

n-3 Polyunsaturated fatty acids and cancer

Bougnoux, Philippe

Author Information

Université François-Rabelais, Tours, France Correspondence to Professor P. Bougnoux, CORAD, Hôpital Bretonneau, F-37044 Tours, France. Tel: +33 247 474776; fax : +33 247 476012; e-mail: bougnoux@med.univ-tours.fr

Abstract

n-3 Polyunsaturated fatty acids are promising molecules in cancer prevention and the potentiation of cancer treatment. Recent studies have highlighted the importance of their interactions with other food components. Their effects on tumor growth depend upon background levels of n-6 polyunsaturated fatty acids and antioxidants, and this could account for previously inconsistent results in experimental carcinogenesis. Recognition of the role of lipoperoxidation in the anti-tumor effects of polyunsaturated fatty acids, which is apparent in a variety of in-vitro or in-vivo systems, has been a major advance in the field. Consequently, n-3 polyunsaturated fatty acids appear to be excellent substrates for lipid peroxidation in situations where an oxidative stress is involved, such as in the action of several cytotoxic agents in the treatment of cancer.

Introduction

It has been estimated that dietary factors account for between 20% and 60% of the preventable causes of cancer, depending on the site of the cancer ^[1]. Breast, prostate, colorectal and pancreas cancer, which account for more than half of deaths from cancer, are all likely to be susceptible to diet. No primary prevention is available for these types of cancer, because data concerning dietary causes, and mainly dietary lipids, remain highly controversial.

In this review, we will focus on recent reports regarding the effects of n-3 polyunsaturated fatty acids (PUFA) on cancer as a disease, and not on cancer as a

process. The effects of n-3 PUFA on immune defenses, or on the biochemical and molecular mechanisms potentially involved, will not be considered, since these fields have been extensively reviewed very recently [\[2,3\]](#).

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Effects of n-3 PUFA on tumor growth and development

Colon cancer and colon carcinogenesis

A large, prospective study (the New York University Women's Health Study) by Kato *et al.* [\[4\]](#) reported that certain types of fish might protect against colorectal cancer in women, in agreement with the idea that n-3 PUFA inhibits some steps in colon carcinogenesis. This seems to be confirmed in a variety of experimental animal systems. Comparing fish oil (n-3 PUFA) to corn oil (n-6 PUFA), butter or beef tallow (saturated fatty acids), Kim *et al.* [\[5\]](#) found that colon cell proliferation, an intermediate biomarker for colon carcinogenesis, was lower in rats that had been fed fish oil. Using azoxymethane or dimethylhydrazine as carcinogens, Paulsen *et al.* [\[6\]](#) report that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both ethyl esters, inhibited the formation and growth of aberrant crypt foci in rat colon, another surrogate biomarker for colon carcinogenesis. In the azoxymethane-induced rat colon carcinogenesis model, a fish-oil-enriched diet resulted in a lower incidence of adenocarcinoma than a corn oil diet [\[7\]](#), as a consequence of increased apoptosis and differentiation, rather than decreased proliferation. The inhibitory effects of n-3 PUFA provided as fish oil are also apparent on colon tumor growth and metastasis in the nude mice transplantable human HT29 cancer cell line model [\[8\]](#).

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Hepatocarcinogenesis

In a diethylnitrosamine-induced hepatocarcinogenesis rat model, Okuno *et al.* [\[9\]](#) found that n-3 PUFA, and also n-6 PUFA, inhibited the multiplicity of liver adenoma but not that of carcinoma. However, the source of n-3 PUFA used in that study was perilla oil, which is rich in alpha-linolenic acid (ALA), but does not contain DHA or EPA. The inhibitory effect of dietary EPA and DHA (individually supplemented as ethyl esters) has been documented in the growth of Morris hepatocarcinoma cells transplanted into rats [\[10\]](#). The anti-tumor effect of EPA was related mainly to its inhibition of cell proliferation, whereas that of DHA corresponded with its induction of apoptosis.

