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(n-3) Fatty Acids and Cancer Therapy[1]

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ABSTRACT Supplementing the diet of tumor-bearing mice or rats with oils containing (n-3) (omega-3) or with purified (n-3) fatty acids has slowed the growth of various types of cancers, including lung, colon, mammary, and prostate. The efficacy of cancer chemotherapy drugs such as doxorubicin, epirubicin, CPT-11, 5-fluorouracil, and tamoxifen, and of radiation therapy has been improved when the diet included (n-3) fatty acids. Some potential mechanisms for the activity of (n-3) fatty acids against cancer include modulation of eicosanoid production and inflammation, angiogenesis, proliferation, susceptibility for apoptosis, and estrogen signaling. In humans, (n-3) fatty acids have also been used to suppress cancer-associated cachexia and to improve the quality of life. In one study, the response to chemotherapy therapy was better in breast cancer patients with higher levels of (n-3) fatty acids in adipose tissue [indicating past consumption of (n-3) fatty acids] than in patients with lower levels of (n-3) fatty acids. Thus, in combination with standard treatments, supplementing the diet with (n-3) fatty acids may be a nontoxic means to improve cancer treatment outcomes and may slow or prevent recurrence of cancer. Used alone, an (n-3) supplement may be a useful alternative therapy for patients who are not candidates for standard toxic cancer therapies. J. Nutr. 134: 3427S–3430S, 2004.

KEY WORDS: • *(n-3) fatty acids* • *cancer* • *nutrition* • *alternative cancer therapy*

Using animal models, researchers have repeatedly shown that the growth of chemically induced cancers and of human cancer xenografts can be slowed or completely inhibited by incorporation of (n-3) fatty acids in the diet [examples: (1–5)]. There are a few articles indicating that (n-3) fatty acids may be beneficial for human cancer therapy [examples: (6,7)]. The objective of this article is to briefly review the evidence for the effects of (n-3) fatty acids on cancer growth or cancer therapy, and to highlight rational mechanisms for those effects. Knowledge in this field is rapidly expanding as a result of new molecular biology techniques that allow the identification of novel mechanisms for the actions of fatty acids and increased interest in nontoxic alternative therapies for cancer.

What are (n-3) fatty acids?

Fatty acids are hydrocarbon chains with a carboxyl group at the head (δ) end and a methyl group at the tail (n) end (**Fig. 1**). The carbons may be connected by single or double bonds. The number of carbons in the chain and the type of bond between the carbons give rise to the different types of fatty acids. The bonds between all carbons in saturated fatty acids are fully saturated with hydrogen and are single bonds. Monounsaturated fatty acids and PUFA have bonds that are not saturated with hydrogen, thus one or more double bonds connect the carbons. The first double bond in an (n-6) fatty acid is 6 carbons from the n end; the first double bond in an (n-3) fatty acid is 3 carbons from the n end. Mammals, including humans, can synthesize saturated fatty acids and monounsaturated (n-9) fatty acids but cannot synthesize either the (n-6) or the (n-3) double bond. The (n-3) and (n-6) fatty acids are essential components in cell membrane phospholipids and as a substrate for various enzymes; thus, fatty acids containing these bonds are essential fatty acids (EFA)[3] and must be obtained in the diet. The (n-6) fatty acid is consumed primarily as linoleic acid [abbreviated as 18:2(n-6), meaning 18 carbons, 2 double bonds, (n-6) type] from vegetable oils but some arachidonic acid [AA; 20:4(n-6)] is also obtained from meats (8). The (n-3) fatty acids may be consumed as α-linolenic acid [18:3(n-3)], which is contained in various amounts in some oils [canola (11%), 18:3(n-3); flaxseed (57%); soybean (8%)] and in leafy green vegetables. Longer-chain (n-3) fatty acids, mainly EPA [20:5(n-3)] and docosahexaenoic acid [DHA, 22:6(n-3)], are found in fish and fish oils. The (n-3) and (n-6) fatty acids cannot be interconverted, but both can

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[3] Abbreviations used: AA, arachidonic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LOX, lipoxygenase; NFκB, nuclear factor κB.

