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Review Article

ROLE OF FISH OIL AGAINST CANCER

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ABSTRACT

Cancer represents the largest cause of mortality in the world as the millions of humans and animals die every year. Chemotherapy being a major treatment modality used for the control of advanced stages of malignancies and as a prophylactic against possible metastasis, exhibits severe toxicity on normal tissues. Medicinal plants, including vegetables are known to have good immunomodulatory antioxidant activities, leading to anticancer effect. They act by stimulating both non-specific and specific immunity, and may promote the host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. However, the interest in the potential benefits of the fish oils has been greatly emerged. The cardiovascular diseases and cancer incidence rates have been found low due to the fish oils. Who eat a diet high in fish fat and low in carbohydrates (instead of the consumption of a high fat diet from animal and vegetable oils) have low incidence of cancer. The animal fats contain saturated fatty acids, and vegetable oils (e.g., corn oil and safflower oil) contain high levels of polyunsaturated fatty acids (PUFAs) of omega-6 type. Beneficial effects of the fish oils come from their unique composition of high levels of the omega-3 PUFAs, viz., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In addition, these omega-3 PUFAs can increase the HDL (so-called good cholesterol) levels. Fish oils also provide antiinflammatory and antiaggregatory effects.

KEYWORDS: Cancer/tumour, fish oils, PUFAs (EPA and DHA).

INDRODUCTION

Billions of dollars or rupees are being spent every year all over the world, but no perfect remedy of cancer could be investigated so far. “Cancer” is a frightful disease of human and other multicellular animals in which patients suffer pain, disfigurement and loss of many physiological processes. Cancer may be uncontrollable and incurable, and may occur at any time at any age in any part of the body. It is caused by a complex, poorly understood interplay of genetic and environmental factors. Cancer represents the largest cause of mortality in the world as the millions of humans and animals die every year. Thus, cancer is one of the most dreaded diseases, and is leading cause of death[1-2]. According to the WHO, cancer is the second largest cause of mortality and morbidity in the world after heart disease. Cancer rates continue to rise each year and it kills over 16 million people worldwide per year. However, in India the incidence of cancer may be as high as 3 million cases and more than 12,00,000 deaths occur every year from various types of cancer[3]. As per the other reports[2,4], cancer is the second leading cause of death in America; colon cancer is the second most common cause of cancer deaths and prostate cancer, second to skin cancer is the most frequently diagnosed cancer among men in the USA; while breast cancer is the most common of cancer in women worldwide. With increase in longevity, it is going to be a problem even in India. Cancers affecting the digestive tract are among the most common of all the cancers associated with ageing. The major causes of cancer are smoking, dietary imbalances, hormones and chronic infections leading to chronic inflammation.

Although many cancers can be controlled, the chronicity of the disease and expenses on supportive treatment are the valid reasons of not getting the cancer cured. Chemotherapy being a major treatment modality used for the control of advanced stages of malignancies and as a prophylactic against possible metastasis, exhibits severe toxicity on normal tissues. The plant kingdom serves as food and medicinal sources, and thus maintains the health and vitality of human beings as well as animals without causing any toxicity. More than 50% of all modern drugs in clinical use are of natural products, many of which have the ability to include apoptosis in various tumour cells of human origin. As per the WHO, more than 80% people in developing countries depend on traditional medicine or plants for their primary health needs. A recent survey shows that more than 60% of cancer patients use medicinal plants at some point in their therapy. Medicinal plants, including vegetables are known to have good immunomodulatory antioxidant activities, leading to anticancer effect. They act by stimulating both non-specific and specific immunity, and may promote the host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. Hence, the consumption of vegetables is widely accepted as lowering the risk of different types of cancer. Vegetables contain several phytochemicals having potent antioxidant activities. The antioxidant vegetables prevent from the cancer by protecting cells from damage caused by ‘free radicals’- highly reactive oxygen compounds[2]. In spite of the fact that many herbal drugs are prevalent for treatment of cancer but there is no perfect remedy of this disease and still the research is going on world wide[1,5].

