

Controversies Surrounding Omega-3 Fatty Acids and Prostate Cancer

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Abstract

Context: Omega-3 poly unsaturated fatty acids (omega-3 PUFAs) have been widely studied regarding their associations with pathogenesis, prevention, and treatment of prostate cancer (PCa); however, no agreement has been reached as to whether omega-3 PUFAs are protective by reducing the risk of PCa.

Objective: To provide information to public readers regarding the controversies in the effects of individual omega-3 PUFA species, including α -Linolenic acid (ALA) eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) on PCa, and regarding the causes underlying these controversies.

Data Sources: Research articles archived online related to the effects of omega-3 PUFAs on PCa published in the past four decades. The protective effect of each omega-3 PUFA species on PCa was evaluated in study categories of epidemiological survey/food query, plasma/RBC membrane, prostatic tissue, PCa cell line *in vitro*, and clinical trial/animal model *in vivo*.

Conclusions: Controversies surrounding omega-3 PUFAs and PCa broadly exist in each individual omega-3 PUFA species, between omega-3 PUFAs from plant and sea food sources, and among omega-3 PUFAs from sea food sources in every study categories. These controversies are mainly due to: 1) presuming that the levels omega-3 PUFAs in circulation, in RBC membranes and in estimates in diet intake are proportional to those in prostate; 2) using percentage changes to represent alterations in real concentrations of omega-3 PUFAs between two pathological conditions in data analysis, and 3) administering omega-3 PUFA(s) to PCa cells *in vitro* with doses far above physiological levels in human prostate in some studies.

Prostate cancer (PCa) threatens men's health worldwide¹⁻³. In the US, PCa is the most diagnosed non-skin cancer and second leading cause of cancer deaths in men³. According to the American Cancer Society's estimates, there will be about 174,650 new cases and 31,620 deaths of prostate cancer in US for 2019⁴. PCa has become a tremendous burden on health care and socioeconomics in our society. In working toward the ultimate goal of eliminating suffering and death from PCa, we need to identify all risk factors, and importantly to know how to modify modifiable risk factors.

Age is the greatest risk factor for PCa. The incidence of PCa strongly increases with age. Based on report on cancer statistics from US Surveillance, Epidemiology and End Results Program from 2000-2008, the incidence rate of prostate cancer was 9.2/100,000 for men aged 40-44 years, but it increased sharply to 984.8/100,000 in men aged 70-74 years⁵. Race is also a well-established risk factor for PCa. There is more than a 60-fold difference in age-adjusted incidence rates between population groups with the highest in African American (AA) men and the lowest in Asian men living in their native countries. In US, PCa is prominently disparate between AA men and Caucasian Americans (CA) men. As compared to CA men, AA men are younger at onset, have a higher incidence and mortality rate, experience more aggressive clinical courses, and exhibit poor responses to therapies. They also have a higher rate of recurrence and development of advanced PCa, and are 2.4 times more

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likely to die from PCa⁶⁻¹¹. A positive family history is highly related to future PCa development, particularly in men who have first-degree relatives affected from PCa¹²⁻¹⁴. Therefore, family history is considered to be another established risk factor for PCa¹⁵.

Age, race, family history and sex are well-established risk factors of PCa, and are not modifiable. Thus, efforts should be made to identify modifiable risk factors in order to prevent occurrence, blocking progression, and improve outcomes of patients with PCa. Modifiable risk factors include life style¹⁶, obesity¹⁷⁻¹⁹, sexual activity, smoking^{20,21}, and inflammation^{22,23}. Among those, dietary intake of fatty acids has been most widely investigated.

