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석사학위 청구논문

Therapeutic Effects of Omega-3 Fatty Acids in Colon Cancer Patients

2015

성신여자대학교 대학원

식품영양학과

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이 논문을 석사학위논문으로 제출함

2014 년 12 월

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심태부의 석사학위 논문으로 인준함.

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Abstract

Incidence of colorectal cancer is increasing in worldwide with economic development. The causes of colorectal cancer are associated with the lack of physical activity, obesity, excessive intake of fat and meat, and lack of dietary fiber intake. Epidemiological studies suggested that there is an inverse correlation between consumption of fish and cancer risk and positive correlation between consumption of meat and meat products and colon cancer incidence. Both the type and amount of dietary fats consumed have been implicated in colon cancer etiology. A diet rich in saturated fatty acids have been known as an established risk factor for the onset of colon cancer. Whereas, omega 3 (n−3) fatty acids has been known to lower the incidence of this malignancy. A large number of studies have shown that fat composition has the potential to prevent and treat cancer. Increased ratio of omega 6 (n−6) to n−3 fatty acid contributes to the colon carcinogenesis. The level of n−6 fatty acids in the Western diet is more than 40 times higher than those in n−6 fatty acids. Therefore, the Western style diet has been known to be implicated

in colon carcinogenesis, tumor growth, invasion and metastasis of colon cancer.

n-3 fatty acids and their metabolites exert anti-carcinogenic activities in various cancer models by influencing the gene expression or activation of signal transduction molecules involved in the control of cell proliferation, differentiation apoptosis, angiogenesis, and metastasis. In addition, oral administration of n-3 fatty acids has shown that the inhibition of tumor growth and apoptosis in the various types of cancers, including lung, colon, pancreatic, esophageal, liver, breast, prostate, brain. Especially, docosahexaenoic acid (DHA) present in fish oil reduces expression of cyclin D1, cyclin E, cyclin A- associate kinases, which lead to cell cycle arrest in colon cancer cells. DHA-mediated stimulation of TRAIL(tumor necrosis factor-related apoptosis inducing ligand)-induced apoptosis was associated with extensive engagement of mitochondrial pathway (Bax/Bak activation, drop of mitochondrial membrane potential, cytochrome c release), activation of endoplasmic reticulum stress response, decrease of anti-apoptotic protein (XIAP, cIAP1) levels and significant changes in sphingolipid metabolism. In addition, DHA down-regulated the several other proteins regulated by the TCF-beta-catenin pathway and peroxisome proliferator-activated

receptor-delta, membrane type 1(MT1)-matrix metalloproteinase (MMP), MMP-7 and vascular endothelial growth factor.

Moreover, dietary intake of n-3 fatty acids improves efficacy of chemotherapeutic agents in the clinical and preclinical studies through suppression of inflammation. N-3 supplement decreased the level of inflammatory markers (tumor necrosis factor-α, interleukin-1β, soluble interleukin-2 receptor, interleukin-6, and interleukin-8 in the serum of colon cancer patients. N-3 fatty acids sensitize the cancer cells to chemotherapeutic agents in colon cancer patients. Also fish oil improves numbers and function of neutrophil in cancer surgery patients undergoing chemotherapy. In addition, n-3 fatty acids reduced the side effects of chemotherapeutic agents.

Moreover, n-3 fatty acids improve the cachexia in the colon cancer patients. Cancer patients who consumed n-3 fatty acids as a supplement showed the weight gain and increase the lean body mass (LBM) than the individuals without n-3 fatty acids, which is associated with enhancement of plasma eicosapentanoic acid (EPA) levels. Cancer patients who consumed n-3 fatty acids as a supplement showed weight gain, increased LBM and fat mass, high opportunity of physical activity, enhancement of life quality, survival period, and immune function.

Taken together above findings, n−3 fatty acid, especially, EPA and DHA have potent anti−inflammatory, anti−apoptosis, anti−proliferative, anti−angiogenesis, anti−invasion, and anti−metastatic effects. N−3 fatty acids as a supplementation offer the variable health benefits at a biochemical, clinical, and functional level in the colon cancer patients. The recommended intake of DHA and EPA set by the American Heart Association is 0.5 g/day EPA+DHA for those without heart disease, 0.8−1.8 g/day of EPA+DHA for those with heart disease, and no more than 3 g/day EPA+DHA unless under the supervision of a physician, due to increased risk of bleeding. In the most clinical trials, colorectal cancer patients received nutritional supplement providing 1 ~ 2 g of n− 3 fatty acids per day.

Intake of omega 3 fatty acid as an adjuvant is a supportive therapy to decelerate cancer progression and to enhance the cancer therapy and to prevent relapse. However, future investigations on the beneficial/risk effects of n−3 and n−6 fatty acids in colon cancer prevention/treatment are required to find reliable and best way to use these n−3 fatty acids for colon cancer patients.

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Introduction

Incidence of colorectal cancer is increasing worldwide [1,2,3,4,5]. Colon cancer in the world has increased at a rapid pace with economic development. It is also, increasing rapidly in developed countries today it is recognized as the current common malignant tumor [6].

Changes in dietary habits and lifestyle are believed to be the reasons. The cause of colon cancer is considered a source of dietary fats [7]. A large number of results show that nutritional fat composition has the potential to prevent and treat a number of diseases, including cancer [8,9]. Both the type and amount of dietary fats consumed have been implicated in colon cancer etiology. Since the industrial revolution, humans in the West have fundamentally changed their dietary habits towards increased consumption of animal protein and animal fat, decreased consumption of anti-oxidants, and increased omega 6 : 3 fatty acid ratio. The Western diet is more than 40 times higher in omega 6 fatty acids. The Western style diet is therefore carcinogenesis, tumor growth, invasion and metastasis enhances [10]. In several studies in which the effect of fish consumption on cancer risk was investigated,

meat and meat products were positively related to cancer risk, suggesting that cancer risks might be reduced more effectively when meat and meat products in meals are replaced by fish [11]. A diet rich in saturated fatty acids is an established risk factor for the onset of colon cancer, where as omega 3 fatty acid supplementation lowers the incidence of this malignancy [12].

Fish consumption has long been associated with a lower incidence and mortality of colon and cancers in many human populations [13]. Ecological studies have indicated that omega 3 fatty acids could be involved in the relationship between diet and colon cancers [14]. The incidence of colon cancer may differ from region [7]. The Japanese are large fish consuming populations [15]. For example, Japanese who migrated to the United States and adopted a Western diet in omega 6 fatty acids show an increased mortality rate from colorectal cancer [16].

Recently, the interest in the study to suppress the metastasis and induce apoptosis in cancer cells are concentrated by using a material of omega 3 fatty acids extracted from food [17]. The beneficial effects of fish oil seem to be due to its high content of the n−3 polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosa−pentaenoic acid (EPA) [18].

When humans ingest fish or fish oil, the ingested EPA and DHA partially replace the n−6 fatty acids in cell membranes, especially those of platelets, erythrocytes, neutrophils, monocytes and liver cells. High intake of omega 6 fatty acids shifts the physiologic state to one that is pro−thrombotic and characterized by increases in blood viscosity, vasospasm, and vasoconstriction, and decreases in bleeding time [19]. Dietary fish oil has been shown to have beneficial effects on some chronic degenerative diseases such as cardiovascular disease, rheumatoid arthritis, diabetes, other autoimmune diseases, and cancer [20]. Several experimental studies, epidemiological, and clinical data have demonstrated the beneficial role of omega 3 fatty acids, which prevent inflammation and colon cancer [10,21]. One of the possible beneficial factors may be fish intake or the n−3 PUFAs from fish, as found in epidemiological and clinical studies. Evidence from epidemiological studies suggests that diets rich in omega 3 fatty acids may be associated with reduced cancer risk [11]. These observations have formed the rationale for exploring the mechanisms by which omega 3 fatty acids may be chemoprotective and have resulted in significant advances in our mechanistic understanding of omega 3 fatty acids action on tumor growth [22]. Omega 3 PUFA influence cancer at all stages of

initiation, promotion, progression, and neoplastic transformation. More recently, experimental studies have reported enhanced tumor cell death with chemotherapy when fish oil is provided while toxic side effects to the host are reduced [23].

In this paper, we deal with molecular mechanisms involved in chemopreventive effects of omega 3 fatty acids in the in vitro, in vivo studies, and chemotherapeutic effects of omega 3 fatty acids in the clinical trials with the patient intake with omega 3 fatty acids. Omega 3 fatty acid is for nutritional support of cancer patients to prevent weight loss and modulate the immune system.