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Breast cancer and mammary carcinogenesis

Data from epidemiologic studies remain inconclusive. In a prospective cohort study carried out in northern Sweden, Chajès *et al.* [\[11\]](#) found no association between n-3 PUFA in serum phospholipids taken as biomarkers of past fatty acid intake and risk of breast cancer.

Mammary carcinogenesis data evaluating the effects of n-3 PUFA also remain inconsistent. They differ among animal experimental systems, and depending on nutritional conditions, the origin of n-3 PUFA (from oil or purified compounds), interaction with other PUFA or fatty acid classes, and the interaction with antioxidants. Using the dimethylbenz(a)anthracene (DMBA)-induced mammary tumors model in rats, Noguchi *et al.* ^[12] found that dietary ethyl esters of EPA and DHA decreased tumor incidence, but not tumor growth, in the presence of antioxidants. In their updated meta-analysis covering 97 studies extending from 1966 to 1994, Fay *et al.* ^[13] showed that n-6 PUFA have a strong tumor-enhancing effect and that saturated fats have a weaker tumor-enhancing effect. n-3 PUFA have a small protective effect. However, the confounding effect of antioxidants or the ratio of n-3 with other classes of fatty acids were not taken into account.

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Metastasis

Recent data ^[14-16] have shown that dietary n-3 PUFA inhibits mammary tumor metastasis. In the nude mice model of transplanted human breast cancer cell lines, EPA produced a reduction in tumor cell growth and metastasis ^[14]. Menhaden oil reduced fat pad tumor growth and lung metastasis from a human breast cancer cell line ^[15]. Using their syngenic transplantable tumor model, Hubbard *et al.* ^[16] found that diets containing n-3 fatty acids in fish oil decreased primary breast tumor growth and its metastasis.

Animal models for tumor metastasis that rely on tumor cell injection have always been of questionable relevance to spontaneous metastases. In this context, the action of n-3 PUFA on liver metastasis remains essentially inconsistent. Dietary EPA (as ethyl ester) has been shown to inhibit colon carcinoma cells liver metastasis ^[17]. In contrast to the effects of n-3 PUFA provided as ethyl esters, dietary fish oil induced more liver metastases than a safflower-oil-enriched diet (linoleic acid) in a similarly designed rat experiment ^[18]. Similarly, in a mouse transplantable lung carcinoma cell line, a diet containing n-3 PUFA as fish oil or linseed oil elicited more liver metastases than a diet with n-6 PUFA or saturated fatty acids ^[19]. The reasons for these discrepancies are not known and may need further experimentation in other in-vivo models.

Using a mouse transplantable highly metastatic colon carcinoma cells model, Iigo *et al.* ^[20] found that dietary EPA and DHA (ethyl esters) led to a reduction of lung metastasis compared with linoleic acid or arachidonic acid. Thus, when no antioxidants were added, DHA treatment exerted marked anti-metastatic activity in this system.

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Relative proportions of n-3 and n-6 PUFA

In older studies of experimental mammary carcinogenesis, tumor growth was shown to be suppressed only when equal parts of n-3 and n-6 PUFA-rich oils were fed ^[21,22]. Recently, the role of PUFA with respect to saturated fatty acids was investigated by

Sasaki *et al.* ^[23•]. They used a 10% fat diet in the DMBA rat model, and modified the relative proportion of n-3 and n-6 PUFA by mixing coconut oil (rich in saturates), safflower oil (rich in linoleate) and fish oil (from sardines, rich in EPA and DHA) in such a way that the ratio of total PUFA to saturated fatty acid was kept constant. They found that increasing the n-3/n-6 ratio (from 0.01 to 7.8) did not suppress the incidence or reduce the latency of mammary tumor development, but even promoted the development of tumors. The potential confounding effect of antioxidants was not examined.

Simonsen *et al.* ^[24•] reported a case-control study in postmenopausal breast cancer cases and controls, in five European countries differing greatly in their dietary fat intakes and in their breast cancer risk (European Community Multicentre Study on Antioxidants, Myocardial Infarction, and Cancer of the Breast (EURAMIC) breast cancer study, 1991-1992). Buttock adipose tissue was used as a biomarker of PUFA exposure. Similar to previous studies, they found no significant inverse association between total n-3 PUFA and the risk of breast cancer. In contrast, when they examined the balance between different types of PUFA, they found an inverse association between the ratio of long-chain n-3 fatty acids to total n-6 fat and breast cancer in four of five centers. Their data give strength to the hypothesis that n-3 PUFA might inhibit breast cancer, depending on background levels of n-6 PUFA. This important paper emphasizes the need to take into account all components of lipids.