Fatty acids are a large group of macromolecules comprised of hydrocarbon chains terminating with carboxylic acid groups. In general, fatty acids play important roles in energy generation, building blocks in cellular membranes, signal-transduction pathways, composition of hormones and complex lipids, and modification of proteins, and energy storage in triglycerides and cholesteryl esters. Importantly, fatty acids are of special significance to PCa. While cancer cells in most malignancies exhibit increased glycolysis and glucose utilization for proliferation²⁴⁻²⁶, PCa cells depend on oxidation of fatty acids as the main energy source for their proliferation. This is accomplished by a dominant uptake of fatty acids over glucose, increased *de novo* synthesis of fatty acids, accumulation of fatty acids in the form of cholesteryl esters or triglycerides, and up-regulation of enzymes in oxidation of fatty acids²⁷⁻³¹.

In past decades, numerous research articles and reviews have addressed the influences of fatty acids, especially those with 14-24 carbon chains in individual species, in total and in groups, on PCa. Fatty acids without double bonds in carbon chains are grouped as saturated fatty acids (SFA). Among SFA species, myristic acid has been rarely reported to be associated with risk of PCa. Palmitic acid related to increased PCa risk was reported in few studies³²⁻³⁴; and stearic acid inversely related to risk of PCa³⁴⁻³⁸.

Fatty acids with one double bond in carbon chains are grouped as monounsaturated fatty acids (MUFA). Among those, oleic acid has been the most investigated species, but with a mixed results. Some studies suggest that elevated level of oleic acid, or the ratio oleic to stearic acid in dietary intake, correlates with a high risk of PCa^{35,39-41} and promotes aggressive behavior of PCa cells^{42,43}. Others however, suggest that elevated level of oleic acid, or the ratio oleic to stearic acid in dietary intake plays a protective role in the pathogenesis of PCa^{37,44-47}.

Fatty acids with more than one double bond in carbon chains are grouped as polyunsaturated fatty acid (PUFA), including omega-6 (n-6) PUFAs and omega-3 (n-3) PUFAs. It has been reported in several studies that omega-6 PUFAs increase risk and promote progression of PCa⁴⁸⁻⁵⁵. However in a few studies it was shown to reduce the risk of PCa^{56,57}. In one study it was shown not to be related to the risk of PCa⁵⁸. As compared to omega-6 PUFAs, omega-3 PUFAs are more involved in pathogenesis, progression, prevention, and treatment of PCa.

Omega-3 PUFAs are a group of polyunsaturated fatty acids with the first double bond in the third carbon position from the methyl terminal. Main omega-3 PUFA species and their metabolic pathways are shown in **Figure 1**. Human beings can only form carbon-carbon double bonds after the 9th carbon from the methyl end of a fatty acid. Therefore, α -Linolenic acid (ALA) must be obtained from the diet and is the only essential fatty acid among omega-3 PUFAs. ALA is widely present in plant oils, such as flaxseed, soybean, and canola oils⁵⁹. Other important omega-3 PUFAs are eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). Although these omega-3 PUFAs can be converted from ALA, conversion rates from ALA to other omega-3 PUFAs, especially to DHA are low⁶⁰. Thus dietary intake is the main source for these omega-3 PUFAs. Unlike ALA, these omega-3 PUFAs are present in sea foods such as fish, fish oils, and krill oils, because sea fishes accumulate omega-3 PUFAs in their tissues through consumption of phytoplankton that themselves consumed microalgae, which originally synthesize omega-3 PUFAs⁵⁹.