Ⅱ. Omega 3 fatty acid and cancer

1. Cancer chemopreventive effects of omega 3 fatty acids

DHA has a chain length of 22 carbons with six double bonds, which makes it the longest chain and most polyunsaturated 3 fatty acid commonly found in biological systems. It is either acquired from the diet or it is derived from eicosapentaenoic acid (EPA) via docosapentaenoic acid (DPA) as an intermediate [24] In the body, it is either acquired from the diet or it is derived from EPA via DPA as an intermediate. The pathway is known as Sprecher's shunt and involves a 24-carbon chain intermediate, followed by β-oxidation : EPA is twice elongated yielding 24:5 n-3, then desaturated to 24:6 n-3, then shortened to DHA [25,26]. The three main dietary omega 3 fatty acids are α-linolenic acid (C18:3omega3, all-cis-9,12,15-octadecatrienoic acid), found in green leafy vegetables, walnuts, canola oil, soybean oil, and flaxseed; and the longer chain EPA (C20:5 omega 3,all-cis-eicosa-5,8,11, 14,17-pentaenoic acid) and DHA (C22:6 omega 3, all-cis-docosa-4,7,10,13,16,19-hexaenoic acid), found primarily in coldwater fatty fish [27]. Fish is the major food source of long-chain omega 3 PUFA,

including EPA and DHA. Alpha-linolenic acid (ALA) is the plant derived omega 3 fatty acid found in a relatively limited set of seeds, nuts, and their oils [18]. The principal dietary source of omega 3 fatty acids is from oily cold water fish namely EPA and DHA. Omega 6 fatty acid is consumed as linoleic acid or arachidonic acid found in meats, and vegetable oils. [28,29]. In particular, alpha-linolenic acid, such as omega 6 fatty acids is closely related to the occurrence of cancer EPA and DHA, such as omega 3 fatty acids are known to reduce the risk of cancer [30,31,32].

Both omega-3 and omega-6 fatty acids are used as substrates for the production of eicosanoids that are a class of compounds including prostaglandins (PGs), thromboxanes and leukotrienes intimately involved in immunomodulation, inflammation and tumour formation. Eicosanoids produced using omega-6 fatty acids (arachidonic acid, AAA) as a substrate stimulate inflammation and tumour angiogenesis, whereas eicosanoids produced from omega 3 fatty acids, EPA and DHA are anti-inflammatory and do not stimulate angiogenesis [33,34,35]. Omega 6 fatty acids is related to carcinogenesis including growth, invasion and metastasis, in contrast, omega 3 fatty acids promote anticancer activity

via apoptosis and autophagy in cancer cells [36,37]. (Fig. 1) Cancer is the abnormal cell to proliferate by the activation of the cell involved in the mutation with the signal pathway, the cell growth, and inhibited the tumor suppressor gene [38].

Many mechanisms have been proposed for suppression of tumor cell growth by omega 3 fatty acids and new mechanisms are frequently reported as we gain additional knowledge of the regulation of gene expression by omega 3 fatty acids. Some of the mechanisms proposed for the action of omega 3 fatty acids against cancer [35]. Supplementing the diet of tumor-bearing mice or human with containing omega 3 fatty acid has showed the growth inhibition of various types of cancers, including lung [39], colon [40], pancreatic [41], esophageal [42], liver [43], breast [44], prostate [45], brain [46]. The omega 3 fatty acid increased the efficacy of the chemotherapy drugs used in treatment of various cancers [35]. For instance, the chemo drug efficacies of Paclitaxel [47], Doxorubin [48], Cisplatin [49], Carboplatin [50], Celecoxib [51], Epirubicin [52], CPT-11 [53], 5-fluorouracil [54], Mitomycin C [55], Tamoxifen [56], Radiation therapy [57] have been increases when omega 3 fatty acids were included in the diet. The omega

3 fatty acid raised the effectiveness and safety for the symptoms of patients with incurable or advanced cancer [58]. Another, advantage of the omega 3 fatty acids is that they improve the cachexia condition [59].

Cancer cachexia is a debilitating consequence of disease progression, characterised by the significant weight loss through the catabolism of both skeletal muscle and adipose tissue, leading to a reduced mobility and muscle function, fatigue, impaired quality of life and ultimately death occurring with 25–30 % total body weight loss [60]. Omega 3 fatty acid helps to suppress the loss of body fat and muscle mass in cachexia status [61].

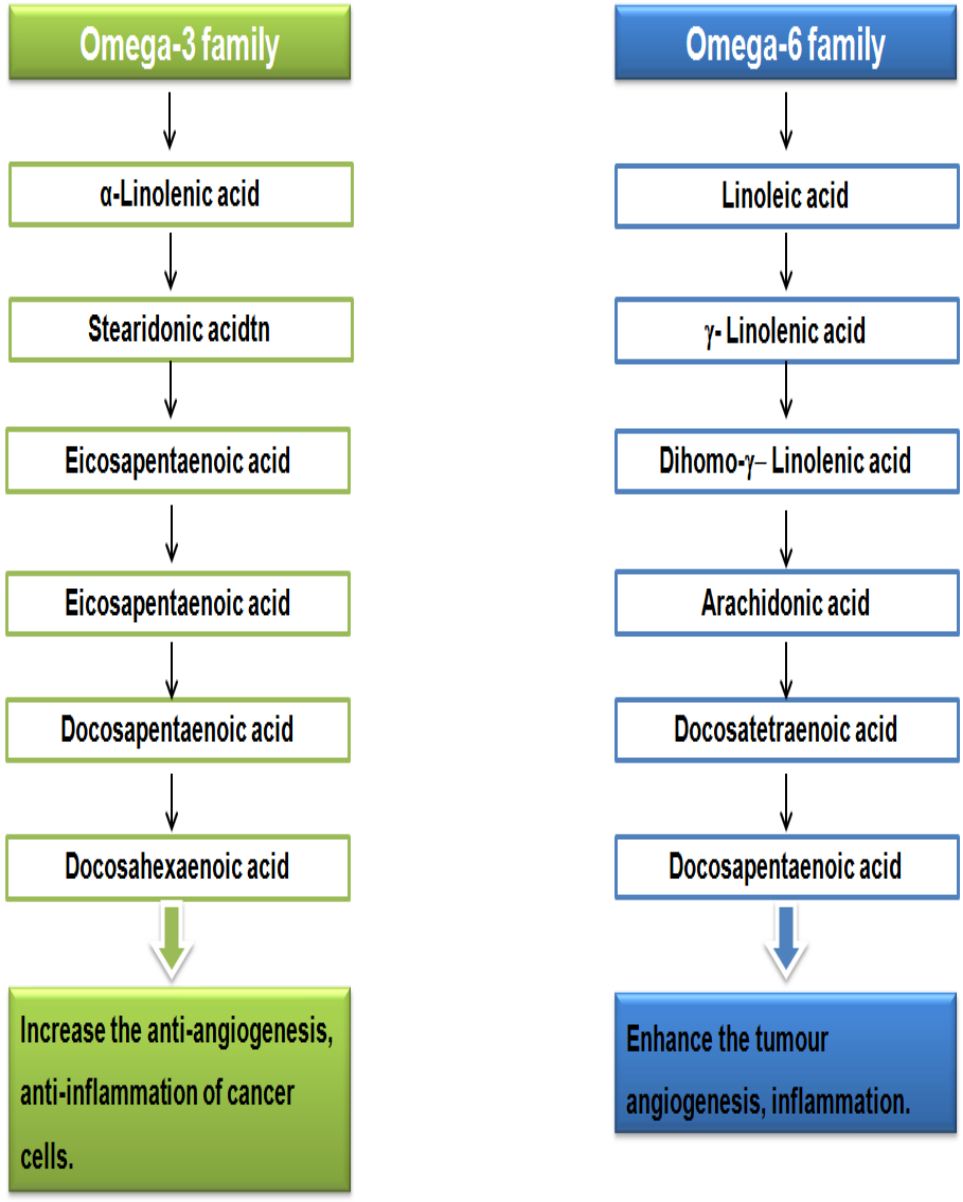

Fig. 1 Metabolism of omega 3 fatty acid and omega 6 fatty acids

2. Potential molecular mechanisms underlying anti-carcinogenic activities of omega 3 fatty acids

Dietary intake omega 3 fatty acids and their metabolites may exert some of their antitumor effects by influencing gene expression or the actions of signal transduction molecules involved in the control of cell proliferation, differentiation apoptosis, angiogenesis and metastasis [22,62]. Inhibition of colon carcinogenesis by omega 3 fatty acids is mediated through alteration of the expression of genes involved in colon cancer growth [63]. Omega 3 fatty acids prevent colon inflammation and carcinogenesis. Epidemiological studies suggested that higher concent-rations of omega 3 fatty acids in cell membranes are associated with lower cancer risk [9]. Inflammation has been hypothesized to increase the production of free radicals and reactive oxygen species, which leads to carcinogenesis. Although omega 6 fatty acids augment these events through the over production of AA-derived pro-inflammatory eicosanoids, the omega 3 fatty acids suppress inflammation and thus the overproduction of free radicals and carcinogenesis. Omega 3 fatty acid can affect tumor biology at multiple levels of the plasma membrane, intracellular and nuclear compartments. Omega 3 fatty acid play a crucial

roles in regulating apoptosis, cell proliferation, cell signaling, gene regulation, angiogenesis, and metastasis [23,35,64]. (Fig.2)