However, the interest in the potential benefits of the fish oils has been greatly emerged. The cardiovascular diseases and cancer incidence rates have been found low due to the fish oils. The populations that eat a diet high in fish fat and low in carbohydrates (instead of the consumption of a high fat diet from animal and vegetable oils) have low incidence of cancer. The animal fats contain saturated fatty acids, and vegetable oils (e.g., corn oil and safflower oil) contain high levels of polyunsaturated fatty acids (PUFAs) of omega-6 type. Because a high intake of animal fat is related to an increased risk of heart disease, and PUFAs (corn oil) can

lower the cholesterol (beneficial to heart disease prevention) levels, one may tend to consume more vegetable oils than animal fats. Researchers found that the fish oil can significantly inhibit the cholesterol production. Beneficial effects of the fish oils come from their unique composition of high levels of the omega-3 PUFAs, viz., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In addition, these omega-3 PUFAs can increase the HDL (so-called good cholesterol) levels. Fish oils also provide antiinflammatory and antiaggregatory effects which play a crucial role in the formation of atherosclerosis and thrombosis. Due to these findings, it is believed that both healthy people and heart disease patients can benefit from the fish oil supplementation[6].

With this background, the present article has been put forth to describe the beneficial effects of the fish oils against different types of cancer/tumour as evident from various experimental and clinical studies.

Scientific reports on beneficial effects of fish oils in cancer

The fish oils show significant inhibitory effects against various human cancers in animal models, including breast cancer, colon cancer, skin cancer, pancreatic cancer, prostatic cancer, lung cancer, larynx cancer, etc. Unlike fish oil which is high in omega-3 PUFAs, fats that are high in omega-6 PUFAs (like corn oil) can increase the tumour growth. Using a chemical carcinogen-induced cancer model, the investigators found that a high intake of fish oil significantly lower the cancer incidence in animal studies as compared to animals fed either low fat diets or high corn oil diets. By implanting human tumours into immune-deficient (nude) mice, it was found that a high fish oil diet can slow the tumour growth. These results suggest that the fish oil can be used for both prevention and treatment of cancer. Over 40% of cancer patients died from “cachexia”, but not from cancer itself. Cachexia is the malnutrition and wasting away caused by cancer. The cachectic patients are characterized by extreme weakness and emaciation. If we can overcome this cancer-induced malnutrition, we can potentially save or prolong the life of over 40% of cancer patients. The researchers found that the fish oil could significantly prevent cachexia. Feeding the animals a high fish oil diet (compared to either a low fat diet or a high corn oil diet), significantly decreased the loss of body weight caused by cachexia, and at the same time, muscle mass was significantly increased. Additionally, fish oil showed a dramatic anticancer effect which was as effective as some chemotherapy. One of the big concerns in cancer treatment is “metastasis” (the process by which tumour cells spread from the primary location to distant parts of the body), which is increased by a high intake of omega-6 PUFAs (i.e., corn oil), but is inhibited by fish oil. Using a nude (immune deficient) mouse implanted with human breast cancer, it was observed that feeding a high fish oil diet (23%) to mouse significantly reduced human breast cancer cell metastasis to the regional lymph nodes and lungs. This result indicates the significant beneficial effects of fish oil supplementation in cancer treatment[6].

The high fat diets promote the development of mammary tumours induced in rats by 7,12-dimethylbenz(a)anthracene (DMBA), and polyunsaturated fats are more effective than saturated fats. Comparison of the effects of a polyunsaturated vegetable oil (corn oil) containing linoleate with a fish oil (menhaden oil) containing PUFAs derived from linolenic acid showed that higher dietary levels of corn oil increase the yield of DMBA-induced mammary tumours, while corresponding levels of menhaden oil has an inhibitory effect. The promotion of mammary tumorigenesis by polyunsaturated vegetable oils may be mediated by prostaglandins or other biologically active eicosanoids derived from n-6 fatty acids[7]. In another study, the inbred female rats were treated with the carcinogen N-methyl-N-nitrosourea and maintained on diets containing graded levels of different oils. The results indicated that the diets containing 20% menhaden oil (fish oil) produce a reduction in tumour incidence and a prolongation of the tumour latent period. This finding contrasted sharply with the enhanced tumour development and shortened latent period observed in the animals fed the equivalent dietary level of corn oil. Fatty acid analysis performed on the lipids extracted from the tumour and hepatic microsomes of animals on the menhaden oil diets demonstrated that the proportion of eicosapentaenoic acid (EPA) present in these microsomal lipids was related inversely to mammary tumour development[8].

