nutrient, pharmaconutrient and antioxidant. As an antioxidant, omega-3 polyunsaturated fatty acid produces antioxidant enzymes SOD-1, GPx, and CAT to resist the activity of ROS and remove them from the cancer patient's body. And these can reduce the growth of neoplastic cells that causes tumours growth and malignancy can be interrupted. Fish oil containing omega-3 polyunsaturated fatty acid mainly docosahexaenoic acid and eicosapentaenoic acid decreased oncogene AP-1 and ras activity. This anti-oncogenic activity of omega-3 fatty acids can decrease the process of mitosis and cancer cell proliferation. Omega-3 PUFA supplementation most significantly worked as a neuroprotective activator on cancer-related major depression disorder.

With the use of omega-3 supplements on chemotherapy and radiotherapy patients, the pain symptoms like breast cancer pain are reduced. It also prevents cachexia-anorexia syndrome and increases the weight of cancer patients. As an antitumour function of omega-3 polyunsaturated fatty acid, mainly docosahexaenoic acid resists tumour cell development. The pharmaconutrient omega-3 fatty acid reduces the inflammatory response, helps in chemotherapy treatment, and overall improves the cancer patient's survival rate.

Based on the different clinical trials, we have come to the conclusion that the effectiveness of supplementation of omega-3 polyunsaturated fatty acids for cancer patients is incomparable. A daily serving of omega-3 fatty acid will help people with cancer to improve their health and maintain daily normal lifestyle.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer’s disease, other types of dementia, and cognitive impairment. Lipids. 2000 Dec;35(12):1305-12. Jones PJ, Kubow S. Lipids, sterols, and their metabolites. Modern Nutrition in Health and Disease. 1999;11:65-87.
2. Scorletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. Annual Review of Nutrition. 2013 Jul 17;33:231-48.
3. Gerster H. Can adults adequately convert α-linolenic acid (18: 3n-3) to eicosapentaenoic acid (20: 5n-3) and docosahexaenoic acid (22: 6n-3)? International journal for vitamin and nutrition research. 1998;68(3):159-73.
4. Brenna JT. Efficiency of conversion of α-linolenic acid to long chain n-3 fatty acids in man. Current Opinion in Clinical Nutrition & Metabolic Care. 2002 Mar 1;5(2):127-32.
5. Gutteridge JM, Halliwell B. Free radicals and antioxidants in the year 2000: a historical look to the future. Annals of the New York Academy of Sciences. 2000 Jan;899(1):136-47.
6. Mollace V, Gliozzi M, Carresi C, Musolino V, Oppedisano F. Re-assessing the mechanism of action of n- 3 PUFAs. International journal of cardiology. 2013 Dec 20;170(2): S8-11.
7. Vaughan VC, Hassing MR, Lewandowski PA. Marine polyunsaturated fatty acids and cancer therapy. British journal of cancer. 2013 Feb;108(3):486-92.

8. Chamras H, Ardashian A, Heber D, Glaspy JA. Fatty acid modulation of MCF-7 human breast cancer cell proliferation, apoptosis and differentiation. The Journal of Nutritional Biochemistry. 2002 Dec 1;13(12):711-6.

9. Spencer L, Mann C, Metcalfe M, Webb MB, Pollard C, Spencer D, Berry D, Steward W, Dennison A. The effect of omega-3 FAs on tumour angiogenesis and their therapeutic potential. European Journal of Cancer. 2009 Aug 1;45(12):2077-86.

10. D’Eliseo D, Manzi L, Merendino N, Velotti F. Docosahexaenoic acid inhibits invasion of human RT112 urinary bladder and PT45 pancreatic carcinoma cells via down-modulation of granzyme B expression. The Journal of Nutritional Biochemistry. 2012 May 1;23(5):452-7.

11. Horia E, Watkins BA. Complementary actions of docosahexaenoic acid and genistein on COX-2, PGE 2 and invasiveness in MDA-MB-231 breast cancer cells. Carcinogenesis. 2007 Apr 1;28(4):809-15.

12. Borek C. Free-radical processes in multistage carcinogenesis. Free Radical Research Communications. 1991 Jan 1;13(1):745-50.

13. da Silva Paixão EM, Oliveira AC, Pizato N, Muniz-Junqueira ML, Magalhães KG, Nakano EY, Ito MK. The effects of EPA and DHA enriched fish oil on nutritional and immunological markers of treatment naïve breast cancer patients: a randomized double-blind controlled trial. Nutrition Journal. 2017 Dec;16(1):1-1.

