Omega-3 fatty acid and its protective effect against cancer and cancer-related complication

Abstract

Cancer is a combination of various physical complications that make people averse to life. Although 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, antitumouric, 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 health is a major lifestyle factor that can't be maintained by the cancer patient. As a result, they suffer from a major depressive disorder. 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, nutrient, docosahexaenoic acid, eicosapentaenoic acid, fish oil, oxidative stress, antioxidant, anticarcinogen, inflammatory response, pharmaconutrient, depression, lifestyle behaviour.

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 ends one is methyl (– CH_3) 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. In human health there are three types of omega-3 fatty acid involvement are noticed. These are alpha-linolenic acid (ALA) found in plant oils eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) both are found in cold-water marine fish [2]. Our body can't be synthesized omega-3 fatty acids, so they are taken in from outside through food. But eicosapentaenoic acid and docosahexaenoic acid are produced by the conversion of alpha-linolenic acid in the human body [3,4].

Species	LNA	Total EPA + DHA

Oxidative damage of the cell due to the metabolism of primary and secondary environmental pollutants leads to the production of free radicals, which is the most effective phenomenon of carcinogenicity. 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].

Major sources of omega-3 fatty acid

Table No. 1 *Major sources of omega-3 fatty acid*

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	0.2	1.3
Lake Whitefish	0.2	1.3
Sprat	0.0	1.3
Trout, Lean Lake	0.9	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)

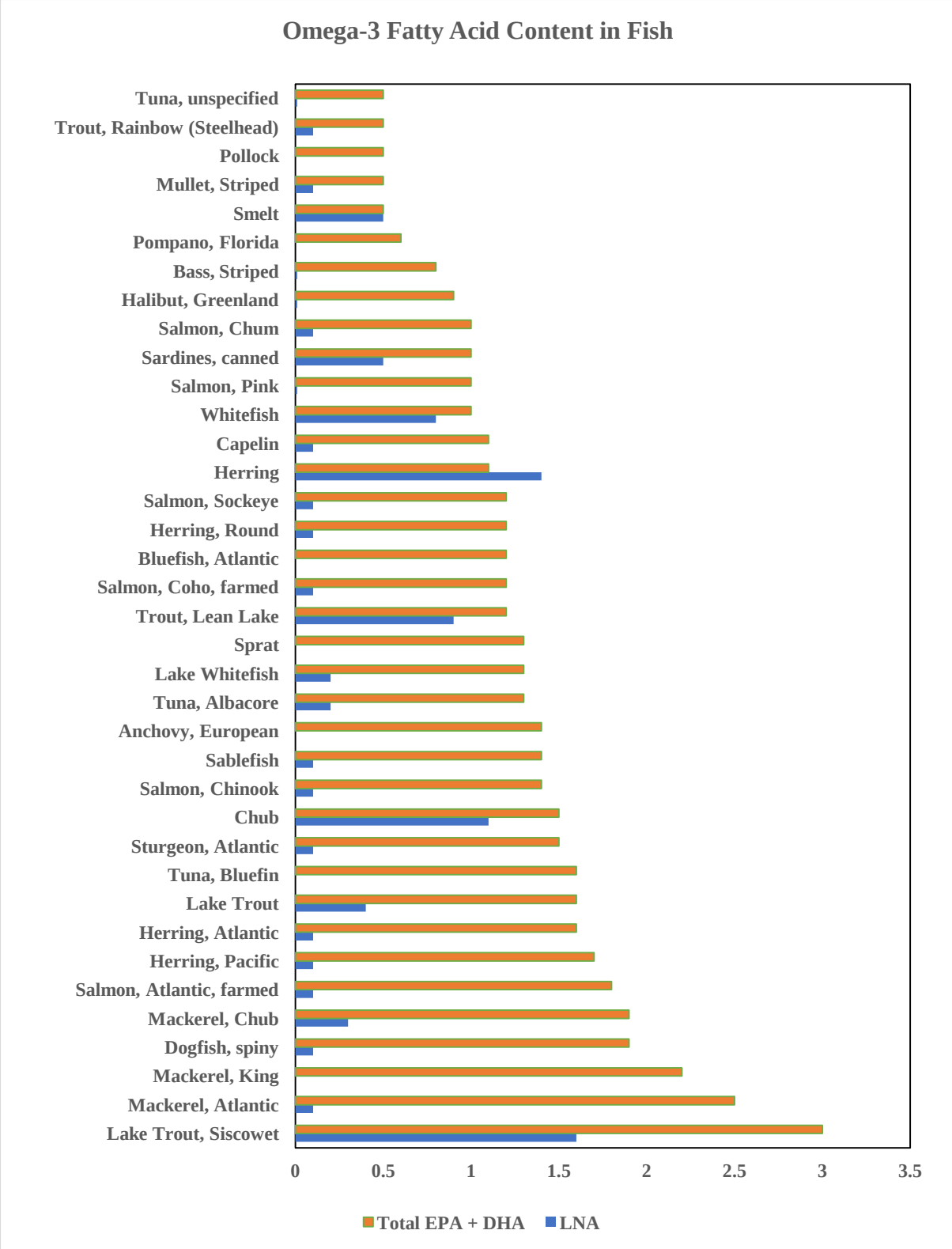

Figure: 1 *Graphical representation of Omega-3 Fatty Acid Content in Fish*

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. 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 [13,14]. The in-vitro and animal experiments suggest that dietary antioxidant availability can reduce the growth of neoplastic cells [14,12].