A reduction in the size of transplantable mammary adenocarcinoma was achieved when female BALB/c mice were fed isocaloric 10% fat diets containing either hydrogenated cotton seed oil or menhaden oil as opposed to those mice fed corn oil. Although the effect of corn oil could not be inhibited when nine times as much hydrogenated cotton seed oil was added to the diet, such growth enhancement was abolished when the diet contained 9 times as much as menhaden oil. There was the involvement of prostaglandins in this process[9]. The effect of dietary intake of different levels of menhaden fish oil on azoxymethane-induced carcinogenesis was examined in male rats fed the semi-purified diets. The results of this study indicate that the fish oils rich in highly n-3 PUFAs do not enhance large bowel carcinogenesis, and that the fatty acid composition of dietary fat is one of the determining factors in large bowel carcinogenesis[10]. Rats fed either fish oil or corn oil in calorically and nutritionally balanced diets were injected with 1,2-dimethylhydrazine, which is a colorectal specific carcinogen; differential colorectal tumour induction was then measured. In addition, plasma peroxide concentrations were measured in rats in each dietary group as well as in a group receiving a low-fat diet, either with or without prior carcinogen treatment. The tumour incidence did not differ between groups fed corn oil and fish oil. The tumour yield in the left colon was significantly lower in rats fed fish oil. Total colorectal tumours induced were also fewer in the rats fed fish oil. The data on tumour yield in the left colon support the hypothesis that a diet rich in n-3 fatty acids, which are found in fish oil, may be less supportive of colorectal tumour development than a diet rich in n-6 fatty acids, which is found in corn oil[11]. It has been further studied that the colon cancer is associated with an increased expression of the cyclooxygenase [COX, officially known as prostaglandin-endoperoxide synthase (PTGS)] enzyme. The study showed that the fish oil can reduce both the COX-2 enzyme level and the risk of colon cancer. There is also evidence that the COX-2 is upregulated in Barrett’s esophagus and esophageal cancer. The researchers, therefore, reasoned that the fish oil supplementation might also be beneficial in Barrett’s esophagus and so, indirectly, lowers the risk of esophageal cancer[12].

A study was initiated in the late 1980s and involved 90,000 Swedish women who were questioned about their dietary habits and then followed for more than a decade. Women who consumed at least one portion of fatty fish each week during the study period ending in 2004 had a reduced risk of

kidney cancer of 74% when compared to those who ate no fatty fish. However, eating lean non-fatty fish produced no protection. In this study, the fatty fish included salmon, raw (pickled) herring, sardines and mackerel. The non-fatty fish included cod, tuna, fresh-water fish, shrimp and lobster. The authors comment that these results support the hypothesis that the lower risk of kidney cancer is possibly due to the increased intake of the fish oil rich in two marine omega-3 PUFAs, viz., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as well as vitamin D. Several test tube (*in vitro*) and animal experiments have clearly shown that the long-chain omega-3 PUFAs, viz., EPA and DHA, the main components of fish oil, help inhibit the promotion and progression of cancer. Their beneficial effect is particularly pronounced in hormone-dependent cancers such as breast and prostate cancer. Some, but not all, epidemiologic studies have also found a beneficial effect. Researchers conclude that omega-3 PUFAs are protective against cancer progression, while omega-6 PUFAs, notably arachidonic acid and its derivatives, help promote the growth of cancer[13]. Many studies showed that the fish oils retard ageing and suppress so-called free radical diseases like atherosclerosis and cancer. Other studies showed that a daily EPA + DHA intake in excess of 2.3 g decreases the production of superoxide, a potent cancer promoter. The researchers also confirm that the fatty, cold-water fish are the best sources of EPA and DHA and that the conversion rate of alpha-linolenic acid (flax seed oil) to EPA is very low, even in healthy humans, probably in the order of 2 to 5%[14].