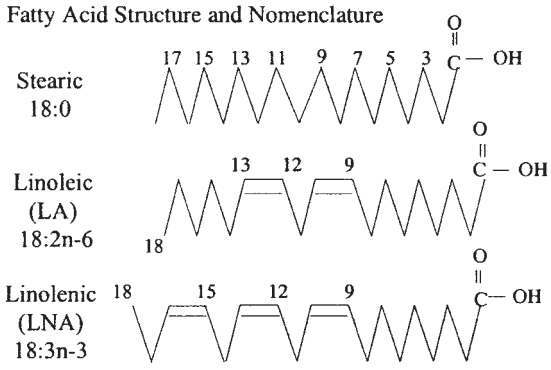

FIGURE 1 Structures of fatty acids. Stearic acid is an 18-carbon saturated fat. Linoleic acid is an 18-carbon fatty acid with 2 unsaturated bonds and with an unsaturation in the (n-6) position, thus the abbreviation is 18:2(n-6). Alpha-linolenic acid is an 18-carbon (n-3) fatty acid with 3 double bonds.

be elongated and desaturated to form other fatty acids of the same series (9). Humans have the enzymes to elongate 18:3(n-3) to EPA and DHA, but it is not clear how important this pathway is in humans. Certainly the best source of EPA and DHA is from fish or fish oils in the diet. The production of AA from linoleic acid by the Δ-5 and Δ-6 desaturases is suppressed by α-linolenic acid, EPA, and DHA, the 3 major (n-3) fatty acids (10).

Suppression of AA production by (n-3) fatty acids also suppresses the production of AA-derived eicosanoids. Cyclooxygenase (COX) and lipoxygenase (LOX) act on 20-carbon fatty acids to produce cell-signaling molecules. COX activity on AA or EPA produces prostaglandins or thromboxanes; LOX activity on AA or EPA produces the leukotrienes. The 2-series prostaglandins produced from AA tend to be proinflammatory and proproliferative in most tissues. The 3-series prostaglandins produced from EPA tend to be less promotional for inflammation and proliferation; thus, EPA-derived prostaglandins are less favorable for the development and the growth of cancer cells.

COX has 2 isozymes: COX 1 and COX 2. COX 1 is constitutively produced by most cell types, and COX 2 is produced as part of the inflammatory response. Incorporation of (n-3) fatty acids has been shown to suppress the production of COX 2 (11,12) and can reduce the inflammatory response (13) by changing the types of eicosanoids that are produced. Because inflammation has been associated with cancer promotion, the use of COX inhibitors to reduce inflammation has shown promise as a cancer preventive strategy (14–16).

Effects of (n-3) fatty acids on cancer

Supplementing the diet of tumor-bearing mice or rats with oils containing EPA or DHA has slowed the growth of various types of cancers, including lung (17,18), colon (19,20), mammary (21–23), and prostate (24). The (n-3) fatty acids have been shown to increase the efficacy of various cancer chemotherapy drugs and of radiation therapy against cancer. For example, the efficacies of doxorubin, (17,25,26), epirubicin (27), 5-fluorouracil (28), mitomycin C (29), arabinosylcytosine (30), tamoxifen (31), and CPT-11 (22,28), and of radiation therapy (32) have been enhanced when long-chain (n-3) fatty acids were included in the diet of rodents or culture medium of cells being treated.

Another potential benefit of (n-3) fatty acids supplementation is the effect of these fats on cachexia. Cachexia is the wasting away of lean mass that is not corrected by increasing energy consumption. Pancreatic cancer patients often develop debilitating cachexia. Some have shown weight gain and improved quality of life after daily supplementation of the diet with an energy- and protein-dense (610 kcal, 32.2 g protein) liquid supplement containing 2.2 g EPA and 0.96 g DHA (33). Patients who consumed the supplement that contained energy and protein but that did not contain the (n-3) fatty acids did not gain weight.

Why are (n-3) fatty acids effective against cancer?

Many mechanisms have been proposed for suppression of tumor cell growth by (n-3) fatty acids, and new mechanisms are frequently reported as we gain additional knowledge of the regulation of gene expression by fatty acids. It is likely that suppression of tumor cell growth by (n-3) fatty acids is due to the combination of these mechanisms rather than to a single, unique activity that is the sole mechanism of action. Some of the mechanisms proposed for the action of (n-3) fatty acids against cancer are as follows.