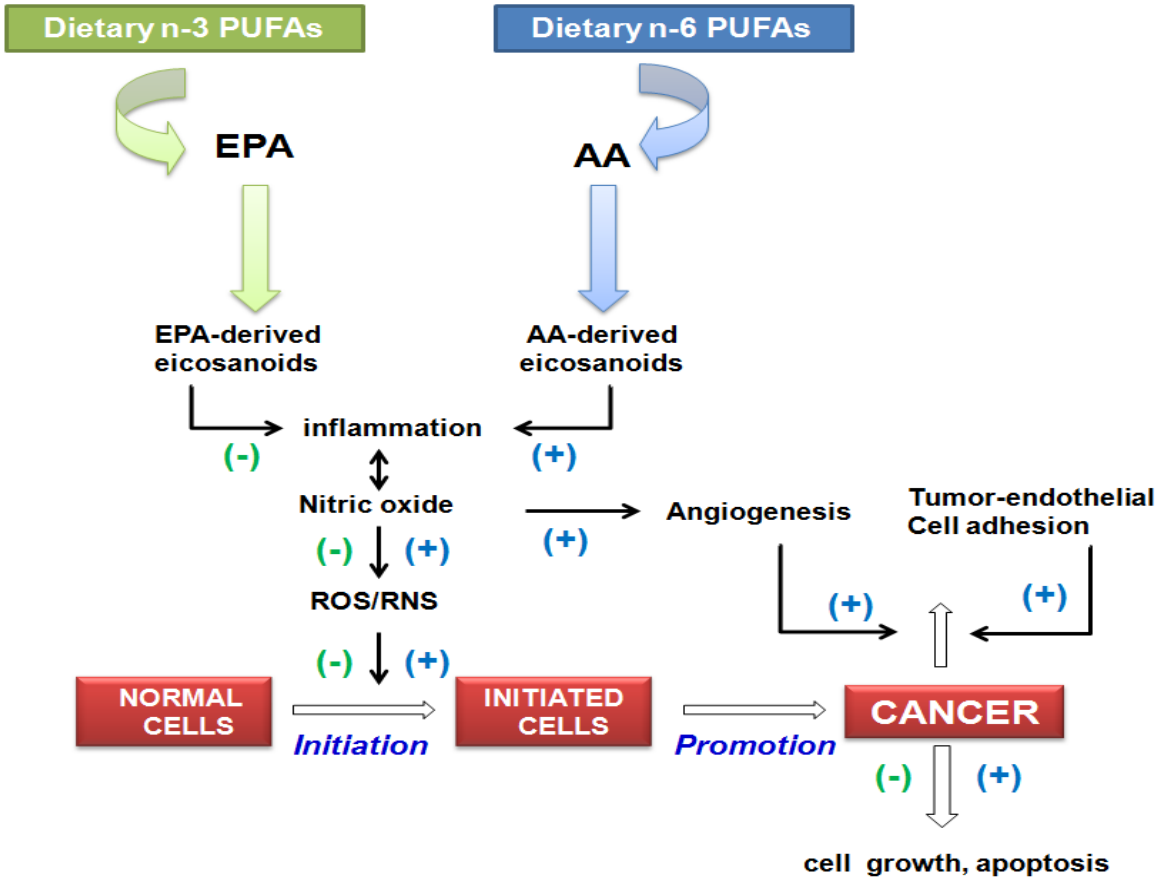

Fig. 2 Effects of n−3 and n−6 polyunsaturated fatty acids on carcinogenesis Cell cycle arrest

DHA can suppress AA-induced cell proliferation. DHA directly reduced PGE2-induce cell proliferation in a dose-dependent manner [65]. Change was identified enriched biological processes and pathways related to cell cycle, endoplasmic reticulum stress response and apoptosis after intake of fish oil. These processes and pathways are involved in normal cell function and may ultimately influence whole body health [66]. DHA, a major component of fish oil diets, is able to reduce serum-stimulated cyclin D1-, E-, and A- associate kinases activity in synchronized-HT-29 cells. EPA and DHA reduced the level of cyclin D1 [67,68]. DHA effectively inhibited HT-29 cell proliferation in a dose and time dependent manner. DHA were arrested in G1 phase and increased the proportion of HT-29 cells in Gl phase compared with that of the control group, while the proportion of the cells in S phase decreased significantly. The content of omega 6 fatty acid decreased and omega 3 fatty acid content increased and the ratio of omega 6 : 3 lowered significantly in colorectal cancer cells treated with DHA [69]. Chemotherapies aim to inhibit the cell cycle or induce apoptosis in cancer cells. Hence, targets of these drugs are generally cell cycle progression proteins such as cyclins, cyclin dependent kinases (CDK), and CDK inhibitors [70].

Apoptosis

DHA seem to indicate a lipid peroxidation-induced apoptosis in addition to effect reflected on the modification of cell cycle regulatory genes. Activation of cytochrome c which triggers caspases was associated with the elevated expression of pro-apoptotic caspases 10, 13, 8, 5 and 9 in DHA treated cells [71]. DHA mediated stimulation of TRAIL-induced apoptosis was associated with extensive engagement of mitochondrial pathway (Bax/Bak activation, drop of mitochondrial membrane potential, cytochrome c release) [72]. DHA induces apoptosis of cancer cells at both the intrinsic and the extrinsic pathways [73,74,75]. DHA-mediated stimulation of TRAIL(tumor necrosis factor-related apoptosis inducing ligand)-induced apoptosis was associated with extensive engagement of mitochondrial pathway (Bax/Bak activation, drop of mitochondrial membrane potential, cytochrome c release), activation of endoplasmic reticulum stress response, decrease of anti-apoptotic protein (XIAP, cIAP1) levels and significant changes in sphingolipid metabolism [76]. DHA induced apoptosis in variety cancer cell lines (ex HT-29, HCT116 and DLD-1 cells, SW480) [71,75,77,78,79], and cellular location of GRP78 in colon cancer cell lines [78]. GRP78 in the endoplasmic reticulum, goes to the tumor surface to promote the growth and

metastasis, and confers drug resistance to the treatment of cancer [80]. Thus, GRP78 supports the important role DHA pro-apoptotic effect [75].

Transcription factor p53 is a protein that functions in tumor suppression by inducing various genes and is known to play an important role in the regulation of cell cycle arrest and apoptosis. DHA is the primary tumor suppressive omega 3 fatty acid in vivo and in vitro and inhibits cancer growth by p53 dependent and independent pathways, while the marginal inhibition by EPA is p53 independent [67,81]. Also, p53 has many mechanisms of anticancer function, and plays a role in apoptosis, genomic stability and inhibition of angiogenesis [82]. In conclusion, DHA suppresses colon tumor growth by multiple mechanisms depending on the p53 status which potentially broadens the spectrum of tumors that could be impacted by DHA intervention. DHA affects several anti-apoptotic proteins as a target for chemotherapy.

Angiogenesis

Angiogenesis is required for invasive tumor growth and metastasis and constitutes an important point in the control of cancer progression. Therefore, inhibition of angiogenesis is a promising strategy for

treatment of cancer [83,84]. DHA, at the same range of concentrations, was also able to induce apoptosis by a caspase-3-dependent mechanism and to cause as dose and time dependent decrease of survivin, an apoptosis inhibitor which is undetectable in normal tissues and expressed in colorectal cancer through TCF-beta-catenin stimulation. DHA down-regulated the several other proteins regulated by the TCF-beta-catenin pathway and involved in regulation of tumor growth including peroxisome proliferator-activated receptor-delta, membrane type 1(MT1)-matrix metalloproteinase (MMP), MMP-7 and vascular endothelial growth factor [85].