Lung cancer is the leading cause of cancer deaths in Japan even though the incidence and mortality is still less than two-thirds of that found in the USA and the UK. Japanese researchers found that both men and women who ate cooked or raw fish 5 times a week or more had half the incidence of lung adenocarcinoma when compared to participants who ate cooked or raw fish less than once a week. Women who consumed tofu (soybean curds) 5 times a week or more were found to have half the risk of adenocarcinomas, as compared to women who consumed tofu fish less than once a week. Frequent consumption of carrots was found to be beneficial for women, but detrimental for men, especially to smokers. Green vegetables were found to be highly beneficial for men, but not statistically so for women. There was also some evidence that increased coffee consumption is associated with an increased risk of squamous cell and small cell lung carcinomas in men. Increased consumption of dried or salted fish was not beneficial for men or women. The researchers speculate that this is because the processing destroys the healthy omega-3 oils (EPA and DHA) present in raw and cooked fish[15]. Cachexia (abnormally low weight, weakness and general bodily decline) is common in patients suffering from pancreatic cancer. Cachexia makes patients more prone to infections, can shorten their survival and reduce their mobility. The investigators observed that the fish oil supplementation can halt and even reverse cachexia in patients with pancreatic cancer. The patients were started out on 2 g/day of fish oils (containing 360 mg of EPA and 240 mg of DHA). The dose was subsequently increased by 2 g/day every week until the patients' body tolerance was reached. The average final intake was 12 g/day. Prior to entering the trial the average weight loss among the patients was 2.9 kg (6.3 lbs) per month. After 3 months of fish oil supplementation, an average weight gain of 0.3 kg/month was observed among the patients. The concentration of EPA in plasma phospholipids increased from 0 to 5.3% of total fatty acids after one month of supplementation, while the concentration of DHA increased to 6.6% from a base level of 3.5%. The researchers conclude that the fish oil supplementation arrests weight loss in cancer patients with cachexia[16].

The presence of benign polyps (adenomas) is a significant risk factor for full-blown colon or rectal cancer. Animal studies have shown that the omega-3 PUFAs (EPA and DHA) inhibit the development of colon cancer; and the epidemiological studies have shown that fish consumption is inversely proportional with the incidence of colon cancer. Therefore, the researchers at the Catholic University of Rome set out to determine if fish oil supplementation would inhibit the development of benign polyps, the precursors of colon cancer. The patients were divided into 4 groups. Group 1 was supplemented with 1.4 g of EPA and 1.1 g of DHA per day; group 2 with 2.7 g of EPA and 2.4 g of DHA; group 3 with 4.1 g of EPA and 3.6 g of DHA; while group 4 received *placebo* capsules containing mainly olive oil. Biopsy samples from the lower part of the colon lining and blood samples were taken, and analyzed at the start of the trial and 30 days later at the end of the supplementation period. Overall, patients in the fish oil groups experienced a significant decline in the number of abnormal cells in their colon lining as compared to members of the *placebo* group. Further analysis showed that the reduction in the number of abnormal cells was limited to patients who had a large number of abnormal cells at the beginning of the trial. The researchers also noted a very significant increase in EPA and DHA levels, and a significant drop in arachidonic acid level in the biopsy samples from the fish oil supplemented patients. A separate 6-month trial in the patients taking 1.4 g per day of EPA and 1.1 g per day of DHA also showed a significant drop in the number of abnormal colon lining cells. The workers conclude that the low-dose supplementation with fish oils inhibits the proliferation of abnormal cells (a precursor to polyps) in patients at risk for colon cancer, and that this effect can be maintained with long-term treatment. The authors also advised to increase the vitamin E intake during fish oil administration[17].

Proposed mechanisms of fish oil against cancer growth

Although there is no clear mechanism to explain the anticancer effect of fish oils, many potential models of action of the fish oils have been proposed[6]:

(a) Alteration of cell membrane composition- After ingestion, the fish oil is easily incorporated into cell membranes (especially tumour cells), which changes the cell membrane composition. This alteration will change the cell's response to growth factors, hormones, antibodies, etc.

(b) Inhibition of prostaglandin production- The prostaglandin can stimulate tumour cell growth. The fish oil can inhibit the enzyme responsible for prostaglandin synthesis called COX or prostaglandin synthase (PTGS). After a high intake of fish oil, the prostaglandin (especially in the tumour cells) is decreased significantly, which in turn, slows the cancer growth.

(c) Immune system stimulation.

(d) Hormone profile changes- This may provide important benefits for hormone-related cancers like breast cancer.

(e) Tumour cell toxicity, probably by causing lipid peroxidation in the tumour cells.

It is believed that the n-3 PUFAs exert their beneficial effects in many ways: they suppress the synthesis of pro-inflammatory eicosanoids from arachidonic acid and thus