If (n-3) fatty acids are available, they will be used as a substrate by COX 2. It has been reported that DHA inhibits eicosanoid synthesis from AA (34), EPA is a better substrate for COX than AA (35), and EPA competes more successfully than AA for COX activity (13,35). The result is that if (n-3) fatty acids are included in the diet and are incorporated into cell membranes, then less of the inflammation-producing and growth-promoting prostaglandin E2 will be produced in normal and in tumor tissues.

Residual and metastatic tumor cells must multiply for the tumor to recur or for metastatic cells to grow into a life-threatening tumor. AA promotes growth by activating protein kinase C to stimulate mitosis (36); (n-3) fatty acids do not. The (n-3) fatty acids decrease activation of oncogenic transcription factors *ras* and AP1 (37,38), which are transcription factors for many growth-promoting genes. The AA-derived products of COX and LOX stimulate mitosis, whereas the EPA-derived products of COX and LOX decrease cancer growth (39,40). Thus (n-3) fatty acids can slow growth of cancer cells by direct action and by their activity as second messengers.

When activated, the transcription factor, nuclear factor κB (NFκB), blocks programmed cell death or apoptosis (41). NFκB is often upregulated in cancer cells, resulting in cells that are resistant to chemotherapy drugs or radiation and do not die in response to the genetic damage that has occurred. The Bcl-2 family of genes and COX 2 expression can also block apoptosis, resulting in cells that do not die at the appropriate time. The (n-3) fatty acids can restore functional apoptosis by downregulating NFκB (41), which in turn downregulates COX 2 expression (42,43), and by downregulating the expression of Bcl-2 family genes (44,45).

The (n-3) fatty acids have been shown to induce differentiation of breast cancer cells (46). Terminally differentiated cells do not multiply, so induction of differentiation could stop the growth of tumors.

As cancers grow, new blood vessels must develop to supply nutrients to the cells and to remove wastes. Inhibition of angiogenesis has been proposed as a strategy to inhibit or to limit tumor growth. The (n-3) fatty acids inhibit angiogenesis by multiple mechanisms, including alterations in prostaglandin production and inhibition of protein kinase C (42,47–50).

Many early breast cancers are estrogen dependent. Prostaglandin E2, a product of AA, activates P450 aromatase and

increases the production of estrogen (51). The (n-3) fatty acids could decrease the growth of estrogen-dependent breast cancers by decreasing estrogen stimulation of these tumors.

In summary, multiple mechanisms can play a role in suppression of tumor growth by (n-3) fatty acids. Some of the mechanisms may play a more dominant role in particular tumor types (i.e., alteration of estrogen is likely to be more important for suppression of breast cancer than for esophageal cancer). However, the proposed mechanisms are not mutually exclusive, and it is likely that multiple mechanisms contribute to suppression of cancer growth.

Feasibility of use in human cancer treatment

The results of animal studies are quite promising that (n-3) fatty acids may be a clinically useful addition to cancer therapy. However, a very high level of (n-3) supplement was used in many of the animal studies, often 20–24% (by weight) of the diet. These results may be a useful proof of concept, but it is also important to know how much (n-3) fat can be consumed by humans and whether this amount can effectively suppresses cancer growth.

Burns et al. (52) reported the results of a phase 1 (dose tolerance) trial using an (n-3) supplement showing that the maximum tolerated dose of this supplement was 0.3 g/kg per day or up to 21 g/d for a 70-kg patient (52). Twenty-one capsules contained 13.1 g of EPA plus DHA per day. A number of reports from the group of K. C. Fearon, M. J. Tisdale, S. J. Wigmore, M. D. Barber et al. cite the effects of (n-3) fatty acid supplements on weight loss in pancreatic cancer patients. Early studies (53) used as much as 12 g fish oil (18% EPA/12% DHA) per day and found that weight loss was ameliorated and that the patients actually began to gain weight. The results of a later study indicated that 2.2 g/d of EPA + 0.96 g DHA contained in a protein- and energy-dense supplement would ameliorate weight loss and improve the quality of life of pancreatic cancer patients significantly better than the supplement without EPA (33). This group has also reported the effects of the nutritional supplement on metabolic mediators in pancreatic cancer patients (7). In this study, serum IL-6 and excreted proteolysis-inducing factor were significantly reduced in the group that consumed EPA. The results of a study on the effects of EPA with or without megestrol acetate indicated that EPA increased appetite and weight gain in patients with cancer-associated wasting (54), but the increase was not any better than the increase due to megestrol. The patients in the later study consumed 2.18 g/d of EPA. Information gained from the 2 studies indicates that an effective dose of EPA to reduce cachexia may be between 2 and 4 g/d. These data indicate that humans can consume enough (n-3) fatty acids to influence cytokine production and that only small amounts of (n-3) may be required to significantly influence cell cytokines.