Omega 3 fatty acids have been known as anti-inflammatory and anti-angiogenic agents via inhibition of these factors and others including VEGF and PDGF. These n-3 PUFA is able to PGE2, nitric oxide, cyclooxygenase(COX)-2, nuclear factor-KB(NF-KB) and inhibits VEGF expression in colon cancer cells. Therefore, n-3 PUFAs has been proposed anti-angiogenic compounds in colon cancer therapy [86,87]. EPA and DHA induced reduction in VEGF expression may be related to the parallel reduction of COX-2 protein expression in HT-29 cells both in vitro and in vivo conditions [86]. Thus, inhibition of angiogenesis can

be a strategy for the treatment of cancer [88]. EPA has been shown to be significantly more effective than DHA in reducing tumorigenesis in animal models of colorectal cancer [89], whereas others have shown DHA to accelerate dysplastic tissue transformation [90]. It is not surprising, therefore, that the use of pure EPA, over EPA/DHA blends or indeed pure DHA, is gathering interest as a safe and potentially viable chemopreventive agent. EPA has been shown to reduce intestinal adenoma multiplicity by 79% in animal models of familial adenomatous polyposis and later in humans [91].

Colorectal adenoma and adenocarcinoma cell line are highly susceptible to omega 3 fatty acids induced apoptosis [92]. EPA supplement reduces the size and number of polyps, colon cell growth and increases apoptosis in mice harboring APC mutations and in patients with a previous history of colon adenomas [91,93].

Indeed, when compared to placebo, the effect of EPA on rectal polyp growth in patients with polyposis produced a 22.4% decrease in adenoma numbers and a 29.8% reduction in adenoma size [94]. In addition, inhibit carcinogen induced colon tumor-angiogenesis in rats and reduce the growth of transplantable colon carcinoma implanted in mice [95,96,97].

Anti-inflammation

A possible mechanism by which fish consumption would decrease colorectal cancer risk is by reducing inflammation [98]. Beyond positive anti-inflammatory effects, in vitro and animal studies suggest that these long chain omega 3 fatty acids may also have several additional anti-neoplastic effects, including inhibition of tumor growth or increased apoptosis and suppression of angiogenesis [86,99,100].

The p38 MAPKs are activated by inflammatory cytokines and environmental stresses and may contribute to diseases like asthma and autoimmunity [101]. Levels of the pro-apoptotic proteins phosphorylated p38 MAPK and growth arrest inducible, and DNA damage inducible gene 153/C/EBP homologous protein incremented. DHA induce apoptosis in cancer cells and that this effect is mediated by the PI3-kinase signaling pathway [102]. Several small animal models have identified that omega 3 fatty acid enriched diets have inhibitory effects on COX-2 and prostaglandin production [103,104]. Synergistic inhibitory effects on the growth of experimentally induced tumours of cells from colon cancer cell lines treated with omega 3 fatty acids and COX-2 inhibitors have recently been demonstrated [51,105]. Athymic nude mice

transplanted with the cells expressing enzymatically active COX were fed same calories diets containing either safflower oil or fish oil. The fish oil feeding diet mice, tumor volume and tumors volume/bodyweight were significantly reduced [106]. Moreover, the COX-2-reduced expression was accompanied also by decreased levels of prostaglandin-E2 (PGE2) in the supernatants of HT-29 cells cultured in the presence of EPA or DHA and in tumors of PUFA-treated mice [86]. These results indicate that the COX-2/PGE2/ERKp/HIF-1 pathway of VEGF expression is likely to be a chief target of n-3 PUFA action [9,86].

Anti-oxidents

The pro-oxidant stressors and their connections to oxidative stress, the intestinal microbiota, intestinal cells, COX-2 and colorectal cancer are detailed. Environmental oxidative stressors are causally related to the development of colorectal cancer. The molecular and cellular details whereby oxidative environmental stress is translated into genotoxic damage to the epithelial cells of the large intestine are becoming increasing clear as detailed above[107] .

The multifaceted role of DHA in the expression of inducible nitric oxide synthase (iNOS) and of related pro-inflammatory genes, those have been shown to play a role in tumor progression [63]. INOS and COX-2-dependent angiogenesis are modulated by VEGF in human colorectal cancer and in turn VEGF-mediated angiogenesis is also dependent on nitric oxide production [108,109]. However, DHA inhibit COX-2 and iNOS activity in colon tumors. Preclinical model assays indicate that dietary fish oil inhibits COX-2 activity and enhances apoptosis in colon tumors. Including inhibition of translocation of NF-κB shows anti-inflammatory omega 3 fatty acid concentrate [110]. Clearly demonstrate that diets rich in omega 3 fatty acids, including DHA, induce apoptosis, and inhibit COX-2 and iNOS activity in colon tumors [110]. Including inhibition of translocation of NF-κB shows anti-inflammatory omega 3 fatty acid concentrate. NF-κB, which regulates several genes that are involved in the inflammatory process, provides an excellent target for development of new chemopreventive agents such as DHA [63,111].

Lipid raft

Lipid rafts are subdomains of the plasma membrane that contain high concentrations of cholesterol and glycosphingolipids. Caveolae are small

plasma-membrane invaginations that can be viewed as a subset of lipid rafts [112]. The presence within lipid rafts (and caveolae) of a variety of membrane proteins involved in cell signaling has led to the consensus that these lipid domains play an important role in the process of signal transduction [113,114]. Caveolin-1 is a ubiquitously expressed integral membrane protein and essential for the formation of so called Caveolae, small invaginations of the plasma membrane [115]. Caveolin-1 is frequently over expressed in a large range of tumor entities and the data point at a critical role of this integral membrane protein in carcinogenesis, tumor progression, metastatic spread and therapy resistance [116].

DHA can influence cellular membrane composition, thus changing plasma membrane properties, including membrane fluidity, phase behavior, permeability, fusion, flip-flop and protein function, following incorporation into membrane phospholipids [117]. DHA is known to be incompatible with cholesterol which is a critical component for lipid rafts, plasma membrane microdomains. DHA decreases cell surface levels of lipid rafts via their internalization, which is reversed by cholesterol [118]. Cholesterol reduction may be a potential therapy for suppressing cancer cell adhesion and migration. DHA enrichment was associated with a 70%

decrease in the cholesterol level in caveolae/lipid rafts compared with control, whereas palmitic acid16:0 treatment had no significant impact on cholesterol levels. Lowering the level of cholesterol disturb the regulated CD44 membrane localization that is necessary for enhanced cancer cell adhesion and migration [119]. DHA is effectively incorporated into phospholipids of caveolae/lipid rafts and significantly alters the lipid environment of these specialized membrane microdomains [120].

Furthermore, DHA down regulates and inactivates lipid raft-associated oncoproteins such as epidermal growth factor receptor (EGFR) and Hsp90. DHA decreases the levels of Hsp90 client proteins, including EGFR, HER2, Akt, and Src. DHA could exert its anti-cancer effect via modulation of lipid raft-associated signaling events [118]. (Fig.3)