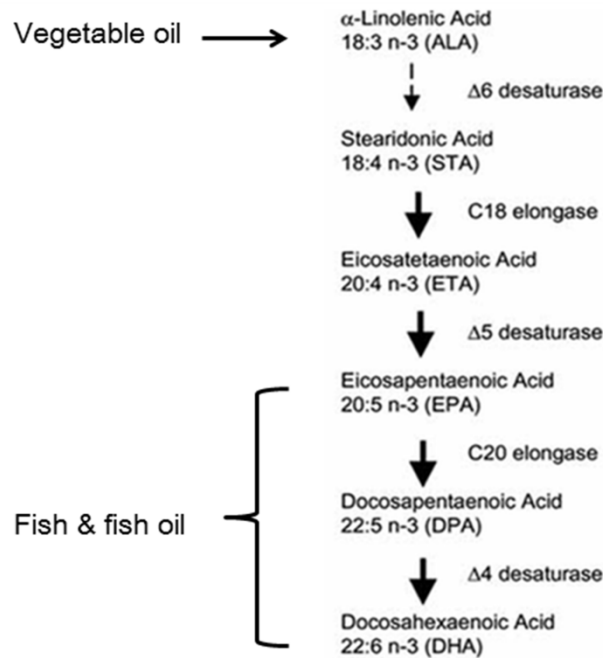


Figure1. Main omega-3 poly unsaturated fatty acid species (PUFAs) and their metabolic pathways.

This review evaluates the effects of each of main omega-3 PUFA species, namely, ALA, EPA, DPA and DHA separately on PCa.

Effects of α -linolenic Acid (ALA) on PCa

Chua et al. found that high intake of ALA may reduce risk of prostate cancer, while intake of other long-chain omega-3 fatty acids did not have a significant effect⁶¹. Fu et al also found that dietary ALA was inversely associated with PCa risk⁶². However, Brouwer et al. indicated in two reviews that the risk of prostate cancer increased in men with a high intake of ALA, although high ALA intake was associated with reduced risk of fatal heart disease in prospective cohort studies^{63,64}. The influences of ALA on PCa from individual studies were also inconsistent in different study categories as shown in **Table 1**. In study category of Epidemiological Survey/ Food Query, seven studies revealed that higher intake of ALA was associated with an increased risk of PCa^{32,46,58,65-68}. Only one study suggested that ALA in dietary intake was inversely associated with PCa risk⁶². In study category of Plasm/RBC Membrane, the association of ALA in plasma or in phospholipids of RBC membranes with risk of PCa was very controversial: ALA related to decreased risk of PCa in seven studies^{61,62,69-73}, increased risk of PCa in five studies^{32,46,63,74,75}, and no correlation to PCa in four studies^{67,74,76,77}. In study category of Prostatic Tissue, only two studies were conducted regarding the correlation of prostatic level of ALA with the risk of PCa: Christensen et al. found that increased prostatic level of ALA correlated with the presence of PCa, and to higher level of PSA in men with PCa⁷⁴; Azrad et al. also found that 1) the level of prostatic ALA was independent of the amount of ALA consumed, and 2) the level of prostatic ALA was significantly associated with patient's PSA value ($P=0.028$) and expression level of Ki67 ($P=0.037$)⁸⁵. No study showed an association of prostatic ALA level with decreased PCa risk. Two *in vitro* studies found that ALA was able to inhibit PC-3 and LNCaP cell proliferation through regulating genes involved in fatty acid synthesis, inflammation, cell cycle, and apoptosis⁸⁰; and inhibit PC-3 and RWPE-1 cells proliferation through changing production of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), lipoxin A4, and free radical generation⁷¹. However one *in vitro* study indicated that ALA, as well as other PUFAs at low concentrations (1ng/ml) was able to promote proliferation

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of many human and animal cell lines⁸¹. In study category of Clinical Trial/Animal Model *in vivo*, several studies on human clinical trials and on animal models suggest that increase in dietary intake of ALA show decreased growth potential in PCa^{85,86,93,94}. In a multisite, randomized controlled trial the Demark-Wahnefried research team tested the effects of low-fat vs. flaxseed-supplemented (rich in ALA) diets on the biology of the prostate and other biomarkers. They found that proliferation rates were significantly lower ($P=0.002$) among men who took flaxseed-supplemented diet⁸⁴. Another clinical trial (The Alpha Omega Trial) involved 1,622 patients aged 60-80 years with a history of myocardial infarction and an initial PSA concentration <4 ng/ml. In this study, patients received additional amount of 2 g of ALA per day slightly increased PSA by 0.10ng/ml, but no evidence showed a clinically significant effect of ALA intake on PCa risk⁷⁶. Therefore, the effects of ALA on PCa are controversial. ALA may reduce risk and inhibit progression of PCa in some studies; but it increase risk and promote progression of PCa in other studies.

