Minireview

Journal of Nutrigenetics and Nutrigenomics

J Nutrigenet Nutrigenomics 2009;2:149–158
DOI: 10.1159/000235565

Published online: September 23, 2009

ω–3 Fatty Acids, Genetic Variants in COX-2 and Prostate Cancer

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Key Words

Cyclooxygenase 2 · Diet · Gene · Genetic variation · ω–3 fatty acids · Polyunsaturated fatty acids · Prostatic neoplasms · Single nucleotide polymorphism

Abstract

Dietary intake of fish and ω–3 polyunsaturated fatty acids (ω–3 PUFAs) may decrease the risk of prostate cancer development and progression to advanced stage disease. This could reflect the anti-inflammatory effects of PUFAs, possibly through mediation of cyclooxygenase (COX), a key enzyme in fatty acid metabolism and inflammation. Despite promising experimental evidence, epidemiological studies have reported somewhat conflicting results regarding the effects of fish/PUFAs on prostate cancer development and progression. The literature suggests that fish, and particularly long-chain ω–3 PUFAs, may have a more pronounced protective effect on biologically aggressive tumors or on their progression, and less on early steps of carcinogenesis. Moreover, the impact of LC ω–3 PUFAs may be modified by variation of the *COX-2* gene. Overall, results to date support the hypothesis that long-chain ω–3 PUFAs may impact prostate inflammation and carcinogenesis via the COX-2 enzymatic pathway.

Introduction

Prostate cancer is the most common non-cutaneous malignancy diagnosed in men [1]. In 2009 alone, there are projected to be 191,000 new cases of prostate cancer in the USA, accounting for approximately 25% of new cancer diagnoses [1]. There are a few well-accepted risk factors for prostate cancer, including family history, African-American ethnicity and particular genetic variants. However, a large percentage of men with prostate cancer do not carry these risk factors, suggesting that there remain important unexplained components to the pathogenesis of disease. Potential environmental risk factors for prostate cancer, including the effects of diet, have shown mixed results. Nevertheless, identifying environmental risk factors for prostate cancer carcinogenesis and studying gene-environment interactions are critically important to advance our understanding of the biology of this disease, and to aid in the development of potential therapeutic interventions.

Equally important is the discovery of factors that predict prostate cancer aggressiveness. This is crucial because despite the ubiquitous nature of the disease, the clinical behavior of prostate cancer is widely heterogeneous. In fact, low-grade, localized cancer that is left un-

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treated often poses little risk to the patient in terms of symptoms or cancer death; the majority of these patients will ultimately die of other causes [2]. In fact, recent data from CaPSURE, a prostate cancer registry from 40 academic and community-based practices across the USA reported that men diagnosed with very low-risk prostate cancer have only a few percent risk of prostate cancer-specific mortality at 10 years, but have an almost 25% risk of all-cause mortality [3]. In contrast, high-grade advanced disease is frequently rapidly progressive and fatal. As an example, data from CaPSURE supports a more than 20% prostate cancer-specific mortality at 10 years for the most aggressive forms of prostate cancer. Despite advances in treatment strategies, prostate cancer remains the second most common cause of cancer-related mortality in the USA, surpassed only by lung cancer [1].

Due to the adoption of widespread PSA screening in the USA in the early 1990's, there has been a significant stage migration, with the majority of tumors in the modern era diagnosed at an early, clinically localized stage [4]. Although most of these tumors could be treated successfully, today's most popular treatment modalities – surgery and radiation therapy – are associated with substantial long-term side effects including erectile dysfunction and urinary incontinence [5]. Thus, the focus of clinical research in recent years has shifted towards identifying those patients with aggressive disease who are at risk for progression, metastases and death and thus warrant definitive treatment despite the associated side effects. Similarly, a growing body of basic research and observational studies are focusing on identifying environmental and genetic factors that predispose to advanced disease.