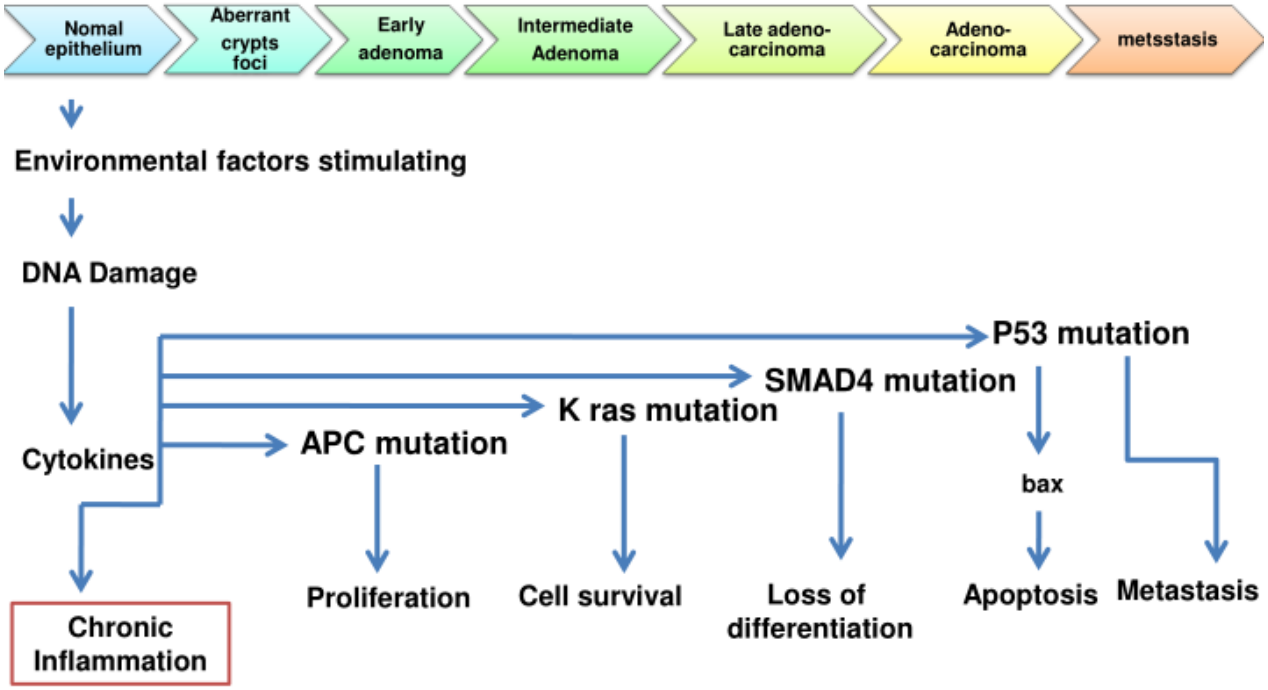

Fig. 3 Colon carcinogenesis

3. The efficacy of DHA as an adjuvant of chemotherapeutic agents

Several experimental evidences, in both humans and animal models indicate that dietary intake of omega 3 fatty acids can improve response to chemotherapeutic. [47]. The omega 3 fatty acids were shown in some cases to sensitize the cells to cytotoxic drugs [48]. In addition, DHA, an omega 3 fatty acid present in fish oil, may exert cytotoxic and/or cytostatic effects on colon cancer cells when applied individually or in combination with some anticancer drugs [76]. Providing omega 3 fatty acids, in cancer patients receiving chemotherapy after surgical tumor removal is able to improve the function. Of several papers suggest that a higher content of omega 3 fatty acids improves the treatment functioning of the cells. Also fish oil improves neutrophil numbers and functions in cancer surgery patients undergoing chemotherapy [121]. A combined treatment with troglitazone sensitizes tumor cells to induced apoptosis TRAIL induced apoptosis via various mechanisms, thereby minimizing the risk of obtained cancer cell resistance. Thus, a combination of troglitazone and omega 3 fatty acids will be the treatment of increasing the TRAIL induced apoptosis [122].

Chemotherapeutic therapy of 5-fluorouracil (5-FU) is to improve the pro-apoptotic effects. 5-FU is enhanced thereby more effective when used with the DHA-containing fish oil than when used alone on the tumor cells. DHA increases the inhibitory effect of 5-FU on the expression of a significant anti-apoptotic protein BCL-XL and BCL-2 [123,124]. The combination of fish oil (FO) with 5-FU results in an additive is growth inhibitory effect. DHA synergized with 5-FU in reducing colon cancer cell growth. The potentiating effect of DHA was attributable to the enhancement of the pro-apoptotic effect of 5-FU [124].

The report here that in an in vitro system using colon cancer cell line CaCo-2 the efficacy of DHA and p-XSC(1,4-phenylene bis seleno-cyanate) in combination is mediated through a cascade of events in which the primary inhibitory effect may be on expression of b-catenin, followed by reduced expression of the nuclear transcription factor NF-kB and COX2 and iNOS. In vivo studies in preclinical models using low doses of p-XSC in combination with DHA appear to be a highly promising approach that may evolve into a realistic chemopreventive strategy for colon cancer [125]. Thus, FO enhanced the cytotoxic and

pro-apoptotic effect of anticancer drug (5-fluorouracil, oxaliplatin, irinotecan) in HT-29 cells. This is induction of apoptosis through the Bax-dependent mitochondrial pathway to change. FO induced a loss of mitochondrial membrane potential in HT-29 cells. The fish oil could amplify the anti-tumor effect of the three drugs through a Bax-related intrinsic mitochondrial pathway for a stronger apoptosis induction [54].

Furthermore, apoptosis assay was conducted by adding PUFAs with paclitaxel to confirm the synergetic effect. Incubation of cells with omega 3 fatty acid greatly enhanced the cytotoxicity of the anticancer drug paclitaxel, manifested mainly through enhanced paclitaxel induced apoptosis [47]. Side effect of paclitaxel chemo drug is Axonal sensory peripheral neuropathy. Omega 3 fatty acids have beneficial effects on neurological disorders from their effects on neurons cells and inhibition of the formation of pro-inflammatory cytokines involved in peripheral neuropathy [126]. This is suggesting some synergism between omega 3 fatty acids and celecoxib. Inhibition of colon tumors by celecoxib was associated with lower levels of COX-2 activity and expression in colon tumors. These studies support the use of low doses of celecoxib in

omega 3 fatty acid rich diet as a promising approach for clinical trials [51].

In one study, has been demonstrated new biochemical effect of omega 3 fatty acids, which can be useful to overcome chemoresistance in multidrug resistant (MDR) colon cancer cells. Omega 3 fatty acids were incorporated in whole lipids as well as in detergent resistant membranes (DRM)s of MDR cells, and altered the lipid composition of these compartments [127]. Omega 3 fatty acid can cause a modest but very reproducible reduction of gene expression, protein production, and pump activity of MDR. Through a number of studies, omega 3 fatty acids chemo sensitize MDR colon cancer cells, by modulating the endogenous synthesis of cholesterol and the cholesterol amount in plasma membrane, two factors that affect ABC transporters activity and determine a MDR phenotype [128,129,130,131].

This normalization of tumor vasculature functions under Omega 3 fatty acid diet indicates that such a supplementation, by improving drug delivery in tumors, could be a complementary clinical strategy to decrease anticancer drug resistance [132]. The toxicity inherent in these drugs requires that dosages be limited and delivered in conjunction

with adjuvant therapies or strategies to enhance the toxicity of drugs to tumor cells at low doses and/or offer protection to non-target tissues [20,23]. (Fig. 4)

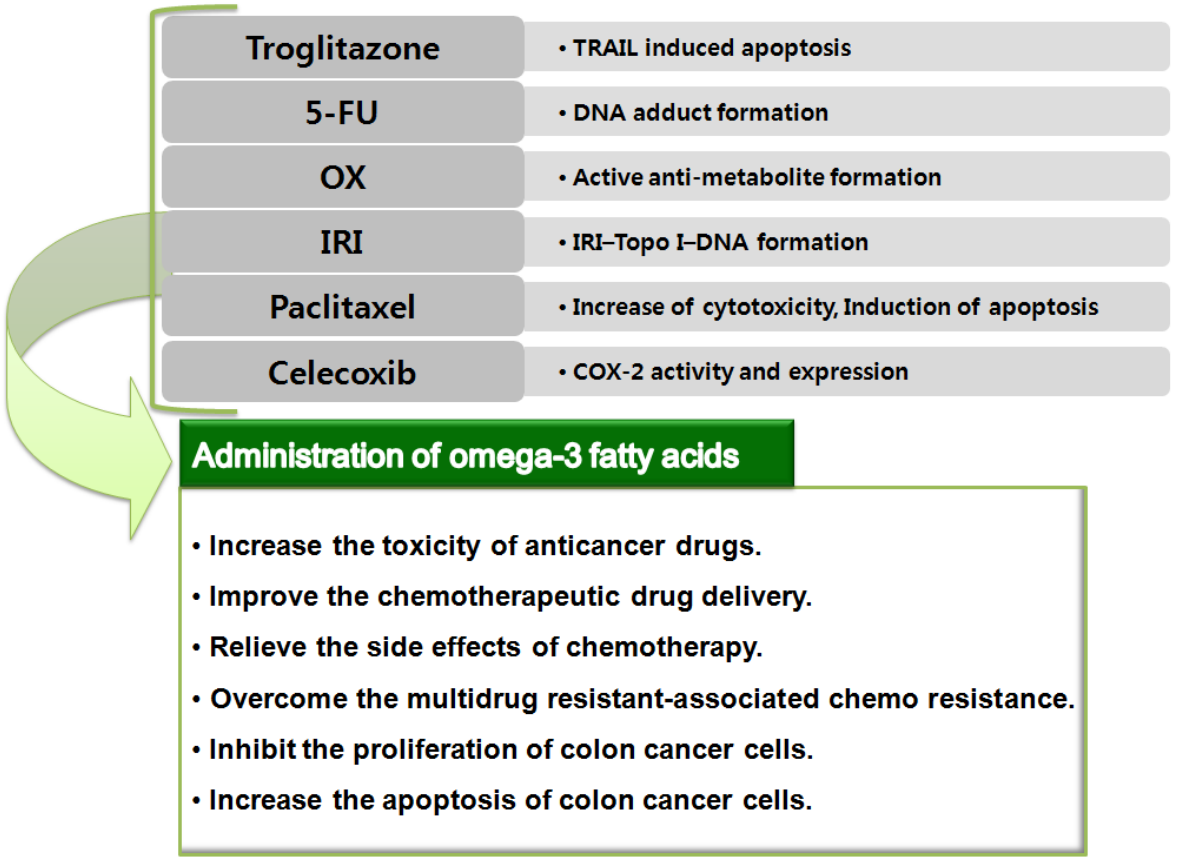

Fig. 4 The efficacy of DHA as an adjuvant of chemotherapeutic agents in the colon cancer patients

4. Clinical trials of omega 3 fatty acids in the cancer patients

Fish consumption is associated with a reduced colon cancer risk [133]. There have been many studies to demonstrate the therapeutic effect of omega 3 fatty acids in the colon cancer patients. Omega 3 supplement, before and after surgery/chemotherapy are seeing a change in colorectal cancer patients. Therefore, his review has attempted to show the clinical study of the interaction with the omega 3 fatty acids and colon cancer cells. I have addressed therapeutic effects of omega 3 fatty acids in the colon cancer patients through analyzing the clinical studies (Table 1). The study design that I analyzed was case-control study, intervention study, and cohort study.