14. Berger MM, Pichard C. Development and current use of parenteral nutrition in critical care—an opinion paper. Critical Care. 2014 Aug;18(4):1-0.

15. Pierre JF, Heneghan AF, Lawson CM, Wischmeyer PE, Kozar RA, Kudsk KA. Pharmacofeeding review: physiological mechanisms. Journal of Parenteral and Enteral Nutrition. 2013 Sep;37:515S-65S.

16. Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. Role of oxygen radicals in DNA damage and cancer incidence. Molecular and Cellular Biochemistry. 2004 Nov;266(1):37-56.

17. Halliwell B. Free radicals and antioxidants: updating a personal view. Nutrition reviews. 2012 May 1;70(5):257-65.

18. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients. 2010 Mar;2(3):355-74.

19. Shahidi F, Ambigaipalan P. Omega-3 polyunsaturated fatty acids and their health benefits. Annual Review of Food Science and Technology. 2018 Mar 25;9:345-81.

20. Li M, Zhu Q, Hu C, Giesy JP, Kong Z, Cui Y. Protective effects of eicosapentaenoic acid on genotoxicity and oxidative stress of cyclophosphamide in mouse. Environmental Toxicology. 2011 Jun;26(3):217-23.

21. Mansara P, Ketkar M, Deshpande R, Chaudhary A, Shinde K, Kaul-Ghanekar R. Improved antioxidant status by omega-3 fatty acid supplementation in breast cancer patients undergoing chemotherapy: a case series. Journal of Medical Case Reports. 2015 Dec;9(1):1-6.

22. Bell GA, Kantor ED, Lampe JW, Kristal AR, Heckbert SR, White E. Intake of long-chain ω-3 fatty acids from diet and supplements in relation to mortality. American Journal of Epidemiology. 2014 Mar 15;179(6):710-20.

23. Khodarahmi M, Azadbakht L. The association between different kinds of fat intake and breast cancer risk in women. International Journal of Preventive Medicine. 2014 Jan;5(1):6.

24. Connolly JM, Rose DP. Effects of fatty acids on invasion through reconstituted basement membrane (‘Matrigel’) by a human breast cancer cell line. Cancer Letters. 1993 Dec 10;75(2):137-42.

25. Sun SN, Jia WD, Chen H, Ma JL, Ge YS, Yu JH, Li JS. Protective effects of eicosapentaenoic acid (DHA) induces apoptosis in human hepatocellular carcinoma cells. International Journal of Clinical and Experimental Pathology. 2013;6(2):281.

26. Virizuela JA, Camblor-Álvarez M, Luengo-Pérez LM, Grande E, Álvarez-Hernández J, Sendrós-Madroño MJ, Jiménez-Fonseca P, Cervera-Peris M, Ocón-Bretón MJ. Nutritional support and parenteral nutrition in cancer patients: an expert consensus report. Clinical and Translational Oncology. 2018 May;20(5):619-29.