Table 1. Influence of α -linolenic acid (ALA) on PCa

Study Category	Effects on PCa	# of Studies	References
Epidemiological Survey/Food Query			
	Decreased risk	2	39, 62
	Increased risk	8	32, 46, 58, 65-68, 78
	No association	2	47, 79
Plasma/RBC Membrane			
	Decreased risk	7	61, 62, 69-73
	Increased risk	5	32, 46, 63, 74, 75
	No association	4	67, 74, 76, 77
Prostatic Tissue			
	Increased risk	2	74, 76
<i>In vitro</i> in PCa Cell Line			
	Decreased risk	2	71, 80
	Increased risk	1	81
Clinical Trial/Animal Model <i>in vivo</i>			
	Decreased risk	5	72, 73, 82-84
	No association	1	76

Effects of Eicosapentaenoic Acid (EPA) on PCa

It was suggested 50 years ago that high fish consumption among the Eskimos of Greenland contributed to their low death rate from coronary heart disease⁸⁶. In 1980's, Karmali et al. suggested that fish oil can inhibit growth of mammary and prostatic tumor cells^{87,88}. This could be because fish and fish oil contain large amount of omega-3 PUFAs, including eicosapentaenoic acid (EPA). EPA has a 20-carbon chain and five cis double bonds. EPA has been extensively investigated as to its relationship to human diseases, including PCa. As shown in **Table 2**, in study category of Epidemiological Survey/Food Query, four studies conducted in human PCa patients were in agreement with Karmali et al. that more dietary fish intake is associated with a lower risk of PCa^{58, 89-91}. But three studies conclude contrarily that more fish intake in diet was associated with a high risk of PCa^(78,104,105). Four studies claimed that fish intake or circulatory level of EPA is not associated with risk of PCa^{32, 79, 92, 93}.

In study category of Plasma/RBC Membrane, the level of EPA in plasma or in phospholipids in RBC membranes has been related to decreased risk of PCa. One study suggests that the circulatory level of EPA is higher in men without prostatic diseases than patients with benign prostatic hyperplasia (BPH), and lowest in patients with

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PCa⁴⁸. Two other studies found circulatory EPA inversely correlated to PCa risk as well^{90,94}. Surprisingly, no correlation was found between EPA level and PCa risk in seven studies^{32,55,74,77,93,95,96}.

Table 2. Influence of eicosapentaenoic acid (EPA) on PCa

Study Type	Effect on PCa	# of Studies	References
Epidemiological Survey/Food Query			
	Decreased	4	58, 89-91
	Increased risk	3	67, 100, 102
	No association	4	32, 79, 92, 93
Plasma/RBC Membrane			
	Decreased risk	3	48, 90, 94
	Increased risk	3	67, 100, 102
	No association	7	32, 55, 74, 77, 93, 95, 96
Prostatic Tissue			
	Decreased risk	4	72, 97-99
	Increased risk	1	100
	No association	2	74, 95
In vitro in PCa Cell line			
	Improve outcomes	2	103, 104
	Inhibit proliferation	11	53, 71, 80, 97, 101, 105-110
	Stimulate proliferation	1	81
Clinical Trial/ Animal Model <i>in vivo</i>			
	Decreased risk	2	100, 111
	No association	2	95, 112

In prostatic tissues, higher EPA levels correlate with a decreased risk of PCa, and improved patient's clinical outcomes^{72,97-99}. But in one study, higher EPA levels correlate with increased risk of PCa¹⁰⁰. No correlation was found between prostatic EPA level and risk of PCa in two studies^(86,107). In 1985, Begin et al. found that when human cancer cells and normal human fibroblasts were co-cultured in the absence of PUFAs, the malignant cells overgrew the normal ones; when eicosapentaenoic acid (EPA, 20:5n-3) and other PUFAs were added to the co-cultures, the normal cells outgrew the malignant cells¹⁰¹. Since then EPA has been found to be able to enhance therapeutic effects^(112,113) and inhibit proliferation of many PCa cell lines^(53,83,90,109,114-120). Only one study indicated that EPA actually promoted prostatic cell lines growth at low concentrations (1ng/ml). But at higher concentrations, EPA did inhibit prostate cell growth⁽⁹¹⁾.