A report by Bougnoux et al. (55) presents some evidence that (n-3) fatty acids may be useful during human cancer therapy. These results indicate that the level of DHA in breast adipose tissue of patients with complete or partial remission in response to cytotoxic drugs was higher than in patients with no response or progression. This higher level represented increased long-term consumption of (n-3) fatty acids by these patients. It is also possible to increase DHA in breast tissue by short-term (3 mo) consumption of (n-3) fatty acids (56). Even though scant in number, these reports provide encouraging evidence that (n-3) fatty acids may be beneficial for cancer therapy in humans.

In conclusion, preclinical studies indicate that (n-3) fatty acids should be beneficial for cancer treatment. Mechanistic studies indicate feasible mechanisms for the influence of (n-3) fatty acids on tumor growth, survival, and response to chemotherapy. A limited number of clinical studies indicate that (n-3) fatty acids may be beneficial when consumed before chemotherapy. It seems important to commence human trials using an (n-3) fatty acid as a supplement to standard chemotherapy.

LITERATURE CITED

1. Begin, M. E., Ells, G., Das, U. N. & Horrobin, D. F. (1986) Differential killing of human carcinoma cells supplemented with n-3 and n-6 polyunsaturated fatty acids. J. Natl. Cancer Inst. 77: 1053–1062.
2. Deschner, E. E., Lytle, J. S., Wong, G., Ruperto, J. F. & Newmark, H. L. (1990) The effect of dietary omega-3 fatty acids (fish oil) on azoxymethanol-induced focal areas of dysplasia and colon tumor incidence. Cancer 66: 2350–2356.
3. Fernandes, G., Friedrichs, W., Schultz, J. & Venkatraman, J. (1989) Modulation of MCF-7 tumor cell growth in nude mice by omega-3 fatty acid diet. Breast Cancer Res. Treat. 14: 179 (abs.).
4. Reddy, B. S. & Sugie, S. (1988) Effect of different levels of omega-3 and omega-6 fatty acids on azoxymethane-induced colon carcinogenesis in F344 rats. Cancer Res. 48: 6642–6647.
5. Rose, D. P. & Connolly, J. M. (1993) Effects of dietary omega-3 fatty acids on human breast cancer growth and metastasis in nude mice. J. Natl. Cancer Inst. 85: 1743–1747.
6. Bougnoux, P., Germain, E., Chajes, V., Hubert, B., Lhuillery, C., Le Flock, O., Body, G. & Calais, G. (1999) Cytotoxic drugs efficacy correlates with adipose tissue docosahexaenoic acid level in locally advanced breast carcinoma. Br. J. Cancer 79: 1765–1769.
7. Barber, M. D., Fearon, K.C.H., Tisdale, M. J., McMillan, D. C. & Ross, J. A. (2001) Effect of a fish oil-enriched nutritional supplement on metabolic mediators in patients with pancreatic cancer cachexia. Nutr. Cancer 40: 118–124.
8. Li, D., Ng, A., Mann, N. J. & Sinclair, A. (1998) Contribution of meat fat to dietary arachidonic acid. Lipids 33: 437–440.
9. de Gomez, I.N.T. & Brenner, R. R. (1975) Oxidative desaturation of alpha-linolenic, linoleic and stearic acids by human liver microsomes. Lipids 10: 315–317.
10. Hague, T. A. & Christoffersen, B. O. (1984) Effect of dietary fats on arachidonic acid and eicosapentaenoic acid biosynthesis and conversion of C_{22} fatty acids in isolated liver cells. Biochem. Biophys. Acta 796: 205–217.