Role of Inflammation in Carcinogenesis

Chronic inflammation has been implicated as a causative factor in a wide range of malignancies, including lung, colorectal, pancreatic, bladder and hepatocellular carcinomas [6]. In fact, inflammation is thought to play a role in the causation of approximately 20% of all human cancers [7]. Increasing evidence supports the role of prostatic inflammation as a risk factor for both development and progression of prostate cancer. It is hypothesized that pro-inflammatory mediators within the prostate can lead to a state of chronic inflammation, resulting in lesions of proliferative inflammatory atrophy that may transition to prostatic intraepithelial neoplasia and eventually adenocarcinoma [7]. Several sources of inflammation may influence the risk of prostate cancer, including dietary [8], genitourinary bacterial [9, 10] and viral [11] infections, and intraprostatic urine reflux [12, 13]. With regard to diet, a number of nutritional factors may reduce the risk and progression of prostate cancer through antioxidant and anti-inflammatory effects [8]. These include ω–3 polyunsaturated fatty acids (PUFAs), fish, selenium, vitamins D and E, and lycopene [8].

PUFAs are classified according to their molecular configuration: ω–3 or ω–6. The pro-inflammatory ω–6 PUFAs, such as linoleic acid and arachidonic acid, are metabolized through the cyclooxygenase (COX) pathway into inflammatory eicosanoids, including prostaglandin E_2, which has been linked to carcinogenesis in studies of prostate and other tumors [14, 15]. In contrast, the anti-inflammatory ω–3 PUFAs, such as α-linolenic acid (ALA) 18:3, eicosapentaenoic acid (EPA) 20:5, docosahexaenoic acid (DHA) 22:6 and docosapentaenoic acid (DPA) 22:5, exhibit their anti-inflammatory properties by competitively inhibiting the arachidonic acid cascade, mainly at the COX pathway [16]. This inhibition reduces the production of pro-inflammatory prostaglandins derived from arachidonic acid, potentially preventing their carcinogenic effect. The long-chain ω–3 PUFAs (LC ω–3), EPA, DPA and DHA, appear to be the most potent inhibitors of the COX inflammatory pathway.

PUFAs appear to be beneficial in the prevention and treatment of numerous disease states, including cardiovascular disease, neurodegenerative disorders and cancer [17]. The anti-neoplastic effect of PUFAs in vitro has been demonstrated in breast, colon, lung, liver, pancreatic and leukemia cell lines [18]. This beneficial effect may be mediated through the anti-inflammatory properties of PUFAs, or their modulation of cytokine production.

Foods rich in ω–3 PUFAs include canola and linseed oil, as well as various fish, including herring, salmon, trout, tuna and cod [19]. In the typical Western diet, the main sources of LC ω–3 PUFAs are dark fish and shellfish. The actual LC ω–3 content varies according to fish type; however, these fatty fish are often recommended as an important component of a healthy diet. Epidemiologic studies investigating cancer risk in populations with increased intake of these PUFA-rich foods have been somewhat equivocal. Although some have replicated the promising results of the in-vitro studies, many have found no beneficial effect of PUFAs on the incidence of various malignancies [20]. Investigators have hypothesized that the lack of an anti-neoplastic effect of PUFAs in these studies may be due to an inability to accurately quantify PUFA intake from diet and the potential contamination of PUFA-rich foods with carcinogenic substances. Thus,

as the laboratory and epidemiological data is often conflicting, further investigation is needed to clarify the effects of PUFAs on carcinogenesis and disease progression in various malignancies.

Experimental Support for PUFA/COX-2 Involvement in Prostate Cancer

Multiple lines of evidence suggest that PUFAs play a role in prostate carcinogenesis. This effect appears to be at least partially mediated through the enzyme COX. COX, also known as prostaglandin H synthase or prostaglandin-endoperoxide synthase, catalyzes the rate-limiting step in the formation of inflammatory prostaglandins. While the first form of the enzyme (COX-1) is involved in production of prostaglandins for cellular housekeeping functions, the second form (COX-2) is inducible and is associated with biologic events such as injury, inflammation and proliferation. As stated above, ω–3 and ω–6 PUFAs are both substrates for COX and directly compete for access to the enzyme. COX metabolism of ω–6 PUFAs results in production of pro-inflammatory prostaglandins; however, this metabolic pathway can be blocked by ω–3 PUFAs.