EPA was found to be able to reduce PCa risk in two clinical trials^(105,121), and did not correlate PCa risk in other two studies^(107,122). Recently, the Guertin research team¹¹³ attempted to evaluate the effects of long-chain omega-3 polyunsaturated fatty acids, more precisely eicosapentaenoic acid monoacylglyceride (MAG-EPA) supplementation, on prostate cancer proliferation, inflammatory mediators, and quality of life among men who will undergo radical prostatectomy. They proposed a phase IIb, randomized, double-blind placebo-controlled trial, in which MAG-EPA supplementation was administered to 130 men who will undergo radical prostatectomy as treatment for a prostate cancer of Gleason score ≥ 7 . Participants will be randomized to 6 capsules of 625 mg of fish oil (MAG-EPA, per capsule containing 500mg of EPA) daily or to identically looking capsules of high oleic acid sunflower oil (HOSO) as placebo. This study is ongoing. Thus, conclusions on risk or protective effect of EPA

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to PCa were highly inconsistent. Taking together, EPA has been widely investigated as to its relationship with risk and progression of PCa. Although EPA shows effects in decreasing risk and improving outcomes of PCa in many studies, it also shows effects in increasing risk and stimulating proliferation of PCa in some studies.

Effects of Docosapentaenoic Acid (DPA) on PCa

Docosapentaenoic acid (DPA, specifically refer to omega-3 DPA isomer) is a member of omega-3 PUFAs intermediary between EPA and DHA. As compared to its substrate EPA and its product DHA, DPA has been less studied regarding its association with risk of PCa. As shown in **Table 3**, in study category of Epidemiological Survey/Food Query, three studies concluded that higher DPA play a role in reducing risk of PCa^{62, 100, 102}. For example, in a dose-response meta-analysis of prospective observational studies, Fu et al. found that a 0.2% increase in blood DPA concentration was associated with a 3% reduced risk of PCa ($P=0.05$ for linear trend)⁶². No relationship between DPA and PCa was reported in two studies^{32, 47}.

In study category of Plasma/RBC Membrane, higher concentration of DPA in plasma or in phospholipids in RBC membranes related to decreased risk of PCa were reported six studies^{62, 67, 72, 73, 100, 102}. One study indicated that no association between circulatory level of DPA and the risk of PCa³². In prostatic tissues, the concentration of prostatic DPA was reported to correlate to decreased risk of PCa in one study¹¹⁴, increased risk of PCa in one study⁵⁶, and no association with risk of PCa in one study¹⁰⁰. No study has been specifically conducted to investigate effects of DPA on proliferations *in vitro* in PCa cell lines. *In vivo* study, DPA together with other omega-3 PUFAs demonstrated to be able to decrease risk of PCa in two phase II clinical trials^{83, 100} and in two animal models^{72, 114}. One *in vivo* in animal model study failed to demonstrate an association between DPA and risk of PCa¹¹⁵. In summary, it is still controversial in the effect of DPA on risk of PCa, although most studies favored that DPA correlated to decreased risk of PCa.