11. Hamid, R., Singh, J., Reddy, B. S. & Cohen, L. A. (1999) Inhibition by dietary menhaden oil of cyclooxygenase-1 and -2 in N-nitrosomethylurea-induced rat mammary tumors. Int. J. Oncol. 14: 523–528.
12. Obata, T., Nagakura, T., Masaki, T., Maekawa, K. & Yamashita, K. (1999) Eicosapentaenoic acid inhibits prostaglandin D2 generation by inhibiting cyclo-oxygenase-2 in cultured human mast cells. Clin. Exp. Allergy 29: 1129–1135.
13. Needleman, P., Raz, A., Minkes, M. S., Ferrendelli, J. A. & Specher, H. (1979) Triene prostaglandins: prostacyclin and thromboxane biosynthesis and unique biological properties. Proc. Natl. Acad. Sci. U.S.A. 76: 944–948.
14. Balkwill, F. & Manzano, L. A. (2001) Inflammation and cancer: back to Virchow. Lancet 357: 539–545.
15. Williams, C. S., Mann, M. & Dubois, R. N. (1999) The role of cyclooxygenases in inflammation, cancer, and development. Oncogene 18: 7908–7916.
16. Thun, M. J., Henley, S. J. & Patrono, C. (2002) Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J. Natl. Cancer Inst. 94: 252–266.
17. Hardman, W. E., Moyer, M. P. & Cameron, I. L. (2000) Dietary fish oil sensitizes A549 lung xenografts to doxorubicin chemotherapy. Cancer Lett. 151: 145–151.
18. Kimura, Y. (2002) Carp oil or oleic acid, but not linoleic acid or linolenic acid, inhibits tumor growth and metastasis in Lewis lung carcinoma-bearing mice. J. Nutr. 132: 2069–2075.
19. Calder, P. C., Davis, J., Yaqoob, P., Pala, H., Thies, F. & Newsholme, E. A. (1998) Dietary fish oil suppresses human colon tumor growth in athymic mice. Clin. Sci. 94: 303–311.
20. Chen, Z. Y. & Istfan, N. W. (2000) Docohexaenoic acid is a potent inducer of apoptosis in HT-29 colon cancer cells. Prostaglandins Leukot. Essent. Fatty Acids 63: 301–308.
21. Hardman, W. E., Barnes, C. J., Knight, C. W. & Cameron, I. L. (1997) Effects of iron supplementation and ET-18-OCH_3 on MDA-MB 231 breast carcinomas in nude mice consuming a fish oil diet. Br. J. Cancer 76: 347–354.
22. Hardman, W. E., Moyer, M. P. & Cameron, I. L. (1999) Fish oil supplementation enhanced CPT-11 (Irinotecan) efficacy against MCF7 breast carcinoma xenografts and ameliorated intestinal side effects. Br. J. Cancer 81: 440–448.
23. Connolly, J. M., Gilhooly, E. M. & Rose, D. P. (1999) Effects of reduced dietary linoleic acid intake, alone or combined with an algae source of docosahexaenoic acid on MDA-MB-231 breast cancer cell growth and apoptosis in nude mice. Nutr. Cancer 35: 44–49.
24. Connolly, J. M., Coleman, M. & Rose, D. P. (1997) Effects of dietary

fatty acids on DU145 human prostate cancer cell growth in athymic nude mice. Nutr. Cancer 29: 114–119.

25. Hardman, W. E., Avula, C.P.R., Fernandes, G. & Cameron, I. L. (2001) Three percent dietary fish oil concentrate increased efficacy of doxorubicin against MDA-MB 231 human breast cancer xenografts. Clin. Cancer Res. 7: 2041–2049.

26. de Salis, H. M. & Meckling-Gill, K. A. (1995) EPA and DHA alter nucleoside drug and doxorubicin toxicity in L1210 cells but not in normal murine S1 macrophages. Cell. Pharmacol. 2: 69–74.