COX-2 is over-expressed in prostate tumors, and thus is speculated to play a role in prostate carcinogenesis [21]. In a mouse model, inhibition of COX-2 suppressed cell growth and led to regression of existing tumors, potentially through induction of apoptosis or decreased tumor angiogenesis [22]. Non-steroidal anti-inflammatory drugs (NSAIDs) have a well-known anti-inflammatory effect in humans, which is partially mediated by COX inhibition. Several epidemiological studies have preliminarily reported that regular NSAID use may in fact decrease the risk of developing prostate cancer in humans [23–25]. Experimental studies in humans have also shown that 3 months of a low-fat, fish-oil-supplemented diet decreased COX-2 expression in prostatic tissue in 4 of 7 men with untreated prostate cancer [26].

Numerous animal studies have demonstrated that adjusting the ratio of ω–3 to ω–6 PUFAs in the diet can alter the behavior of prostate tumors, an effect that appears to be partially mediated through COX-2. In studies of athymic mice with implanted prostate tumors, those mice fed an ω–3 versus an ω–6 PUFA diet exhibited a decreased expression of the inducible pro-inflammatory COX-2 enzyme in tumor cells, as well as decreased tumor cell proliferation and increased apoptosis [27]. Furthermore, ω–3 PUFA fed mice were found to have a decreased rate of prostate cancer recurrence after surgical excision of their tumors (mimicking radical prostatectomy) [27, 28]. It was hypothesized these effects were due to an increased relative concentration of ω–3 PUFAs, leading to a greater degree of COX-2 inhibition. Studies of *Pten*-knockout mice, an immune-competent orthotopic prostate cancer model, showed that a diet rich in ω–3 PUFAs reduces prostate cancer growth, decreases progression and increases survival [29].

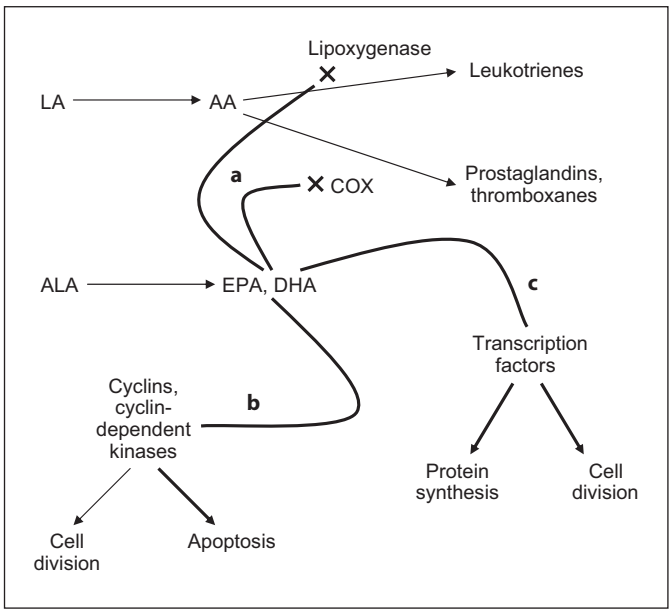

Fig. 1. Simplified schematic illustrating potential mechanisms through which ω–3 PUFAs may exert anti-neoplastic effects. **a** The ω–3 PUFAs EPA and DHA inihibit activity of COX and lipoxygenase enzymes, thus decreasing production of proinflammatory leukotrienes, prostaglandins and thromboxanes. **b** ω–3 PUFAs alter activity of cyclins and cyclin-dependent kinases, preferentially shifting cells towards apoptosis. **c** ω–3 PUFAs alter production and activity of various transcription factors, thus influencing protein production and cell division. AA = Arachidonic acid; LA = linoleic acid.