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Interaction between n-3 PUFA and antioxidants

In a landmark experiment, Gonzalez *et al.* ^[25] showed that the inhibitory effects of fish oil on the growth of a mouse transplantable breast carcinoma were suppressed by vitamin E, and were actually a function of increased lipid peroxidation ^[26] (see ^[27] for review). To test this hypothesis, Hardman *et al.* ^[28] designed a study that attempted selectively to increase lipid peroxidation and to kill the cancer cells without harming normal host tissues. Using implanted human breast tumors in mice consuming fish oil, they found that iron supplementation combined with administration of ET-18-OCH₃, a pro-oxidative drug, resulted in the slowest tumor growth rate, lowest mitotic index, highest level of lipid peroxidation products, increased cytotoxic index in tumors, and resulted in no detectable harm to the host.

This finding was recently developed in the rat N-methylnitrosourea (NMU)-induced mammary carcinogenesis model. Lhuillery *et al.* ^[29•] examined the concomitant effects of dietary antioxidant (vitamin E) and PUFA. They found that tumor incidence and growth was increased in rats that had vitamin E added to their diet, suggesting that even in this model of the late stages of carcinogenesis, oxidized PUFA have an inhibiting role on tumor growth.

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n-3 PUFA may inhibit tumor growth by promoting apoptosis of tumor cells

Oxidation products of n-3 PUFA have been known to contribute to their cytotoxicity. Lipoperoxides are directly cytotoxic, and deficiencies in antioxidant defense mechanisms have been reported to enhance the cytotoxic effect of n-3 PUFA. Numerous recent data underline this emerging important role of PUFA in cancer. Nøding *et al.* [30] found that the sensitivity of cultured tumor cells to DHA and to its oxidation products depends on their antioxidant defense mechanisms, and that hydroperoxy-DHA is one of the major metabolites responsible for its cytotoxicity. Ramesh and Das [31] studied methylcholanthrene-induced sarcoma ascitic tumor cells *in vitro* and *in vivo*. They found that n-3 PUFA (DHA>ALA>EPA) were the most potent inhibitors of the growth of tumor cells. Vitamin E partially blocked the cytotoxicity of these fatty acids, and lipid peroxidation was enhanced by all fatty acids tested.

Two questions that remain are: which type of cell death is involved; and are lipid peroxidation products involved in apoptosis? Finstad *et al.* [32] assessed the sensitivity of 14 different leukemia cell lines to long-chain PUFA. A majority of leukemia cell lines were sensitive to arachidonic acid, EPA and DHA. The sensitive cell lines died by necrosis and apoptosis. Surprisingly, EPA-induced necrosis, but not apoptosis, was counteracted by vitamin E, indicating that, at least in these cell types, lipid peroxidation may not have been involved in apoptosis.

Further evidence of a role for lipid peroxidation in apoptosis induced by PUFA has been presented by Hawkins *et al.* [33]. They carefully examined the type of cell death occurring after the action of several PUFA on pancreatic cancer cell lines and on other cell types. All long-chain PUFA tested, either n-3 (EPA, DHA) or n-6 (arachidonic acid) inhibited the growth *in vitro*, and induced apoptosis. Among 18C PUFA, only gamma-linolenic acid (GLA) induced apoptosis, while linoleic acid and ALA acid did not. The extent of PUFA-induced lipid peroxidation also correlated with the proportion of apoptosis. PUFA-induced apoptosis was oxidative, being blocked by lipid antioxidants.

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Cancer chemotherapy and n-3 PUFA-enhanced apoptosis

The fact that the same PUFA induce or stimulate cell apoptosis in different cancer cell types and under different conditions, and that vitamin E abolishes the response, suggests that such a process may be of wide relevance. Tumor cells undergo apoptotic cell death when treated with a variety of anticancer drugs.