produce an overall antiinflammatory effect; they positively affect gene expression or the activities of signal transduction molecules involved in the control of cell growth, differentiation apoptosis, angiogenesis and metastasis; they suppress excessive production of nitrogen oxide during chronic inflammation and thereby help prevent DNA damage and impaired DNA repair; they decrease estrogen production and thus reduce the estrogen-stimulated growth of hormone-dependent cancer cells; and fish oils improve insulin sensitivity and cell membrane fluidity, and may help prevent metastasis through these effects[13]. Free radicals and reactive oxygen species (ROS) produced in cells may attack PUFAs resulting in the formation of more free radicals, specifically hydroperoxides, which in turn, may damage DNA ultimately leading to cancer. Indeed, these effects have been observed in *in vitro*, but not in actual human beings. At least in one *in vitro* and one animal experiment, it was found that EPA + DHA kill human breast cancer cells via the formation of hydroperoxides, but that this effect is strongly inhibited by vitamin E. Thus, at this point, it is not entirely clear whether EPA + DHA exert part of their beneficial effects through an increase or a decrease in the production of free radicals and ROS. The investigators emphasize that the major benefits of the fish oils probably are associated with their ability to inhibit the synthesis of arachidonic acid-derived, pro-inflammatory eicosanoids[14].

CONCLUSION

The potential benefit of the fish oil against cancer has been greatly achieved. The cardiovascular diseases and cancer incidence rates are low due to use of the fish oil. The populations that eat a diet high in fish fat and low in carbohydrates (instead of the consumption of a high fat diet from animal and vegetable oil) have low incidence of cancer. The fish oil can significantly inhibit the cholesterol production. Beneficial effects of the fish oils come from their unique composition of high levels of the omega-3 polyunsaturated fatty acids (PUFAs), viz., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Additionally, these omega-3 PUFAs can increase the HDL (good cholesterol) levels. Fish oil also provides antiinflammatory and antiaggregatory effects which inhibit the formation of atherosclerosis and thrombosis. Thus, it is believed that both healthy people and diseased patients can benefit from the fish oil supplementation.

REFERENCES

1. Madhuri S. Studies on oestrogen induced uterine and ovarian carcinogenesis and effect of ProImmu in rat. PhD thesis. Jabalpur, MP: RDVV; 2008.
2. Pandey Govind, Madhuri S. Therapeutic approach to cancer by vegetables with antioxidant activity. Int Res J Pharm 2011; 2(1):10-13.
3. Pandey Govind, Madhuri S. Radiations in the pathogenesis of cancer. Jigyasa 2009; 3:86-90.
4. Madhuri S, Pandey Govind. Some anticancer medicinal plants of foreign origin. Curr Sci 2009; 96(6):779-783.
5. Madhuri S, Pandey Govind, Khanna A, Sahni YP. Anticancer effect of a herbal formulation on oestrogen induced ovarian adenocarcinoma in rat. Pl Arch 2012; 12(1):353-357.
6. www.Fish oil and fighting cancer; website, 2012.
7. Braden LM, Carroll, KK. Dietary polyunsaturated fat in relation to mammary carcinogenesis in rats. Lipids 1986; 21(4):285-288.
8. Jurkowski JJ, Cave WT. Dietary effects of menhaden oil on the growth and membrane lipid composition of rat mammary tumors. J Natl Cancer Inst 1985; 74(5):1145-1150.
9. Gabor H, Abraham S. Effect of dietary menhaden oil on tumor cell loss and the accumulation of mass of a transplantable mammary adenocarcinoma in BALB/c mice. J Natl Cancer Inst 1986; 76(6):1223-1229.
10. Reddy BS, Maruyama H. Effect of dietary fish oil on azoxymethane-induced colon carcinogenesis in male F344 rats. Cancer Res 1986; 46(7):3367-3370.
11. Nelson RL, Tanure JC, Andrianopoulos G, Souza G, Lands WE. A comparison of dietary fish oil and corn oil in experimental colorectal carcinogenesis. Nutr Cancer 1988; 11(4):215-220.
12. Mehta SP, et al. Effect of n-3 polyunsaturated fatty acids on Barrett's epithelium in the human lower esophagus. Amer J Clin Nutr 2008; 87:949-956.
13. Wolk A et al. Long-term fatty fish consumption and renal cell carcinoma incidence in women. J Amer Med Asso 2006; 296(11):1371-1376.
14. Larsson SC, et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: A review of potential mechanisms. Amer J Clin Nutr 2004; 79:935-945.
15. Takezaki T, et al. Dietary factors and lung cancer risk in Japanese with special reference to fish consumption and adenocarcinomas. Bri J Cancer 2001; 84:1199-1206.
16. Wigmore SJ, et al. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. Nutrition (suppl) 1996; 12(1):S27-S30.
17. Anti M, et al. Effects of different doses of fish oil on rectal cell proliferation in patients with sporadic colonic adenomas. Gastroenterology 1994; 107:1709-1718.

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