Additional animal studies found that mice fed an EPA-rich diet have higher LC ω–3 content in implanted prostate tumors, as well as a better response to hormone ablation. This indicates that PUFAs may play a role in preventing progression of prostate cancer to the androgen-independent state, an end-stage of disease for which very few effective treatment options are available [30].

Although the mechanisms through which PUFAs may exert anti-neoplastic effects are not entirely clear, several hypotheses have been proposed [18, 31] (fig. 1). Competitive inhibition of the COX and lipoxygenase enzymes by

ω–3 PUFAs leads to decreased production of several inflammatory and potentially carcinogenic molecules, including prostaglandins, thromboxanes and leukotrienes. Additionally, ω–3 PUFAs may modulate the activity of cyclins and cyclin-dependent protein kinases in tumor cells, thus shifting the balance away from cell division and towards apoptosis. Finally, ω–3 PUFAs have been shown to alter the expression of nuclear factor-kappaB, peroxisome proliferator-activated receptor γ and retinoid X receptors, and other transcription factors in vitro [32]. These cellular agents have been implicated in prostate cancer carcinogenesis, and may represent an alternative pathway through which ω–3 PUFAs exhibit antineoplastic activity.

Epidemiological Findings

PUFAs and Risk of Prostate Cancer

Epidemiological studies investigating associations between fish/PUFA intake and the development of prostate cancer have given equivocal findings. Of 26 cohort and case-control studies investigating fish/PUFA intake and incidence of prostate cancer, 11 reported inverse association [33–43], 7 positive association [44–50] and 8 showed no association [51–58] (tables 1, 2). If one looks only at the 15 cohort studies (table 1), again the results are widely conflicting, with 6 studies suggesting a protective effect of fish/PUFAs [33–38], 3 reporting a harmful effect [44–46] and 6 showing no association [51–56].

Overall fish intake, but not the intake of individual PUFAs, has been most consistently inversely associated with prostate carcinogenesis. Although several studies showed no correlation [37, 51, 52, 54], at least 6 studies reported either a trend or a definite association between fish intake and a decreased risk of prostate cancer [33, 34, 39–41, 43]. Terry et al. [34] studied a population of 6,272 Swedish men who were followed prospectively for the development of prostate cancer, and found that those men who ate no fish had a 2- to 3-fold increased risk of cancer compared to those who ate moderate or high amounts of fish. Two case-control studies reported on separate populations of Canadian men, and both found a statistically significant inverse association between fish intake and the incidence of prostate cancer [39, 40], as did Hedelin et al. [43] in a Swedish study. Collectively, these data support a protective effect of fish, which could potentially be mediated through ω–3 fatty acids, probably more specifically through LC ω–3 (EPA + DHA).

Interestingly, however, most studies specifically investigating the overall effects of ω–3 PUFA intake have shown no correlation with prostate cancer risk. Park et al. [37] reported on a large prospective cohort of 82,483 men in the USA and found a trend towards a decreased risk of prostate cancer with ω–3 PUFA intake, although this effect was largely limited to Latino and white men. Two smaller cohort studies, however, found no association between ω–3 PUFA intake and prostate cancer [51, 56].

Several authors have reported on associations between individual ω–3 PUFAs (ALA, DHA, EPA) and prostate cancer, and again reached largely equivocal results [35, 37, 38, 42, 46, 50, 53, 56–58]. Although a number of studies reported a negative association between ALA intake and prostate cancer [35, 37, 42], both Giovannucci et al. [46] and Ramon et al. [50] actually found an increased risk of disease with increasing ALA intake. ALA content is quite high in both red meat and animal fat, which have been implicated as causative factors for prostate cancer [59], possibly due to increasing the production of free radicals [45]. Although one relatively large cohort study reported a negative association between DHA/EPA intake and prostate cancer [38], multiple other studies found no association [35, 37, 56, 58].