In an *in-vitro* study, Timmer-Bosscha *et al.* [34] found DHA to enhance cis-diammine-dichloroplatinum(II)-induced cytotoxicity and apoptosis in human embryonal carcinoma cell lines, as they had previously reported in a human small-cell lung carcinoma cell line. DHA potentiated platinum cytotoxicity to a similar extent in the two embryonal carcinoma cell lines selected for their differential sensitivity to the drug; this makes it likely that a non-specific pathway of apoptosis was affected by DHA treatment. In order to determine which PUFA was the most effective, Tsai *et al.* [35] used a tumorigenic cell line derived after transfection from the non-malignant mouse fibroblastic cell line NIH3T3. They found that EPA had a greater effect than arachidonic acid on the sensitivity to mitomycin C in terms of cell proliferation. They

also reported a protective effect of EPA towards mitomycin C toxicity in the non-malignant cell line.

In experimental mammary tumors, Shao *et al.* ^[36] reported that high levels of dietary fish oil increased the tumor response of transplanted mammary tumors to mitomycin C, an anticancer drug that generates an oxidative stress. Since fish oil is highly unsaturated, its intake caused a significant increase in the degree of fatty acid unsaturation in tumor membrane phospholipids. This alteration in tumor membrane phospholipids made the tumor more susceptible to oxidative stress, as indicated by the increased levels of both endogenous lipid peroxidation ^[36]. Using a dietary intervention with fish oil in rats, Germain *et al.* ^[37] reported that addition of pro-oxidants to the diet increased the response of NMU-induced mammary tumors to anthracyclins, a class of drugs active in breast cancer and generating an oxidative stress. Dietary vitamin E suppressed this response. In addition, none of the dietary conditions influenced the cardiac toxicity of the drug ^[37].

Therefore, n-3 PUFA enhanced the activity of different drugs, which act on different cellular targets and induce a similar pattern of cell death. This suggests that common mediators of apoptosis are involved and stresses the need for further characterization of the role of lipoperoxides.

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DHA and breast cancer response to chemotherapy

The possibility that a similar mechanism operates in humans was explored using adipose tissue as a biomarker of the n-3 PUFA status. Bougnoux *et al.* ^[38] have prospectively studied the association between levels of fatty acids stored in breast adipose tissue and the response of the tumor to neo-adjuvant chemotherapy in patients with an initially localized breast carcinoma. They observed that the level of DHA in adipose tissue was higher in the group of patients with a complete or partial response to chemotherapy than in patients with no response or with tumor progression. Furthermore, the level of DHA in the adipose tissue was an independent predictor for chemosensitivity, suggesting that, at least in breast cancer, DHA may increase the response of the tumor to the cytotoxic agents used.

Germain *et al.* ^[39] examined whether lipid peroxidation is a potential mechanism through which fatty acids could enhance drugs cytotoxicity. They measured long-term cell viability in the human breast cancer cell line MDA-MB-231 exposed to an anthracyclin. DHA was the most potent in increasing the drug cytotoxicity. This effect, associated with a commensurate increase in cell lipoperoxides, was stimulated by oxidants and abolished by vitamin E. Thus, DHA increased the efficacy of oxiradical-producing drugs through a mechanism involving the generation of lipoperoxides. This observation is highly significant, since it may lead *in vivo* to a modulation of the chemosensitivity of tumor cells by DHA and oxidant agents.

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Selective effect of n-3 PUFA on cancer cells

The selective effect of n-3 PUFA on cancer cells, initially reported by Begin *et al.* [40], is now being further documented *in vivo*. Oxidants inhibited transplanted MDA-MB 231 breast carcinomas in nude mice consuming a fish oil diet without detectable harm to the host [28]. Dietary n-3 PUFA and oxidants increased the efficacy of anthracyclins on NMU-induced mammary tumor in rats without a change in cardiac toxicity [37], in line with an earlier report that a dietary supplement of DHA and EPA increased cardiac tolerance to the cardiotoxicity of an anthracyclin in rats [41].