Table 3. Influence of docosapentaenoic acid (DPA) on PCa

Study Types	Effect on PCa	# of Studies	References
Epidemiological Survey/Food Query			
	Decreased risk	3	62, 100, 102
	No association	2	32, 47
Plasma/RBC Membrane			
	Decreased risk	6	62, 67, 72, 73, 100, 102
	Increased risk	3	38, 57, 70
	No association	1	32
Prostatic Tissue			
	Decreased risk	1	114
	Increased risk	1	56
	No association	1	100
Clinical Trial/Animal Model <i>in vivo</i>			
	Decreased risk	4	72, 83, 100, 114
	No association	1	115

Effects of Docosahexaenoic Acid (DHA) on PCa

Docosahexaenoic acid (DHA) is a carboxylic acid with a 22-carbon chain and six cis double bonds. DHA cannot be synthesized *de novo* in human, and therefore must be obtained in the diet primarily through fish, nutraceuticals, and functional foods (food have a potentially positive effect on health beyond basic nutrition)¹¹⁶

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or converted within the body from α -linolenic acid (ALA). In addition to playing a very important role in human pathophysiology, such as in brain ⁽¹²⁹⁾ and cardiovascular system ⁽¹³⁰⁾, DHA also has an impact on occurrence and progression of many cancers by inducing cancer cell apoptosis, reducing cancer cells proliferation *in vitro* and *in vivo* through potential mechanisms including membrane incorporation, lipid peroxidation, and stalling progress of cell cycles ⁽¹³¹⁻¹³³⁾. The relationship between DHA and PCa has been widely investigated as listed in Table 4.

Table 4. Influence of docosahexaenoic acid (DHA) on PCa

Study Type	Effect on PCa	# of Studies	References
Epidemiological Survey/ Food Query			
	Decreased risk	2	58, 118
	Improve outcomes	1	89
	Increased risk	4	67, 93, 100, 102
	No association	2	32, 92
Plasma/RBC Membrane			
	Decreased risk	5	48, 55, 71, 90, 117
	Increased risk	3	67, 93, 100
	No association	4	32, 74, 77, 95
Prostatic Tissue			
	No association	4	56, 74, 100, 119
In vitro in PCa Cell Line			
	improved outcomes	2	120-122
	Inhibit proliferation	10	53, 80, 104, 105, 109, 110, 122-125
	No association	2	71, 74
Clinical trial/Animal Model <i>in vivo</i>			
	Decreased risk	4	83, 88, 99, 114, 115
	No association	1	100

In study category of Epidemiological Survey/Food Query, the association between PCa risk and DHA level in dietary intake or in phospholipids in RBC membranes was evaluated in two studies. One study followed 47,866 US men aged 40-75 year-old with no cancer history for 14 years, to prospectively evaluate the association of DHA in diet intake and risk of PCa. Another study examined the relationship between PCa risk and DHA (and EPA) level in phospholipids in RBC membranes in a population-based case-control study involving 317 PCa cases and 480 age-matched community controls. Both studies concluded that high level of DHA in dietary intake or in phospholipids in RBC membranes related to decreased risk of PCa ^{58, 90}. One study prospectively evaluated the association between diet intakes of PUFAs including DHA and risk of PCa in patients diagnosed with PCa: men consuming fish 5 times/wk. or more had a 48% lower risk of PCa death than did men consuming fish less than once weekly ⁸⁹. These three studies hinted that DHA played a protective role either in preventing prostatic oncogenesis, or on PCa progression. However conclusions from other four studies were contrary: higher DHA levels in dietary intake correlated with higher grade of PCa ^(76,103-105). Two studies reported that there was no correlation between level of DHA in dietary intake and PCa risk ^(32,102). Similar controversies were found in study category of Plasma/RBC Membrane, in which the concentration of DHA in plasma or in phospholipids in RBC membranes related to decreased risk of PCa in five studies ^{48, 55, 71, 90, 117}, increased risk of PCa in three studies ^{67, 93, 100}, and did not relate to risk of PCa in four studies ^{32, 74, 77, 95}.

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In study category of Prostatic Tissue, there was no significant difference in DHA level between PCa and adjacent benign prostatic tissues, between PCa and benign prostatic hyperplasia (BPH), or between PCa with and without progression in four studies^{56, 74, 100, 119}.