Finally, most studies found no association between ω–6 PUFA intake and prostate cancer [36, 37, 50, 56]. However, there is a suggestion of decreased risk of disease with increasing intake of linoleic acid, the most prevalent ω–6 PUFA. Two cohort studies, from the Netherlands [35] and Finland [36], reported a non-significant trend towards a decreased risk with linoleic acid intake, whereas an Italian case-control study found statistically significant inverse associations [42]. This effect may be mediated through the preferential intake of foods rich in linoleic acid over those high in saturated fats, as occurs with the substitution of margarine for butter.

PUFAs and Risk of Advanced Prostate Cancer

Whereas the literature reports widely variable effects of fish/PUFA intake on prostate cancer incidence, there is stronger data supporting the ability of these foods to decrease the risk of advanced stage disease, metastases and death (tables 1, 2). Augustsson et al. [33] reported on a large prospective cohort from the US Health Professionals Follow-Up Study and found that men who ate fish more than 3 times per week were approximately half as likely to develop metastatic cancer as those who ate fish less than twice per month. Three additional cohort studies reported significantly reduced rates of prostate can-

Table 1. Summary of published cohort studies

Author, year	Country	Study size n	Cases n	PUFA studied	Effect on overall CaP incidence	Effect on incidence of advanced CaP	Ref.
Giovannucci, 1993	USA	47,855	300	LA, ALA	non-significant positive association with ALA	ALA positively associated with extra-prostatic or metastatic disease	45
Veierod, 1997	Norway	25,708	72	all PUFAs	no association	not studied	55
Schuurman, 1999	Netherlands	58,279	642	fish intake	no association	no association	54
Schuurman, 1999	Netherlands	58,279	642	all PUFAs, LA, ALA, DHA, EPA	non-significant negative association only with ALA and LA	no association	35
Terry, 2001	Sweden	6,272	466	fish intake	negative association with fish intake	fish intake negatively associated with mortality	34
Augustsson, 2003	USA	47,882	2,482	fish intake	non-significant negative association with fish intake	fish intake negatively associated with metastatic disease	33
Allen, 2004	Japan	18,115	196	fish intake	positive association with fish intake	not studied	44
Laaksonen, 2004	Finland	2,002	46	all PUFAs, ω–6 PUFAs, LA	negative association with PUFAs and LA	not studied	36
Leitzmann, 2004	USA	47,866	2,965	LA, ALA, EPA, DHA	negative association only with EPA and DHA	positive association with ALA, negative association with EPA and DHA in predicting extra-prostatic, metastatic or fatal tumors	38
Koralek, 2006	USA	29,592	1,898	ALA	no association with ALA	no association	53
Park, 2007	USA	82,483	4,404	all PUFAs, ω–6 PUFAs, ω–3 PUFAs, ALA, EPA, DHA	non-significant negative association with ω–3 PUFA and ALA. Association stronger in Latinos and whites	non-significant negative association between ω–3 PUFA/ALA and non-localized or high-grade disease	37
Wallstrom, 2007	Sweden	10,564	817	all PUFAs, LA, ALA, EPA, DHA	positive association only with EPA and DHA	no association	56
Giovannucci, 2007	USA	51,529	3,544	ALA	positive association with ALA	ALA positively associated with mortality	46
Crowe, 2008	several European nations	142,520	2,727	all PUFAs, fat from fish	no association with PUFAs or fish	inverse association between PUFAs and high-grade (but not advanced stage) disease	52
Chavarro, 2008	USA	20,167	2,161	fish intake, ω–3 PUFA fish	no association with fish or ω–3 PUFA fish	fish and ω–3 PUFA intake associated with decreased mortality	51
Pham, 2009	Japan	5,589	21 deaths	fish intake	not studied	fish intake negatively associated with mortality	60

CaP = Prostate cancer; LA = linoleic acid.

cer-specific mortality in those men consuming larger quantities of fish [34, 51, 60].