27. Germain, E., Lavandier, F., Chajès, V., Schubnel, V., Bonnet, P., Lhuillery, C. & Bougnoux, P. (1999) Dietary n-3 polyunsaturated fatty acids and oxidants increase rat mammary tumor sensitivity to epirubicin without change in cardiac toxicity. Lipids 34: S203 (abs.).

28. Hochwald, S. N., Li, J., Copeland, E. M., III, Moldawer, L. L., Lind, D. S. & Mackay, S. L. (2002) Inhibition of NF-κB activation potentiates the cytotoxicity of 5-FU and CPT-11 chemotherapy in human gastric cancer cells. Proc. Am. Assoc. Cancer Res. 43: 1251 (abs.).

29. Shao, Y., Pardini, L. & Pardini, R. S. (1995) Dietary menhaden oil enhances mitomycin C antitumor activity toward human mammary carcinoma MX-1. Lipids 30: 1035–1045.

30. Cha, M. C., Meckling, K. A. & Stewart, C. (2002) Dietary docosahexaenoic acid levels influence the outcome of arabinosylcytosine chemotherapy in L1210 leukemic mice. Nutr. Cancer 44: 176–181.

31. DeGraffenried, L. A., Friedrichs, W. E., Fulcher, L., Fernandes, G., Silva, J. M., Peralba, J. M. & Hidalgo, M. (2003) Eicosapentaenoic acid restores tamoxifen sensitivity in breast cancer cells with high Akt activity. Ann. Oncol. 14: 969–970.

32. Colas, S., Paon, L., Denis, F., Prat, M., Louisot, P., Hoinard, C., Le Floch, O., Ogilvie, G. & Bougnoux, P. (2004) Enhanced radiosensitivity of rat autochthonous mammary tumors by dietary docosahexaenoic acid. Int. J. Cancer 109: 449–454.

33. Moses, A. W., Slater, C., Preston, T., Barber, M. D. & Fearon, K. C. (2004) Reduced total energy expenditure and physical activity in cachexia patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br. J. Cancer 90: 996–1002.

34. Rose, D. P. & Connolly, J. M. (2000) Regulation of tumor angiogenesis by dietary fatty acids and eicosanoids. Nutr. Cancer 37: 119–127.

35. Yang, P., Felix, E., Madden, T., Chan, D. & Newman, R. A. (2002) Relative formation of PGE2 and PGE3 by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in human lung cancer cells. Proc. Am. Assoc. Cancer Res. 43: number 1533 (abs.).

36. Blobe, G. C., Obeid, L. M. & Hannun, Y. A. (1994) Regulation of protein kinase C and role in cancer biology. Cancer Metastasis Rev. 13: 411–431.

37. Collett, E. D., Davidson, L. A., Fan, Y.-Y., Lupton, J. R. & Chapkin, R. S. (2001) n-6 and n-3 polyunsaturated fatty acids differentially modulate oncogenic Ras activation in colonocytes. Am. J. Physiol. Cell Physiol. 280: C1066–C1075.

38. Liu, G., Bibus, D. M., Bode, A. M., Ma, W.-Y., Holman, R. T. & Dong, Z. (2001) Omega 3 but not omega 6 fatty acids inhibit AP-1 activity and cell transformation in JB6 cells. Proc. Natl. Acad. Sci. U.S.A. 98: 7510–7515.

39. Abou-El-Ela, S. H., Prasse, K. W., Farrell, R. L., Carroll, R. W., Wade, A. E. & Bunce, O. R. (1989) Effects of D,L-2-difluoromethylornithine and indomethicine on mammary tumor promotion in rats fed high n-3 and/or n-6 fat diets. Cancer Res. 49: 1434–1440.

40. Rose, D. P. & Connolly, J. M. (1990) Effects of fatty acids and inhibitors of eicosanoid synthesis on the growth of a human breast cancer cell line in culture. Cancer Res. 50: 7139–7144.

41. Schwartz, S. A., Hernandez, A. & Evers, B. M. (1999) The role of NF-κB/IκB proteins in cancer; implications for novel treatment strategies. Surg. Oncol. 8: 143–153.

42. Connolly, J. M. & Rose, D. P. (1998) Enhanced angiogenesis and growth of 12-lipoxygenase gene-transfected MCF-7 human breast cancer cells in athymic nude mice. Cancer Lett. 132: 107–112.