27. Ryan AM, Power DG, Daly L, Cusken SJ, Bhuachalla ÉN, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital.
closet 40 years later. Proceedings of the Nutrition Society. 2016 May;75(2):199-211.
28. Gangadharan A, Choi SE, Hassan A, Ayoub NM, Durante G, Balwani S, Kim YH, Pecora A, Goy A, Suh KS. Protein calorie malnutrition, nutritional intervention and personalized cancer care. Oncotarget. 2017 Apr 4;8(14):24009.
29. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer treatment reviews. 2013 Aug 1;39(5):534-40.
30. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. The Lancet Oncology. 2014 Oct 1;15(11): e493-503.
31. Talvas J, Garrat G, Goncalves-Mendes N, Rouanet J, Vergnaud-Gauduchon J, Kwiatkowski F, Bachmann P, Bouteloup C, Bienvenu J, Vasson MP. Immunonutrition stimulates immune functions and antioxidant defense capacities of leukocytes in radiochemotherapy-treated head & neck and esophageal cancer patients: a double-blind randomized clinical trial. Clinical Nutrition. 2015 Oct 1;34(5):810-7.
32. Hamza N, Darwish A, O’Reilly DA, Denton J, Sheen AJ, Chang D, Sherlock DJ, Ammori BJ. Perioperative enteral immunonutrition modulates systemic and mucosal immunity and the inflammatory response in patients with periampullary cancer scheduled for pancreaticoduodenectomy: a randomized clinical trial. Pancreas. 2015 Jan 1;44(1):41-52.
33. Chagas TR, Borges DS, de Oliveira PF, Mocellin MC, Barbosa AM, Camargo CQ, Del Moral JÂ, Poli A, Calder PC, Trindade EB, Nunes EA. Oral fish oil positively influences nutritional-inflammatory risk in patients with haematological malignancies during chemotherapy with an impact on long-term survival: a randomised clinical trial. Journal of Human Nutrition and Dietetics. 2017 Dec;30(6):681-92.
34. Bougnoux P, Hajjaji N, Ferrasson MN, Giraudeau B, Couet C, Le Floch O. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. British Journal of Cancer. 2009 Dec;101(12):1978-85.
35. Ouldamer L, Goupille C, Vildé A, Arbion F, Body G, Chevalier S, Cottet JP, Bougnoux P. N-3 polyunsaturated fatty acids of marine origin and multifocality in human breast cancer. PLoS One. 2016 Jan 26;11(1):e0147148.
36. Freitas RD, Campos MM. Protective effects of omega-3 fatty acids in cancer-related complications. Nutrients. 2019 May;11(5):945.
37. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. Pain. 1999 Sep 1;82(3):263-74.
38. Lara-Solares A, Ahumada Olea M, Basantes Pinos AD, Bistre Cohén S, Bonilla Sierra P, Duarte Juárez ER, Simon Escudero OA, Santacruz Escudero JG, Flores Cantisani JA. Latin-American guidelines for cancer pain management. Pain Management. 2017 Jul;7(4): 287-98.
39. Falk S, Dickenson AH. Pain and nociception: mechanisms of cancer-induced bone pain. J Clin Oncol. 2014 Jun 1;32(16):1647-54.
40. Shinko D, Diakos CI, Clarke SJ, Charles KA. Cancer-related systemic inflammation: the challenges and therapeutic opportunities for personalized medicine. Clinical Pharmacology & Therapeutics. 2017 Oct;102(4):599-610.
41. de Aguiar Pastore Silva J, Emilia de Souza Fabre M, Witzberg DL. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: A systematic review. Clinical Nutrition; 2015.
42. Trabal J, Leyes P, Forga M, Maurel J. Potential usefulness of an EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition. Nutricion Hospitalaria. 2010;25(5):736-40.
43. Hershman DL, Unger JM, Crew KD, Awad D, Dakhil SR, Gralow J, Greenlee H, Lew DL, Minasian LM, Till C, Wade III JL. Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor–induced musculoskeletal pain: SWOG S0927. Journal of Clinical Oncology. 2015 Jun 10;33(17):1910.
44. Marchesi F, Giannarelli D, Gumenyuk S, Pisani F, Renzi D, Galié E, Mengarelli A. Prevention of bortezomib-related peripheral neuropathy with docosahexaenoic acid and α-lipoic acid in patients with multiple myeloma: preliminary
data. Integrative Cancer Therapies. 2018 Dec;17(4):1115-24.

45. Shen S, Unger JM, Crew KD, Till C, Greenlee H, Gralow J, Dakhil SR, Minasian LM, Wade JL, Fisch MJ, Henry NL. Omega-3 fatty acid use for obese breast cancer patients with aromatase inhibitor-related arthralgia (SWOG S0927). Breast Cancer Research and Treatment. 2018 Dec;172(3):603-10.

46. Muliaiwa Y, Haroen H, Rotty L. Cancer anorexia-cachexia syndrome. pathogenesis. 2012;5(5).

47. Lavir DS, Neves PM, Ravasco P. Should omega-3 fatty acids be used for adjuvant treatment of cancer cachexia?. Clinical nutrition ESPEN. 2018 Jun 1; 25:18-25.

48. Freitas RD, Campos MM. Protective effects of omega-3 fatty acids in cancer-related complications. Nutrients. 2019 May;11(5):945.

49. Ries A, Trottenberg P, Elsner F, Stiel S, Haugen D, Kaasa S, Radbruch L. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. Palliative Medicine. 2012 Jun;26(4):294-304.

50. Persson C, Glimeilis B, Rönnelid J, Nygren P. Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: a randomized pilot study. Nutrition. 2005 Feb 1;21(2):170-8.