Inflammation is a common feature in cancer. Liang ea al, colorectal cancer patients are given total parenteral nutrition supplemented with either soybean oil or a combination with fish oil (1.2g lipid/kg per day) for 7 day postoperatively. Compared with those on postoperative d 1, serum IL-6 levels on postoperative d 8 were significantly depressed in the FO group than in the reference group. Simultaneously, the ratios of CD4+/CD8+ were significantly increased in the FO group. In addition, depression of serum TNF-alpha levels and elevation of CD3+ and

CD4+ lymphocyte percentage were higher in the FO group than in the reference group. Patients in the FO group tended to need a shorter postoperative hospital stay. Postoperative supplement of omega 3 fatty acids may have a favorable effect on the outcomes in colorectal cancer patients undergoing radical resection by lowering the magnitude of inflammatory responses and modulating the immune response [134]. Sorensen ea al, providing 2.0 g of EPA and 1.0 g of DHA per day or a standard for seven days before surgery colon cancer patients. Lone S. Sorensen et al, study was to evaluate the production of leukotriene B4, 5-hydroxyeicosapentaenoic acid (5-HETE), leukotriene B 5 and 5-HEPE from stimulated neutrophils after seven days of preoperative treatment with an omega 3 fatty acid enriched oral nutritional supplement in patients undergoing colorectal cancer surgery and to study the possible impact on clinical outcome. On the day of operation, there was a significant increase in the production of LTB5 ($p < 0.01$) and 5-HEPE ($p < 0.01$), a significant decrease in the production of LTB4 ($p < 0.01$) and a trend for a decrease in the production of 5-HETE ($p < 0.1$) from stimulated neutrophils in the active group compared with controls. Omega 3 fatty acid exerts anti-inflammatory effects in surgical patients [135]. Postoperative supplementation of omega 3 fatty acids may have a

favorable effect on the outcomes in colon cancer patients by lowering the size/magnitude of inflammatory responses and modulating the immune response.

Silva et al, Inflammation is a common feature in cancer. The presence and magnitude of the chronic inflammation responses may produce progressive nutritional decline. Nutritional and inflammatory markers status was available, both at a baseline (M0), and after 9 wk of chemotherapy (M9) in the SG and in the non supplemented group (NSG). Patients supplemented with fish oil showed a clinically relevant decrease in the C−reactive protein/albumin relation (P = 0.005) [136]. Mocellin et al, Plasma TNF−alpha, IL−1beta, IL−10 and IL−17A, the pro/anti−inflammatory balance (ratio TNF−alpha/IL−10 and IL−1beta/IL10) and serum albumin, showed no significant changes between times and study groups ($p > 0.05$). C−reactive protein (CRP) and the CRP/albumin ratio showed opposite behavior in groups, significantly reducing their values in SG ($p < 0.05$). Plasma proportions of EPA and DHA increased 1.8 and 1.4 times, respectively, while the ARA reduced approximately 0.6 times with the supplementation (9 weeks vs baseline, $p < 0.05$). Patients from SG gained 1.2 kg (median) while the CG lost −0.5 kg (median) during the 9 weeks of chemotherapy ($p = 0.72$). These results demonstrate that 2

g/day of fish oil for 9 weeks of chemotherapy improves CRP values, CRP/albumin status, plasma fatty acid profile and potentially prevents weight loss during treatment [137].

The study by Omer Al-Taan et al, show changes in plasma and erythrocyte omega 6 fatty acids and omega 3 fatty acids in response to intravenous supply of omega 3 fatty acids in patients with hepatic colorectal metastasis. It will be important to link changes in plasma, blood cell and tissue fatty acid composition to biological effects such as the concentrations of lipid mediators and cytokines and to clinical outcomes. Intravenous supply of omega 3 fatty acids in patients with hepatic colorectal metastasis results in a rapid increase of EPA and DHA in plasma phosphatidylcholine (PC) and of EPA in erythrocytes. Intravenous infusion of omega 3 fatty acids could be used to induce a rapid effect in targeting inflammation [138].

Several papers have determined the effect of fish oil on the fatty acid composition of colonic mucosa and mesenteric adipose tissue and on rectal crypt cell proliferation in patients undergoing surgery for colonic carcinoma. EPA from marine oil supplements is rapidly incorporated into the colonic mucosa lipids of humans. Rectal biopsies result, proportion of EPA in mucosal and adipose tissue lipids was significantly greater. This

finding is consistent with the adipose tissue lipid pool having a relatively slow rate of fatty acid turnover compared to the mucosa. Treatment with EPA-FFA for 6 months was associated with a reduction in polyp number and decrease in the sum of polyp diameters. This would be of interest because omega 3 fatty acids have potential beneficial immunological effects that might benefit these patients [94,139,140].

The primary endpoint was infectious and non-infectious complications within 30 days of surgery. Granulocyte levels of EPA, DHA and DPA were significantly higher in the n-3 FA-enriched supplement group compared with the control group ($P < 0.001$). There was no significant difference between groups in infectious or non-infectious postoperative complications ($P = 1.000$). The arachidonic acid level in granulocytes was significantly lower in the enriched group than in the control group ($P < 0.001$). EPA, DHA and DPA were incorporated into granulocytes in patients receiving n-3PUFAs, but this was not associated with improved postoperative outcomes [141].

According to various clinical trial, between the n-3,n-6 PUFA and colon and/or rectal cancer incidence has been clearly shown. but cohort study is omega-3 intake and colorectal cancer is no significant relationship. Nevertheless, association was not found association of the n-3/n-6

PUFA with colon and/or rectal cancer. Fish and n−3 PUFA intake were not associated with colon and/or rectal cancer risk, even though there was a large variation in fish consumption among subjects. (Table. 2)

Table 1. colon cancer human Clinical Trial

References	Study design	No. of Population	Administration period	Dose	Results
[134]	Prospective, double blind, randomized, controlled	Case (20) Control (21)	Baseline end of 7days	1.2 g lipid/kg per day for 7 days post-operatively (colorectal cancer resection)	serum IL-6 levels postoperative 8 day were significantly depressed, ratios of CD4 + / CD8 + increase significant in the lipid FO group. depression of serum TNF-α levels, hospital stay and elevation of CD3+ and CD4+ lymphocyte percentage were higher in the FO group than in the reference group.
[135]	Randomized, Placebo Controlled Intervention	Case (65) Control (64)	Baseline end of 7days	EPA 2g + DHA 1g twice /day for 7days before surgery for patient	LTB5, 5-HETE is increased and LTB4, 5-HETE was decreased. And also suggest anti-inflammatory effect without the risk of postoperative complications.
[140]	randomized, double blind, prospective, placebo controlled, single center, intervention	Case (21) Control (19)	Baseline end of 7days	EPA 2g + DHA 1g twice/ day for 7days before surgery for patient	rapid incorporation of EPA composition into both colonic mucosa and colonic muscular is layer. The increase in the EPA content of the colonic wall may have implications for healing of the bowel an astomosis given that inflammation is an essential. omega 3 fatty acids is regulate inflammatory, immune function, which benefit these patients.
[139]	randomized, placebo-controlled	Case (25) Control (24)	entry, at surgery, and 8-12 week	Fish oil (2g) :EPA 1g + DHA 1g at prior to surgery	Rectal biopsies result, proportion of EPA in mucosal lipids was significantly greater. but there was no effect on mesenteric adipose tissue. but, long time self-reported habitual use of fish oil supplements was associated with a measurable difference in the EPA content of adipose lipids compared to self-reported non users.