Identification of the actual nutritional components of fish that are responsible for this decrease in advanced-stage disease and mortality, however, is complicated. Prior reports have hypothesized that ω–3 PUFAs are the protective factor, but there is only modest data in the literature to support this claim. Whereas several studies have shown at least a trend towards decreased risk of advanced disease or death with ω–3 PUFA intake [37, 51], most studies investigating individual ω–3 PUFAs (ALA, EPA, DHA) have not replicated this finding [35, 37, 53, 56–58, 61]. Of 5 reports investigating the effects of EPA and DHA on advanced disease, only 1 cohort study reported an inverse association [38], whereas the remainder found no association [35, 37, 56, 58]. Contrary to many

Table 2. Summary of published case-control studies

Author, year	Country	Cases n	Controls n	PUFA studied	Effect on overall CaP incidence	Effect on incidence of advanced CaP	Ref.
Rohan, 1995	Canada	207	207	all PUFAs	non-significant positive association with PUFAs	not studied	48
Andersson, 1996	Sweden	526	536	all PUFAs, LA, ALA	no association	no association	57
Ghadirian, 1996	Canada	232	231	all PUFAs	non-significant positive association with PUFAs	not studied	47
Bairati, 1998	Canada	142	242	all PUFAs, LA, ALA	not studied	non-significant negative association between only PUFAs and LA and risk of non-localized disease	61
Fernandez, 1999	Italy	127	7,990	fish intake	non-significant negative association with fish intake	not studied	41
Tzonou, 1999	Greece	320	246	all PUFAs	positive association with PUFAs	not studied	49
Meyer, 1999	Canada	32	382	all PUFAs	not studied	no association with mortality	64
De Stéfani, 2000	Uruguay	217	431	LA, ALA	not studied	ALA associated with increased risk of extra-prostatic or metastatic tumors	62
Ramon, 2000	Spain	217	434	all PUFAs, ω–6 PUFAs, ALA	positive association only with ALA	no association with mortality	50
Kristal, 2002	USA	605	592	all PUFAs, EPA+DHA	No association	no association	58
Bidoli, 2005	Italy	1,294	1,451	all PUFAs, LA, ALA	Negative association of all PUFAs, ALA, and LA	not studied	42
Hedelin, 2007	Sweden	1,499	1,130	fish intake, ω–6 PUFAs, ω–3 PUFAs, LA, ALA, EPA+DHA	negative association with fish intake; positive association with ω–6 PUFAs and LA	not studied	43
Amin, 2008	Canada	386	917	fish intake	negative association with fish intake	no association	39
Mina, 2008	Canada	1,534	1,607	fish intake	negative association with fish intake	not studied	40
Fradet, 2009	USA	506	506	LA, ALA, EPA, DPA, LC ω–3 PUFAs	not studied	negative association between LC ω–3 PUFAs and aggressive CaP	63

CaP = Prostate cancer; LA = linoleic acid.

hypotheses, increasing ALA intake has actually been shown to increase the risk of advanced-stage disease in several studies. Two separate prospective analyses of the US Health Professionals Follow-Up Study first reported increased rates of advanced disease [38], and then death [46], with increasing ALA intake. A separate case-control study of patients with extra-prostatic or metastatic cancer in Uruguay found a positive association between ALA and these adverse outcomes [62].

In our own research, we found strong inverse associations between increasing intake of LC ω–3 EPA, DPA and DHA and aggressive prostate cancer [63]. The decreased risk followed a clear dose-response pattern across increasing levels of LC ω–3 intake, whereby men in the highest quartile of consumption had less than half the risk of aggressive disease in comparison to men in the lowest quartile. Similar inverse associations were observed for increasing intake of dark fish and shellfish, the 2 main sources of LC ω–3.

Epidemiological Studies

The above discussion illustrates the significant controversy in the literature regarding the effects of fish/PUFA intake on the incidence of prostate cancer and the

progression to advanced-stage disease. The explanation for the markedly heterogeneous results remains unclear, but a careful examination of the methods underlying the published studies provides important insights.