51. Shirai Y, Okugawa Y, Hishida A, Ogawa A, Okamoto K, Shintani M, Morimoto Y, Nishikawa R, Yokoe T, Tanaka K, Urata H. Fish oil-enriched nutrition combined with systemic chemotherapy for gastrointestinal cancer patients with cancer cachexia. Scientific Reports. 2017 Jul 6;7(1):1-9.

52. Solis-Martínez O, Plasa-Carvalho V, Phillips-Sixtos G, Trujillo-Cabrera Y, Hernández-Cuellar A, Queipo-García GE, Meaney-Mendoza E, Ceballos-Reyes GM, Fuchs-Tarlovsky V. Effect of eicosapentaenoic acid on body composition and inflammation markers in patients with head and neck squamous cell cancer from a public hospital in Mexico. Nutrition and Cancer. 2018 May 19;70(4):663-70.

53. Schiessel DL, Yamazaki RK, Kryczyk M, Coelho I, Yamaguchi AA, Pequito DC, Brito GA, Borghetti G, Fernandes LC. α-Linolenic fatty acid supplementation decreases tumour growth and cachexia parameters in Walker 256 tumour-bearing rats. Nutrition and Cancer. 2015 Jul 4;67(5):839-46.

54. Caruso R, Nanni MG, Riba M, Sabato S, Mitchell AJ, Croce E, Grassi L. Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. Acta Oncologica. 2017 Feb 1;56(2):146-55.

55. Young K, Singh G. Biological mechanisms of cancer-induced depression. Frontiers in psychiatry. 2018 Jul 10: 9:299.

56. Pan Y, Zhou F, He C, Hui L, Huang T, Wei Y. Leptin-LepRb expressed in gastric cancer patients and related to cancer-related depression. BioMed Research International. 2017 Feb 20:2017.

57. Bigornia SJ, Harris WS, Falcón LM, Ordovás JM, Lai CQ, Tucker KL. The omega-3 index is inversely associated with depressive symptoms among individuals with elevated oxidative stress biomarkers. The Journal of Nutrition. 2015 Apr 1;146(4):758-66.

58. Müller CP, Reichel M, Mühle C, Rhein C, Gulbins E, Kornhuber J. Brain membrane lipids in major depression and anxiety disorders. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2015 Aug 1;1851(8):1052-65.

59. Larrieu T, Layé S. Food for mood: Relevance of nutritional omega-3 fatty acids for depression and anxiety. Frontiers in Physiology. 2018 Aug 6; 9:1047.

60. Dang R, Zhou X, Tang M, Xu P, Gong X, Liu Y, Jiao H, Jiang P. Fish oil supplementation attenuates neuroinflammation and alleviates depressive-like behavior in rats submitted to repeated lipopolysaccharide. European Journal of Nutrition. 2018 Apr;57(3):893-906.

61. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. In: Mayo Clinic Proceedings. 2010 Sep 1; 85(9):838-854. Elsevier.

62. Efthymiou C, Spyratos D, Kontakiotis T. Endocrine paraneoplastic syndromes in lung cancer. Hormones. 2018 Sep;17(3):351-8.

63. Dimitriadis GK, Angelouisi A, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Paraneoplastic endocrine syndromes. Endocr Relat Cancer. 2017 Jun 1;24(6): R173-90.

64. Azuma MM, Gomes-Filho JE, Ervolino E, Pipa CB, Cardoso CD, Andrada AC, Kawai
T, Cintra LT. Omega 3 fatty acids reduce bone resorption while promoting bone generation in rat apical periodontitis. Journal of Endodontics. 2017 Jun 1;43(6):970-6.

65. Tartibian B, Maleki BH, Abbasi A. The calcitropic hormone response to omega-3 supple-mentation during long-term weight-bearing exercise training in post-menopausal women. Journal of Sports Science & Medicine. 2010 Jun;9(2):245.

66. Graus F, Dalmaj J. Paraneoplastic neurological syndromes. Current Opinion in Neurology. 2012 Dec;25(6):795.

67. Sioka C, Fotopoulos A, Kyritis AP. Paraneoplastic immune-mediated neurological effects of systemic cancers. Expert review of Clinical Immunology. 2014 May 1;10(5):621-30.