Various numerous studies have shown that fish oil contains omega-3 fatty acids mainly EPA and DHA which have anticarcinogenic and antioxidant properties [15,16]. **Li *et al.*, (2011)** 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) [17]. The antioxidant enzymes SOD 1, Gpx, and CAT helps to remove the toxic ROS from the cell. **Mansara *et al.*, (2015)** suggest in their study that fish oil which contains more omega-3 fatty acids can improve the antioxidant status in RBC and plasma [18]. Higher supplementation of EPA and DHA decreases the risk of cancer-related mortality [19]. Another study has evaluated that omega-3 fatty acids from fish oil could minimize the risk of breast cancer [20].

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. [21]. 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.*, (2013)**, reported that human hepatocyte carcinoma cell line migration and invasion are prevented by the DHA [22]. Increased acceptance of dietary omega-3 fatty acids mainly docosahexaenoic acid impedes the initiation and formation of tumour cells.

1.4 Omega-3 fatty acid for cancer treatment

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 [23,24]. 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 [25]. High inflammatory conditions of cancer patients contribute to various physical complexity like depression, cachexia, pain, and paraneoplastic syndromes [26, 27]. For maintaining immunocompetence during cancer treatment, immune-nutrition with omega-3 fatty acid is mostly prescribed [28, 29].

Clinical nutrition therapy which depends on functional nutrients is called Pharmaconutrition. Pharmaconutrition is commonly used in medical care treatment through the enteral, internal, or parenteral route. To diminish cancer-related complications, the most employed nutrient supplementation is pharmaconutrients. Currently in modern times, omega-3 fats are considered to 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 [33,34,35]. 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 [36,37].

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 [38]. Pain is mainly related to the localization and presence of tumour cells but these also happen by treatment of chemotherapy

and cancer surgery [39]. Various pain of cancer causes an inflammatory and neuropathic condition that is associated with tumour mass increment [40]. Chemotherapy and radiotherapy dependant toxicity and inflammation develop inflammatory symptoms, decrease the quality of life, and demonize the medicare success of cancer patients [41]. 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 [42,43].

Harshman *et al.*, (2015) 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 [44]. The numerous studies of **Maschio *et al.*, (2018)**, suggest that using 400 mg DHA and 600 mg ALA on humans with multiple myeloma, pain is failed to increase significantly [45]. In another study by **Shan *et al.*, (2018)**, 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 [46].

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 [47]. 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 [48].

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 [49]. However, the omega-3 supplement is important for the recovery of postoperative conditions and decreases the complications like infection and wound in cancer patients [50]. Fish oil supplements stabilize the gastrointestinal cancer patient's body weight [51,52].

According to the study of **Solis-Msrtinez *et al.*, (2018)**, 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 [53]. 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 [54].

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 [55]. Tumour necrosis factor (TNF), interleukin 1 beta (IL-1β), and interferon lambda (IFN-γ) 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) [56]. The hormone leptin is observed in the gastric tissue, which may be involved in gastrointestinal carcinoma-associated depression [57].

Bigornia *et al.*, (2016) suggest that omega-3 supplements are most important and beneficial for a person who is suffering from depression [58]. A lack quantity of omega-3 fatty acids in the brain can increase the probability of depression and anxiety disorder [59]. The omega-3 fatty acids show neuroprotective activity which suppresses the occurrence of brain diseases such as depression and anxiety [60]. 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 [61].

1.7 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 [62].

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 [63]. The complications such as gynecomastia, acromegaly, hypertension, ovarian hyperstimulation, non-islet cell tumour hypoglycaemia, hypercalcemia, and hyperthyroidism are considered a rare paraneoplastic syndrome [64]. The animal model studies of **Azuma *et al.*, (2017)** suggested that the omega-3 supplements can reduce bone resorption by the influx down-regulation of the inflammatory cell [65]. 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 [66].

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 [67]. Neuropathies, cerebellar degeneration, encephalomyelitis, myelitis, neuromyotonia, myasthenic syndrome, and dermatomyositis are the most common neurological paraneoplastic syndromes [67,68]. The omega-3 fatty acid supplementation contributes to neuroprotective activity against traumatic injury. **Yorek *et al*., (2016)** find that fish oil and resolvin D1 (RvD1) promote beneficial activity on neuropathy [69].

Rheumatologic paraneoplastic syndrome increases in the same way as an endocrine paraneoplastic syndrome [70]. 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 osteoarthropathy, tumour-induced osteomalacia, polyarthritis, and cancer-related myositis belong to the rheumatological paraneoplastic syndrome [71]. The docosahexaenoic acid supplementation can decrease the clinical and biochemical symptoms of rheumatoid arthritis patients' inflammation [72]. EPA/DHA supplementation intake can reduce the fibroblast growth factor-23 (FGF23) circulating level in renal transplant patients [73]. Thus, the tumour-associated hypophosphatemia and osteomalacia might be controlled by omega-3 supplementation.

1.8 Efficiency and activity of omega-3 fatty acids in treatment of cancer patient

Omega-3 fatty acids demonstrate their effectiveness in treating cancer patients in various ways.

I. 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 [74]. 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 [74,75].

II. 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 [76]. Linoleic acid and arachidonic acid help inactivation of PKC and cause mitosis [77]. But, in colon carcinogenesis, DHA and EPA reverse the activity of PKC [78,79].

'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 [80,81]. Eicosapentaenoic acid and docosahexaenoic acid resist mitosis and decrease the growth of colon and breast cancer [82,83].

III. 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 [84]. NF-kB exhibits its activation in cancer cells and it blocks apoptosis [74]. 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 [85,86].

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.

Depending on this above information, 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.

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