A total of fifteen studies regarding the correlation of DHA with PCa risk were included in study category of *In vitro* in PCa Cell Line. Surprisingly, no study showed that DHA correlated with increased risk of PCa. Except for two studies that showed no relationship between DHA and risk of PCa^{71, 74}, the remaining thirteen studies concluded that DHA either improves therapeutic effects of androgen depletion therapy (ADT) and other anti-tumor therapeutic agents^{120, 126}, or inhibits proliferation of many prostatic cells, such as PC-3, LNCaP, RWPE-1 and DU-145 by DHA at doses ranged from 10 μ M to 200 μ M^{53, 80, 104, 105, 109, 110, 122-125}. Mechanisms underlying inhibitory effects on cancer cell proliferation by DHA involved numerous pathways such as inhibiting fatty acid synthase, accelerating androgen receptor degradation, and altering signal transduction in AKT, JAK1, STAT1, ERK1/2, JNK and IFN- γ etc.

In study category of Clinical Trials/Animal Model *in vivo*, there were six studies including two clinical trials and four animal models. Three studies used xenograft animal model, in which animal fed with diet containing omega-3 PUFAs including high proportion DHA. The results showed that animals fed with a diet rich in omega-3 PUFAs had significantly smaller tumor volume, significantly inhibited growth, slowed down the growth of castration-resistant tumors, smaller tumor cells with more connective tissue in histological sections, and less intense immunochemical staining for human prostatic acid phosphatase^{88, 99, 114}, as compared to animals fed with a diet rich in omega-6 PUFAs. Another study report that 100% of animals fed with refined, westernized AIN-93-based diets containing corn oil developed PCa by 12 months of age spontaneously; while animals fed with a diet replaced by 50% menhaden oil, contain omega-3 PUFAs, such as DHA escaped from development of spontaneous PCa¹¹⁵. One clinical trial also reported that DHA can decrease risk of PCa⁸³; and another clinical trial suggested no association between DHA and risk of PCa¹⁰⁰. Similar to other omega-3 PUFAs discussed above, DHA shows controversial effects on PCa. Some studies suggest that DHA decreases risk and improves outcome of PCa; others indicate it increases risk of PCa; and several studies show no relationship between DHA and risk of PCa.

Possibilities Underlying the Controversies

Seemingly a panacea, omega-3 PUFAs have been tried for prevention and treatment of a wide spectrum of diseases. For cardiovascular diseases, omega-3 PUFAs could benefit to cardiovascular functions through counteracting the atherosclerotic process¹²⁷⁻¹²⁹, preventing hypertension¹³⁰, lowering cardiovascular mortality¹³¹, and reduce sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease¹³². Epidemiological studies have revealed that omega-3 PUFAs are associated with incidence and progression of many cancers, such as breast¹³³, colon cancer¹³⁴, liver cancer¹³⁵, and pancreatic cancer¹³⁶. But omega-3 PUFAs were most extensively studied on their associations with incidence and mortality rate, progression, prevention, and treatment of PCa. This could be because PCa is unique in dominantly using fatty acids as fuels in energy production. Importantly, PCa has a mostly indolent natural history and long overall survival after diagnosis, providing an opportunity for exploration of non aggressive interventions such as diet and lifestyle to modify the natural clinical course and outcome of PCa.

Previously studies on the associations of omega-3 PUFAs with PCa have greatly helped in seeking modifiable factors to influence pathogenesis, progression, prevention, and treatment of PCa. However, these studies have not reached an agreement on the pros and cons of each omega-3 PUFA species to PCa. Instead, conclusions are highly controversial, inconsistent and even contrary within each individual omega-3 PUFA species, between PUFAs derived from plants and sea foods, and among omega-3 PUFA species derived from sea foods in every study category. The following possibly contribute to the controversies.