[142]	Double blind, randomised, placebo controlled	Case (43) control (45)	of EPA-FFA Treatment was 30days	EPA-FFA 2g/day in patients undergoing liver resection surgery for experimental colorectal cancer liver metastases	Tumour tissue from EPA-FFA-treated patients demonstrated a 40% increase in EPA content. demonstrate anti-angiogenic activity in vitro. In the first 18 months after colorectal cancer liver metastases resection, EPA-FFA-treated individuals obtained overall survival benefit compared with placebo, although early colorectal cancer recurrence rates were similar.
[141]	randomized, double blind, placebo controlled, single centre	Case (65) control (64)	Baseline end of 7 days	EPA 2g + DHA 1g twice/day for 7days before surgery for Patient	Granulocyte levels of EPA, DHA and DPA were significantly higher in the n-3 FA enriched supplement group compared with the control group. The arachidonic acid level in granulocytes was significantly lower in the enriched group than in the control group. There were no statistically significant differences between groups in CRP and albumin levels.
[94]	randomised, double blind, placebo controlled, intervention	Case (28) control (27)	treatment before and after of 6 months	EPA-FFA 2g/day for 6months to Patients rectum postcolectomy	Treatment with EPA-FFA for 6 months was associated with a reduction in polyp number and decrease in the sum of polyp diameters. EPA-FFA treatment led to a mean 2.6-fold significantly increase in mucosal EPA levels. EPA-FFA has chemopreventive efficacy in familial adenomatous polyposis, to a degree similar to that previously observed with selective COX-2 inhibitors.
[138]	double blind, randomized, controlled	Case (11) Control (9)	Baseline end of 5 day end of 12 day	fish oil 2g (600mg EPA&DHA)/day intravenous supply in patients with hepatic colorectal metastases	treatment group showed increases in plasma PC EPA and DHA and erythrocyte EPA and decreases in plasma PC and erythrocyte linoleic acid, with effects most evident late in the infusion period. Intravenous supply of omega-3 PUFAs is results in a rapid increase of EPA and DHA in plasma PC and of EPA in erythrocytes
[136]	randomized, case controlled	Case (10) Control (8)	baseline end of 9week	fish oil 2g (600mg EPA&DHA) / day for 9 week of chemotherapy	fish oil showed a clinically relevant decrease in the CRP/albumin relation. compared to the non-supplemented groups is body mass index and body weight decreased less. low doses of fish oil supplement is able to positive modulate nutritional status and CRP/albumin relationship..

[137]	randomized, rospective, controlled, clinical trial	Case (6) Control (5)	Baseline end of 9weeks	fish oil 2g (600 mg EPA&DHA) / day for 9 week of chemotherapy	C-reactive protein and CRP/albumin were decreased significantly. These results demonstrate that 2 g/day of fish oil for 9 weeks of chemotherapy improves CRP values, CRP/albumin status, plasma fatty acid profile and potentially prevents weight loss during treatment.
[143]	phase II trial	Case (23)	baseline end of 3weeks end of 9weeks	EPA 480ml / day for 3 weeks before commencing chemo-therapy and continued for 3 cycles	between baseline and 3 week : significant increase weight and keep the LBM. after the commencement of chemotherapy : Protein and energy intake significantly decreased. over the first 3 week : increase energy level, plasma phospholipids EPA and maintained quality of life significantly. n-3 PUFAs is correlation between plasma IL-6 and IL-10 concentrations and survival, and between IL-12 and toxicity.

References	population	Results
[144]	Case (68,109)	Although fish and total EPA + DHA intake were not associated with CRC risk overall, these associations varied by genetic risk, with inverse associations observed among low-moderate genetic risk groups and positive associations observed among high risk groups. Results suggest that associations between n-3 PUFA intake and CRC may vary by gender, subsite, and genetic risk, providing additional insight into the potential role of n-3 PUFAs in cancer prevention.
[145]	Case (15,178)	There is no significant relationship between CRC prevalence and dietary n-3 fatty acid intake, dietary n-6 fatty acid intake and n-3 : n-6 fatty acid ratio. These results shed light on the correlation between diet, in this case n-3 and n-6 fatty acids, and CRC risk, lending support for prior reported relationships, although the effects may differ based on age.
[146]	Case (88,658)	Although n-3 PUFA, which are abundant in fish, have shown protective effects on colorectal cancer in laboratory studies, epidemiological studies to date have not been consistent. The study does not support the role of fish and n-3 PUFA in the etiology of colon and rectal cancer in this population whose fish consumption was high and the variation in n-3 PUFA consumption was large.

1. Anti-Inflammation effects

- Increase the level of EPA, DHA, erythrocyte hemoglobin, albumin, LTB5, and 5-HETE
- Decrease the level of CRP, TNF-α , IL-6, and Granulocytes

2. Configuration changes in colon cells

- Increases the level of EPA on the mucosal and adipose tissue (immune function)
- Decrease the colon cancer cell number and size of Polyp

3. Miscellaneous

- Increased the survival rate
- Decreased the hospital stay and complications
- Reduced the colon cancer recurrence (no statistical significance)

4. etc

- low content and no statistical significance in relation to the content of relapse
- N-3 / n-6 ratio colon cancer, colon cancer recurrence is no statistical significance

Table 2. Chemotherapeutic Effects of omega 3 fatty acids in the colorectal cancer patients

5. Effects of omega 3 fatty acids on cachexia in the cancer patients

Patients with cachexia are characterized by the presence of anorexia, early satiety. severe weight loss, weakness, anemia and edema [147]. In most patients, anorexia is more likely the result of the catabolic process rather than the cause of the cachexia. The nutritional status according to physical changes in cancer patients is lacking. Also in most cancer patients cachexia is caused by metabolic abnormalities due to the production of tumor and cytokines by the immune system [148]. More than half of cancer patients suffer from a progressive atrophy of skeletal muscle and adipose tissue, decreased quality of life, and reduced survival time [149]. The syndrome of cancer cachexia is a complicating factor in the management of the cancer patient and has a negative impact on overall survival [150].

The occurrence of cachexia in cancer patients is dependent on the patient response to tumour progression, including the activation of the inflammatory response and energetic inefficiency involving the mitochondria. Interestingly, crosstalk between different cell types ultimately seems to result in muscle wasting [151]. Depending on the

tumors type, and that leads to substantial weight loss, primarily from loss of skeletal muscle and body fat [151]. The total rate of cachexia in the hospitalized patients with digestive system cancer was 15.7%. The highest rate of cachexia was 34.0% in patients with pancreatic cancer followed by gastric cancer 22.4%, colon cancer 21.7%, and rectal cancer 20.1% [152].

Omega 3 supplement demonstrated significant correlations between their supplement intake and weight gain and increase in LBM. The relationship of supplement intake with change in LBM was significantly different between omega 3 supplement and non omega 3 supplement patients. Increased plasma EPA levels in the omega 3 supplement group were associated with weight and LBM gain. Weight increase is deeply associated with improving the quality of life [153]. The beneficial effects of EPA supplement lean body mass (LBM) that were reported in early studies of EPA supplementation. Also significant increase in LBM(+3.2 kg) and significant decrease in fat mass [154]. Cancer associated weight loss may be mediated by an inflammatory response to cancer. Serum levels of EPA and DHA increased as expected with fish oil. Omega 3 supplement was serum levels change for inflammatory markers (tumor

necrosis factor−α, interleukin−1β, soluble interleukin−2 receptor, interleukin−6, and interleukin−8) were improved [154,155]. A protein and energy dense oral nutritional supplement containing omega 3 fatty acids beneficially affects nutritional status during multimodality treatment in patients [61]. Arachidonate has been shown to both inhibit protein synthesis and increase protein degradation in skeletal muscle the latter by the mediation of a PGE2 intermediate [156]. N−3 PUFAs treatment of rats with the COX inhibitor naproxen inhibited muscle protein loss produced [157]. Thus, the possibility arises that the products of fat mobilisation from the adipose tissue may be responsible for increased protein turnover in skeletal muscle. The increased protein degradation in the muscle PGE2 of cachexia body was also inhibited by EPA [158].