In many of the studies reporting no association between PUFAs and prostate cancer incidence, the fish type was not differentiated [37, 54] or individual PUFAs were not distinguished, but rather evaluated overall [35, 55, 64]. Supported primarily by a trend from the more recent literature, LC ω–3 – and fish rich in these nutrients – appear protective, while other ω–3 PUFAs or ω–6 PUFAs may be deleterious for prostate cancer. Not all PUFAs, and even not all ω–3 PUFAs, may be equal regarding their effect on prostate cancer, and it appears important to study each nutrient's effect separately.

Additionally, in many studies the exposure was defined with a single survey, with follow-up 20–30 years later, during which time dietary patterns may have changed significantly. For example, in Japan there is evidence that dietary habits have changed significantly over the past decades [65], during which time 1 study showing a positive association between fish intake and prostate cancer was conducted [44].

These potential measurement issues may explain the absence of association sometimes observed. Prospective studies where exposure is reassessed periodically, such as the Health Professional Follow-up Study [33, 38], provide better measures of adult dietary intake and changing dietary factors, and have shown a protective effect of fish intake on prostate cancer incidence. Moreover, some negative studies were conducted on cohorts with short follow-up, which might be problematic for prostate cancer since it is a relatively latent disease that generally occurs later in life [45, 46].

The level of ω–3/fish intake may affect study results. A very low level of dietary ω–3/fish may make it difficult to detect associations due to the narrow range of exposure variation. In fact, some studies observing no association were conducted in populations where ω–3/fish levels were substantially lower [35, 37, 54] than in studies where significant inverse associations were observed, such as the Health Professionals Follow-Up Study [33]. Of the studies reporting a positive association between LC ω–3/fish intake and prostate cancer risk, 2 were undertaken in populations with much higher fish intake than our study – Sweden [56] and Japan [44] – and they did not differentiate type of fish consumed. Although some have proposed that the effect of LC ω–3 PUFAs may convert from protective to harmful when consumed in excessive quantities, there is no data to support this hypothesis, not even from studies of cardiovascular diseases, where modeling of effect by level of intake has been proposed [66].

Another possible explanation is that the positive association could be attributed to environmental toxins, such as polychlorinated biphenyls or methylmercury compounds contained in fish. These toxins are known to disrupt the androgen/estrogen balance, and exposure has been linked to the risk of prostate cancer in prior reports [67, 68]. Certainly, further investigation is needed to clarify this potentially harmful interaction.

The literature suggests that fish/LC ω–3 may have a more pronounced effect on biologically aggressive tumors or on their progression, and less on carcinogenesis of more benign or earlier stage tumors often detected by screening. This appears to be true across several different geographic areas with significantly varying baseline population levels of fish and LC ω–3 intake [33–35, 38, 44, 54, 56]. The beneficial effect requires further investigation, as clarification and exploitation of this pathway could potentially decrease rates of progression, metastases, and death in men with early-stage, low-grade disease.

Finally, the somewhat inconsistent findings in the literature might reflect the distinct heterogeneity of prostate cancer. The potential protective effect of fish and LC ω–3 appears strongest for aggressive disease, which may exhibit different biological behavior than low-stage, low-grade disease. Even within individual studies, disease heterogeneity could potentially mask a beneficial effect of PUFAs. Those studies investigating prostate cancer incidence often included patients with a wide range of disease, from clinically localized tumors detected through screening, to those patients presenting with extraprostatic or metastatic disease. Thus, the beneficial effects of PUFAs on one stage of disease could potentially be masked by their lack of effect on another. Additionally, tumors are now often detected through PSA screening, whereas earlier studies were conducted prior to the PSA era, or in countries where PSA screening is not routinely practiced. Given the stage migration that has resulted from widespread PSA screening [4], one would expect a larger percentage of early-stage, low-grade tumors in the most recent studies. Since it appears that the protective effect of PUFAs is greater for advanced stage tumors, stage migration towards early-stage disease may bias study results towards finding no associations between PUFAs and incidence of disease, further contributing to the widely conflicting conclusions in the published literature.