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Anderson et al.¹³⁷ summarized several factors related to the inconsistency. For example, using food frequency questionnaires in nutritional epidemiology as a method of assessing dietary intake may produce inaccurate results, because questionnaires are subject to recall bias and the food composition databases they are based upon may lack precision in quantifying actual nutrient intake. Alternatively, erythrocytes have been used as biomarkers for dietary intake of fatty acids; however, they lack complete accuracy too. Some sources indicate erythrocyte membrane fatty acid composition is reflective of a typical diet at approximately 4 months¹³⁸, whereas other research suggests levels of fatty acids in RBC membrane reflect dietary intake after 3 weeks^{139,140}. The levels of fatty acids are not necessarily and accurately proportioned to that estimated in dietary intake and measured in circulation or in phospholipids in RBC membranes, as assumed previously^{141,142}. In addition, prostate cancer exhibits enhanced rates of *de novo* fatty acids synthesis, which makes the fatty acid profile in PCa cells differ from that in circulation¹⁴³⁻¹⁴⁵. Neither are prostatic concentrations of majority of fatty acids proportional to the amount estimated from dietary intake, nor does the presence of prostate cancer affect fatty acid consumption in other tissues such as adipose tissue or erythrocyte membranes⁷⁷. Therefore only prostatic fatty acid profiles are most closely correlated with pathological changes in prostate as suggested by Moreel et al.¹⁰⁰. However, studies on lipid profiling including omega-3 PUFAs performed on prostatic tissues were limited. Especially, lipid profiling on prostatic tissues from African American men was rare: in this study, there were only four research articles performed lipid profiling on prostatic tissues in AA men^{54,95,97,146}. Recently, Figiel S et al.⁹⁷ found that DPA in peri-prostatic adipose tissues from both indolent and aggressive PCa was significantly lower in African-Caribbean men than in CA men. More data from lipid profiling on prostatic tissues from AA and CA men in the US are needed in helping to explain why incidence and mortality rate of PCa are prominently disparate between these two races.

Another important issue possibly responsible for the inconsistencies among studies could be neglected: the percentage of certain targeting fatty acids out of total fatty acids (sum of total detected fatty acid species) was used in data analysis in most previous studies. First, percentage changes were not equal, proportion or even contrary to actual changes in absolute concentrations between PCa and benign prostatic tissues. Second, total fatty acids were determined by varied numbers and species of fatty acids among studies, making results not being comparable. It is better to use absolute concentration (such as micromole, or nanomole per gram prostatic tissues, or per gram protein) to compare difference between PCa and BPT in data analysis.

All four omega-3 PUFA species, especially EPA and DHA were investigated on their effects on PCa using PCa cell line *in vitro*. Interestingly, Both EPA and DHA showed the ability to inhibit PCa cell proliferation *in vitro* in most majority studies. These inhibiting effects were dose-dependent (concentrations ranged 10-200 μM). It cannot be excluded that these inhibiting effects may have been caused by toxic effects from free fatty acids (EPA and DHA) in doses far above tolerance of prostatic cells in physiologic conditions, because when free fatty acid levels are too high they may give rise to a large number of toxic compounds (isoprostanes and other nonenzymatic products)¹⁴⁷. Our recent study showed that the concentration of free form DHA in PCa was less than 0.007 nmol/mg in PCa tissues, which was 1.9×10^{-5} less than total DHA (134 nmol/mg) in PCa tissues. Whether proliferations of PCa cells are inhibited by biological effects of EPA and DHA, or by their toxic effects require further investigation.

In addition, differences in study methods, size of samples, geographic locations, and studied populations might also contribute to the controversies among studies.

CONCLUSIONS

Whether omega-3 PUFAs have risk, protective, or no effect on PCa remains highly controversial. Such controversies are broadly exist in each individual omega-3 PUFA species, between omega-3 PUFAs originated from plants and

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sea foods, and among omega-3 PUFAs originated from sea foods in every study categories. These controversies are mainly owe to: 1) presuming that prostatic levels of omega-3 PUFAs proportion to that in circulation, in phospholipids in RBC membranes, and in estimates from diet intake; 2) using percentages of omega-3 PUFAs to represent changes in absolute concentrations between two pathological conditions in data analysis, and 3) treating PCa cells *in vitro* by omega-3 PUFA(s) with doses far above physiological level in prostatic cells.

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