43. Tsujii, M. & Dubois, R. N. (1995) Alterations in cellular adhesion and apoptosis in epithelial cells overexpression prostaglandin endoperoxide synthase 2. Cell 83: 493–501.

44. Chiu, L.C.M. & Wan, J.M.F. (1999) Induction of apoptosis in HL-60 cells by eicosapentaenoic acid (EPA) is associated with downregulation of bcl-2 expression. Cancer Lett. 145: 17–27.

45. Narayanan, B. A., Narayanan, N. K. & Reddy, B. S. (2001) Docosahexaenoic acid regulated genes and transcription factors inducing apoptosis in human colon cancer cells. Int. J. Oncol. 19: 1255–1262.

46. Wang, M., Liu, Y. E., Ni, J., Aygun, B., Goldberg, I. D. & Shi, Y. E. (2000) Induction of mammary differentiation by mammary-derived growth inhibitor-related gene that interacts with an ω-3 fatty acid on growth inhibition of breast cancer cells. Cancer Res. 60: 6482–6487.

47. Bing, R. J., Miyataka, M., Rich, K. A., Hanson, N., Wang, X., Slosser, H. D. & Shi, S.-R. (2001) Nitric oxide, prostanoids, cyclooxygenase, and angiogenesis in colon and breast cancer. Clin. Cancer Res. 7: 3385–3392.

48. Form, D. M. & Auerbach, R. (1983) PGE_2 and angiogenesis. Proc. Soc. Exp. Biol. Med. 172: 214–218.

49. McCarty, M. F. (1996) Fish oil may impede tumour angiogenesis and invasiveness by down-regulating protein kinase C and modulating eicosanoid production. Med. Hypotheses 46: 107–115.

50. Wen, B., Deutsch, E., Opolon, P., Auperin, A., Frascogna, V., Connault, E. & Bourhis, J. (2003) n-3 polyunsatyrated fatty acids decrease mucosal/epidermal reactions and enhance antitumour effect of ionising radiation with inhibition of tumour angiogenesis. Br. J. Cancer 89: 1102–1107.

51. Noble, L. S., Takayama, K., Zeitoun, K. M., Putman, J. M., Johns, D. A., Hinshelwood, M. M., Agarwal, V. R., Zhao, Y., Carr, B. R. & Bulun, S. E. (1997) Prostaglandin E_2 stimulates aromatase expression in endometriosis-derived stromal cells. J. Clin. Endocrinol. Metab. 82: 600–602.

52. Burns, C. P., Halabi, S., Clamon, G. H., Hars, V., Wagner, B. A., Hohl, R. J., Lester, E., Kirshner, J. J., Vinciguerra, V. & Paskett, E. (1999) Phase I clinical study of fish oil fatty acid capsules for patients with cancer cachexia: cancer and leukemia group B Study 9473. Clin. Cancer Res. 5: 3842–3947.

53. Wigmore, S. J., Ross, J. A., Falconer, J. S., Plester, C. E., Tisdale, M. J., Carter, D. C. & Fearon, K.C.H. (1996) The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. Nutrition 12: S27–S30.

54. Jatoi, A., Rowland, K., Loprinzi, C. L., Sloan, J. A., Dakhil, S. R., MacDonald, N., Gagnon, B., Novotny, P. J., Mailliard, J. A., et al. (2004) An eicosapentaenoic acid supplement verses megestrol verses both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. J. Clin. Oncol. 22: 2469–2476.

55. Bougnoux, P., Chajès, V., Germain, E., Hubert, B., Lhuillery, C., Le Floch, O., Body, G. & Calais, G. (1999) Cytotoxic drug efficacy correlates with adipose tissue docosahexaenoic acid level in locally advanced breast carcinoma. Lipids 34: S109 (abs.).

56. Bagga, D., Capone, S., Wang, H.-J., Heber, D., Lill, M., Chap, L. & Glaspy, J. A. (1997) Dietary modulation of omega-3/omega-6 polyunsaturated fatty acid ratios in patients with breast cancer. J. Natl. Cancer Inst. 89: 1123–1131.