Modification by *COX-2* Genotype

Candidate gene studies have found that sequence variants in the *COX-2* gene influence the risk of prostate cancer [69–71]. Thus, effect modification by *COX-2* genotype was hypothesized as a possible explanation for the wide variation in reported associations between ω–3 PUFA intake and prostate cancer. A recent study of Swedish men confirmed this interaction, finding that frequent consumption of fatty fish – a proxy for long-chain ω–3 PUFAs – was inversely associated with prostate cancer risk (OR = 0.57; 95% CI 0.43–0.76) [43]. Moreover, this effect was modified by the rs5275 (+6364 A>G) single nucleotide polymorphism (SNP) in *COX-2*, whereby only men carrying the variant allele maintained a strong inverse association between fatty fish intake and prostate cancer. This suggests that the potential protective effect of long-chain PUFAs on prostate cancer may be modified by *COX-2*.

In our research, we found that the LC ω–3 inverse association was stronger in carriers of the variant *COX-2* SNP rs4648310 (+8897 A>G) [63]. Interestingly, men with the variant genotype (AG or GG) and low intake of LC ω–3 had a much higher risk of aggressive disease than men with the variant genotype but a high intake of LC ω–3. This suggests that while carriers of the variant SNP had an overall increased risk of aggressive prostate cancer, this deleterious effect was found only in men consuming low levels of LC ω–3, and the association could be reversed by increasing consumption of LC ω–3. This interaction was similar across individual LC ω–3 (EPA, DPA and DHA) and dark fish (interaction p = 0.002, data not shown) – the main source of the PUFAs.

These results are in general agreement with those previously reported in the Swedish study [43]. Although rs4648310 (+8897 A>G) was not genotyped in their study, they found that another *COX-2* SNP (rs5275, +6364 A>G) modified the impact of fish intake on prostate cancer (p interaction < 0.01). In particular, Salmon-type fish consumption – a proxy for LC ω–3 intake – was protective only among men carrying the variant rs5275 genotypes (p trend < 0.01). We did not observe a similar pattern of interaction with rs5275 in our study (p interaction = 0.8). SNPs rs4648310 and rs5275 are not in linkage disequilibrium in our population ($r^2 = 0.01$, among whites).

The functional impact of rs5275, an intronic variant, and rs4648310, flanking the 3′ *COX-2* gene, on *COX-2* activity is not yet known. It is possible that either of these polymorphisms, or another linked variant, may affect function of the COX-2 enzyme. Just as the protective effect of ω–3 PUFAs may be mediated through the *COX-2* SNP rs4648310, we have previously shown that variation at a separate *COX-2* SNP rs2745557 alters the ability of NSAIDs to affect risk of disease [70]. Both LC ω–3 and NSAID compete with arachidonic acid for binding to the COX active site, although their downstream effects appear different [72, 73]. Thus, it could be hypothesized that variation at these *COX-2* SNPs alters the enzyme's structure or function, enabling it to preferentially bind LC ω–3, NSAID or other substrates. This changing affinity for various ligands may affect the enzyme's pro-inflammatory function, and thus modify the risk of developing prostate cancer. Collectively, the combined findings of our study [63] and that of the Swedish population [43] support the overall hypothesis that LC ω–3 modifies prostate inflammation through the COX-2 enzymatic pathway.

Summary

Despite conflicting results in the literature, recent data presents convincing evidence that dietary LC ω–3 are inversely associated with aggressive prostate cancer. This potential protective effect may be modified by genetic variation in *COX-2*. Interestingly, it appears the deleterious effect of 1 SNP (rs4648310, +8897 A>G) can be reversed by increased LC ω–3 intake. These results support the role of inflammation and COX activity in prostate cancer susceptibility and progression. More clinical and biological studies are needed to decipher the mechanisms through which dietary long-chain ω–3 fatty acids and other factors involved with inflammation, such as *COX-2* genotypes, may affect prostate cancer risk and aggressiveness.

Acknowledgments

This work was supported by the National Institute of Health grants CA88164 and CA94211. V.F. is supported by the McLaughlin dean's grant from Laval University.

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