Therefore, omega 3 fatty acids during chemotherapy reduced the side effects of chemotherapeutic agents and can improve the results of chemotherapy when highly integrated [159]. Clinical evidence suggests that the n−3 PUFA status of newly diagnosed cancer patients and individuals undergoing chemotherapy is low. Therefore, both the disease itself and therapeutic treatments may be contributing factors in the decline of n−3 PUFA status. Dietary supplementation to maintain and

replenish n−3 PUFA status at key points in the cancer [23]. In conclusion, Omega 3 supplements have Weight, LBM, Fat Mass, Physical activity opportunities, Quality of Life and Survival is increased. (Fig.5)

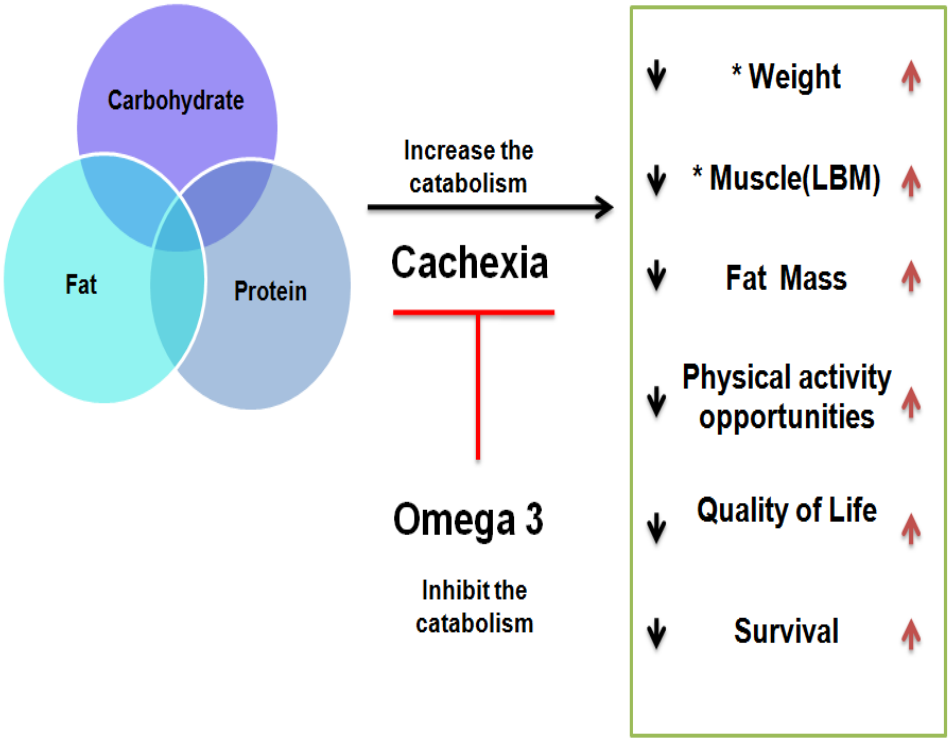

Fig. 5 Effects of omega 3 fatty acids on cachexia of cancer patients

Cancer patients who consumed n−3 fatty acids as a supplement showed weight gain, increased LBM and fat mass, high opportunity of physical activity, enhancement of life quality and survival period. There is a statistically significant difference (*$p<0.05$).

Conclusions

Various interrelated and integrated mechanisms is work by which n−3 PUFA influence cancer at all stages of initiation, promotion, progression, and neoplastic transformation. This paper, have great interest in research concerning omega 3 fatty acids, therapeutic effect to be increased significantly and perioperative outcomes of health benefits and an enhanced quality of life. More recently, experimental studies have reported enhanced tumour apoptosis with chemo−therapy, when n−3 supplement is provided while toxic side effects to the host are reduced [10,17,23]. The conclusions drawn from this review suggest that omega 3 fatty acid in particular EPA and DHA found principally in oily fish have potent anti−inflammatory, anti−apoptosis, anti−proliferative, anti−angiogenesis, anti−invasion, and anti−metastatic effects [33]. Supplementation with omega 3 fatty acids appears to offer benefits that are verifiable at a biochemical, clinical and functional level [160]. However, the recommended dose of omega 3 fatty acids for the enhancement of efficacy of chemotherapeutic agents or treatment of cancer patients was not demonstrated in the current research works. In the most clinical trials, colorectal cancer patients received nutritional supplement providing 1 ~ 2 g of omega 3 fatty acids per day.

The American Food and Nutrition Board of the Institute of Medicine set the adequate intake for LA as 11−12 g/day and 14−17 g/day and for ALA as 1.1 g/day and 1.6 g/day for female and male adults, respectively. The current recommended intake set by the American Heart Association is from 0.5 g/day EPA+DHA for those without underlying heart disease, 0.8−1.8 g/day of EPA+DHA for those with known heart disease, and no more than 3 g/day EPA+DHA unless under the supervision of a physician, due to increased risk of bleeding [161,162,163].

Omega 3 fatty acids have been demonstrated to be involved in cancer treatment in the majority. Omega 3 fatty acids increase the effectiveness of anticancer drugs. Intake of omega 3 fatty acid is a supportive therapy to decelerate cancer progression and to enhance the cancer therapy and to prevent relapse. However, future investigations on the beneficial/risk effects of n−3 and n−6 fatty acids in colon cancer prevention/treatment are required to find reliable and best way to use these n−3 fatty acids for colon cancer patients.

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논문개요

대장암 발생률은 전세계적으로 증가하고 있다. 대장암은 경제발전과 함께 빠른 속도로 증가하고 있으며 오늘날 개발도상국에서 빠르게 증가하는 흔한 악성종양으로 인식되어 있다. 대장암은 식습관과 관련이 많은 대표적인 암이다. 발생요인으로는 활동량 부족, 비만, 지방 및 육류의 과다섭취, 식이섬유소 섭취 부족 등이 기인하는 것으로 알려져 있다. 산업혁명 이후, 서양사람들은 근본적으로 그들의 식사습관이 바뀌었다. 동물성 단백질과 동물성 지방의 소비는 증가했고, 산화방지제의 소비는 감소, 오메가 6:3 지방산 비율은 증가했다. 포화지방산이 풍부한 식이요법이 대장암의 발병에 위험인자인 반면에 불포화지방산인 n-3 지방산은 악성 종양 발생을 낮추는 것으로 알려져 있다.

수많은 연구를 통해 영양상의 지방 구성요소들이 암을 포함한 질병들을 치료하고 예방하는데 잠재력을 가지고 있음을 보여준다. 특히 소비된 음식물의 지방 양과 유형에 따라 대장암의 원인과 깊은 연관되어 있다. 생선에 주로 발견된 EPA와 DHA와 같은 n-3 지방산의 식이섭취와 그들의 대사물질은 유전자 발현 또는 세포 증식의 제어, 세포사멸, 분화, 세포 신호, 유전자 조절, 혈관형성 그리고 암세포의 전의에 관련된 신호전달분자의 행동에 영향을 미치면서 항암효과를 보여준다.

서양식 식이요법은 n-3 지방산 대비 n-6 지방산의 섭취 비율 약 40배 높다. 그러므로 서양식 식이요법은 발암, 종양성장, 암 침입 그리고 암의 전의를 높인다. 여러 연구를 통해 암의 발생 위험을 높이는 육류 및 육류 제품을 생선으로 대체될 때 암의 발생 위험도가 감소될 수 있었다.

n-3 지방산의 암에 대해 항암 작용하는 기전은 아래와 같다. 암세포와 종양이 있는 쥐 또는 인간에게 n-3 지방산 보충 식이를 통해 폐, 대장, 췌장, 식도, 간, 유방, 전립선, 뇌 암 등에서 암세포의 성장을 억제시키거나 세포자살을 높여 주었다. 또한 사람과 동물모델을 통한 실험적 증거들은 n-3 지방산 식이섭취가 화학요법에 대한 반응을 향상 시켜 주었다. 생선기름 또는 n-3 지방산 보조제가 제공하게 되면 항암제와 결합하여 대장암의 세포독성작용을 높이고 약물에 민감하게 반응하는 것을 보여졌다. 뿐만 아니라 항암치료의 부작용을 감소시키고, 치료 효과를 높여 종양 세포자살을 높였다.

또 다른 이점은 오메가 3 지방산은 악액질 상태를 개선시킨다. 오메가 3 지방산 보조제를 보충 시, 체중 그리고 제지방(LBM)을 증가와 연관성을 있음이 보고되었다. N-3지방산 보충한 환자들과 그렇지 않은 환자들 사이에서 LMB 변화는 상당히 차이가 났다. n-3 보충 그룹에서 증가된 혈장 EPA 수준은 체중과 LBM 증가와 관련이 있었다. 오메가 3 보충은 체중, LBM, 지방량, 신체적 활동 기회, 삶의 질을 향상시키고 더 나아가 생존

기간을 증가시킨다. n-3 지방산은 동물 및 임상실험에서 면역력 증진 및 체력보정에 기여하는 것으로 나타났다.

결론적으로 세포주, 동물 모델 및 임상연구 결과를 바탕으로 종합해 볼 때 n-3 지방산은 발암과정을 억제하고 예방하였다. 임상실험에서 n-3 지방산을 보충제로 사용시 암 환자의 항암제에 대한 내성을 향상시켜주며, 염증과 대장암을 예방하고, 항암제의 효능을 향상시키고, 암세포들의 산화 환원 상태를 조절하여 종양세포의 침윤과 전이를 억제하는 것으로 알려졌다. 이러한 결과들은 DHA 를 비롯한 n-3 지방산이 항암치료의 보조제로서 잠재적인 가능성을 제시하였다. 따라서 n-3 지방산 이용을 통한 일차적인 암 예방효과 및 항암제의 효능을 향상시킬 수 있는 항암제의 보조제로서 사용 가능성을 기대해 본다.