Mechanisms other than lipoperoxidation may account for the enhancing effect of n-3 PUFA on tumor chemosensitivity. Shao *et al.* [42] investigated the effects of dietary supplementation of menhaden oil on cyclophosphamide antineoplastic activity. Using mammary tumors transplanted to nude mice, they found that dietary menhaden oil enhanced the anti-tumor effect of cyclophosphamide and had a protective effect against cyclophosphamide toxicity. They proposed that dietary menhaden oil decreased its toxicity and increased its therapeutic effect in modulating the activity of specific liver detoxifying enzymes and of liver and tumor cyclophosphamide activating enzymes.

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PUFA and response of tumor cell line to ionizing radiation

Since the incorporation of n-3 PUFA into tumor cells leads to an enhanced response to several cytotoxic drugs both *in vitro* and *in vivo*, and specifically to drugs generating an oxidative stress, it comes as no surprise that PUFA induce a similar effect on the response of tumors to ionizing radiation, as well as to hyperthermia [43]. In a rat transplanted experimental carcinoma, hyperthermia along with an acute administration of ALA and GLA demonstrated an anti-tumor effect [44]. Vartak *et al.* [45] studied the response of a rat chemically induced malignant astrocytoma cell line to radiation after supplementation with n-6 (GLA) and n-3 PUFA (EPA and DHA). All three PUFA, and particularly GLA, increased the radiation-induced cell kill. Vitamin E blocked the enhanced radiation sensitivity of GLA- and DHA-supplemented cells. Most importantly, neither GLA nor DHA along with radiation appeared to exert a deleterious effect on normal rat astrocytes. The fact that GLA is selectively toxic to the neoplastic astrocytoma cells and not to normal astrocytes suggests that GLA as a therapeutic adjunct may increase the therapeutic efficacy of radiation on this type of tumors [46].

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Feasibility and safety of dietary modulation of n-3 PUFA content in tissues

In the rat, EPA and DHA are incorporated into tissue membrane fatty acids, without increasing their susceptibility to oxidative stress [47]. n-3 PUFA readily incorporate into different cellular compartments in rat liver, reaching a plateau rapidly [48]. However, attention should be paid to physiologic conditions, since, in accordance with oxygen partial pressure, antioxidants may function as pro-oxidants [49]. The prospect of a dietary intervention aimed at increasing n-3 PUFA within tissues implies that more insights are being gained in the pharmacokinetics and dynamics of PUFA in cancer patients. After a 3 month dietary intervention with a low fat diet plus 3 g/day

of EPA and DHA, from a commercially available fish oil supplement, Bagga *et al.* [50] reported that n-3/n-6 PUFA ratios increased in plasma and in breast adipose tissue in patients treated for localized breast cancer. This information is timely and may contribute to opening the way to a dietary manipulation of breast cancer relapse targeted at n-3 PUFA.

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Conclusion

The aphorism 'we do not eat nutrients, we eat food' could be extended to refer to PUFA: 'we don't eat fatty acids, we eat fat'. Recent work showing that the activity of n-3 PUFA depends on other food components (such as n-6 PUFA and antioxidants) definitely indicates that the understanding of n-6 fatty acids as tumor promoters and n-3 fatty acids as inhibitors is oversimplified and should be abandoned. Future nutritional epidemiology studies should take into account this type of interaction in order not to draw premature negative conclusions on the association between dietary fat and cancers.

The extreme importance of lipid peroxidation products is now being acknowledged. Previously considered by nutritional toxicologists as deleterious components that should be prevented by antioxidants, lipoperoxides are now recognized as useful metabolites at certain periods of life, largely involved in the control of tumor growth, and major determinants of tumor sensitivity to anticancer agents. Incorporation of n-3 PUFA in tissues provides excellent substrates for lipoperoxidation.

Another promising finding is the selective cytotoxic effect of PUFA among tumor and non-tumor tissues, apparently caused by a loss of efficacy of several antioxidant defense mechanisms during malignant transformation. Since most of the past advances in cancer treatment have arisen from the recognition and use of differences between normal and malignant tissues, one can expect such a finding to open the way to wider applications.

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