68. Yorek MS, Coppey LJ, Shevalye H, Obrosov A, Kardon RH, Yorek MA. Effect of treatment with salsalate, menhaden oil, combination of salsalate and menhaden oil, or resolvin D1 of C57Bl/6J type 1 diabetic mouse on neuropathic endpoints. Journal of Nutrition and Metabolism. 2016 Jan 1;2016.

69. Azar L, Khasnis A. Paraneoplastic rheumatologic syndromes. Current Opinion in Rheumatology. 2013 Jan 1;25(1):44-9.

70. Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nature Reviews Rheumatology. 2014 Nov;10(11):662-70.

71. Dawczynski C, Dittrich M, Neumann T, Goetze K, Welzel A, Oelzner P, Völker S, Schaible AM, Troisi F, Thomas L, Pace S. Docosahexaenoic acid in the treatment of rheumatoid arthritis: A double-blind, placebo-controlled, randomized cross-over study with microalgae vs. sunflower oil. Clinical Nutrition. 2018 Apr 1;37(2):494-504.

72. Baia LC, Van den Berg E, Vervloet MG, Heilberg IP, Navis G, Bakker SJ, Geleijnse JM, Kromhout D, Soedamah-Muthu SS, De Borst MH, NIGRAM consortium. Fish and omega-3 fatty acid intake in relation to circulating fibroblast growth factor 23 levels in renal transplant recipients. Nutrition, Metabolism and Cardiovascular Diseases. 2014 Dec 1;24(12):1310-6.

73. Schwartz SA, Hernandez A, Evers BM. The role of NF-κB/IκB proteins in cancer: implications for novel treatment strategies. Surgical Oncology. 1999 Nov 1;8(3):143-53.

74. Babcock T, Helton WS, Espat NJ. Eicosapentaenoic acid (EPA): an antiinflammatory ω-3 fat with potential clinical applications. Nutrition. 2000;16(11/12):1116-8.

75. Kikkawa U, Takai Y, Tanaka Y, Miyake R, Nishizuka Y. Protein kinase C as a possible receptor protein of tumour-promoting phorbol esters. Journal of Biological Chemistry. 1983 Oct 10;258(19):11442-5.

76. Craven PA, Derubertis FR. Role of activation of protein kinase C in the stimulation of colonic epithelial proliferation by unsaturated fatty acids. Gastroenterology. 1988 Sep 1;95(3):676-85.

77. Rose DP, Connolly JM. Omega-3 fatty acids as cancer chemopreventive agents. Pharmacology & therapeutics. 1999 Sep 1;83(3):217-44.

78. McCarty MF. Fish oil may impede tumour angiogenesis and invasiveness by down-regulating protein kinase C and modulating eicosanoid production. Medical Hypotheses. 1996 Feb 1;46(2):107-15.

79. Collett ED, Davidson LA, Fan YY, Lupton JR, Chapkin RS. n-6 and n-3 polyunsaturated fatty acids differentially modulate oncogenic Ras activation in colonocytes. American Journal of Physiology-Cell Physiology. 2001 May 1;280(5):C1066-75.

80. Liu G, Bibus DM, Bode AM, Ma WY, Holman RT, Dong Z. Omega 3 but not omega 6 fatty acids inhibit AP-1 activity and cell transformation in JB6 cells. Proceedings of the National Academy of Sciences. 2001 Jun 19;98(13):7510-5.

81. Rose DP, Connolly JM, Rayburn J, Coleman M. Influence of diets containing eicosapentaenoic or docosahexaenoic acid on growth and metastasis of breast cancer cells in nude mice. JNCI: Journal of the National Cancer Institute. 1995 Apr 19;87(8):587-92.

82. Buckman DK, Hubbard NE, Erickson KL. Eicosanoids and linoleate-enhanced growth of mouse mammary tumour cells. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA). 1991 Nov 1;44(3):177-84.

83. Tsuji M, DuBois RN. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. Cell. 1995 Nov 3;83(3):493-501.
84. Narayanan BA, Narayan NK, Reddy BS. Docosahexaenoic acid regulated genes and transcription factors inducing apoptosis in human colon cancer cells. International Journal of Oncology. 2001 Dec 1;19(6):1255-62.

85. Chiu LC, Wan JM. Induction of apoptosis in HL-60 cells by eicosapentaenoic acid (EPA) is associated with downregulation of bcl-2 expression. Cancer Letters. 1999 Oct 18;145(1-2):17-27.

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