Review Article
Prostate cancer

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Evidence on Statins, Omega-3, and Prostate Cancer: A Narrative Review

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Dietary intake selections might play a crucial role in prostate cancer (PCa) occurrence and progression. Several studies have investigated whether statin use could reduce PCa risk but with conflicting results. Nevertheless, a significantly decreased incidence of advanced PCa has been consistently noted. Statins may also reduce the risk of biochemical recurrence (BCR) in men with PCa after receiving active treatment. However, the influence of statin usage on BCR and PCa progression in men with high prostate-specific antigen levels has been found to be insignificant. In contrast, the combined use of a statin and metformin was significantly related to the survival status of PCa patients. However, some studies have revealed that the intake of long-chain omega-3 fatty acid (ω-3) from fish or fish oil supplements may elevate PCa risk. Several meta-analyses on ω-3 consumption and PCa have shown controversial results for the relationship between PCa and ω-3 consumption. However, studies with positive results for various genotypes, fatty acid intake or levels, and PCA risk are emerging. This review highlights the association among statins, ω-3, and PCa. The findings summarized here may be helpful for clinicians counseling patients related to PCa.

Keywords: Omega-3 fatty acid; Prostate cancer; Recurrence; Risk; Statin; Survival

INTRODUCTION

Intriguing correlations between prostate cancer (PCa) and the usage of statin and omega-3 fatty acid (ω-3) have been reported. Statins are common drugs prescribed for dyslipidemia and ω-3s are fish oil supplements. One study [1] concluded the statin administration had a strong correlation with the decreased risk of PCa metastasis and mortality. Another study [2] investigated the effects of edible ω-3 on PCa progression in mice and resulted that its usage could suppress tumor cells' growth. Nevertheless, these interesting associations remains controversial, warranting active research for further elucidation.

EFFECT OF STATINS ON PROSTATE CANCER

Growing evidence that supports the assumption that statin usage is related to a reduced risk of advanced PCa is being reported [3]. However, whether statin use in men with PCa could prevent biochemical recurrence (BCR) or disease progression remains unclear. Thus, the benefits of statins must be evaluated before we can

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recommend statins initiation for males at risk for PCa despite their cholesterol profile. Several clinical findings are summarized in Table 1.

1. Mechanism of statins and effects of statins on prostate cancer

The underlying mechanism of statins is by decreasing cholesterol synthesis *via* suppression of rate-limiting hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins are classified according to solubility as either lipophilic or hydrophilic. Lipophilic statins are presumed to have a larger impact on the prostate than hydrophilic agents [3]. However, this assumption has not been validated by observational investigations of PCa risk and statin usage, partly due to the low number of males using hydrophilic statins.

A positive relationship between PCa presence and cholesterol accumulation in prostatic tissues has already been reported [4]. Some mechanisms related to serve to dysregulation of cholesterol balance in PCa have since been revealed. Lee et al [5] reported that the ABCA1 promoter hypermethylation resulted in decreased encoded cholesterol efflux transporter expression, reduced cholesterol efflux rates, and increased intracellular cholesterol concentrations in PCa cell lines. They also showed that the existence of this epigenetic modification was related to high-grade PCa. Moreover, the mTOR pathway is essential in controlling sterol-regulatory-element-binding proteins (SREBPs), which are transcription factors controlling cholesterol and lipid balance [6]. Yue et al [7] showed that the intracellular aggregation of cholesteryl ester in lipid droplets

Table 1. Clinical studies conducted for statins and PCa

PCa stage	Findings with significance	Reference
Evaluating PCa risk or PCa prevention	Marginally elevated overall PCa risk (OR, 1.07; 95% CI, 1.00–1.16).	[35]
	Decreased advanced PCa risk among users of atorvastatin, lovastatin, and simvastatin (OR 0.61, 95% CI 0.37–0.98; OR 0.61, 95% CI 0.43–0.85; OR 0.78, 95% CI 0.61–1.01, respectively).	[35]
	Untreated hyperlipidemia was associated with slightly increased PCa risk (RR, 1.5; 95% CI, 1.1–2.0).	[37]
	Lower risk of both Gleason low- (score <7: HR, 0.85; 95% CI, 0.74–0.96) and high-grade PCa (score ≥7: HR, 0.54; 95% CI, 0.42–0.69).	[38]
	Lipophilic statins (HR, 0.83; 95% CI, 0.72–0.95) might be more protective than hydrophilic agents.	[38]
	Post-diagnostic statin use was associated with a decreased risk of PCa mortality (HR, 0.76; 95% CI, 0.66–0.88) and all-cause mortality (HR, 0.86; 95% CI, 0.78–0.95).	[39]
Active surveillance	Duration of statin use was inversely correlated with adverse pathology for RP (OR, 0.98; 95% CI, 0.97–0.99; p=0.020).	[40]
BCR after RP or RT	Post-RP statin use was significantly associated with a 36% reduced risk of BCR (HR, 0.64; 95% CI, 0.47–0.87; p=0.004).	[42]
	One-year adjuvant use of atorvastatin was not associated with a lower risk of disease recurrence compared to placebo (HR, 0.96; 95% CI, 0.58–1.60).	[43]
	Statin use was associated with a 21% reduction in the risk of BCR among those treated with RT (pHR, 0.79; 95% CI, 0.65–0.95; p=0.010; 10 studies; I^2=54%).	[47]
	Statin use was associated with a 22% reduction in the risk of metastasis (pHR, 0.78; 95% CI, 0.68–0.87; p=0.001; 6 studies; I^2=0%), and a 24% reduction in risk of both all-cause mortality (pHR, 0.76; 95% CI, 0.63–0.91; p=0.004; 6 studies; I^2=71%), and PCa-specific mortality (pHR, 0.76; 95% CI, 0.64–0.89; p=0.0007; 5 studies; I^2=40%).	[47]
	Statin use was associated with a shorter time to biochemical failure.	[48]
Advanced PCa	The RR of advanced disease was 0.51 (95% CI, 0.30–0.86) and for metastatic or fatal disease, it was 0.39 (95% CI, 0.19–0.77) for current statin use.	[49]
	Post-ADT statin use was associated with a decreased risk of PSA relapse (HR, 0.73; 95% CI, 0.65–0.82) and PCa death (HR, 0.82; 95% CI, 0.69–0.96).	[50]
	Statin use significantly lowered the risk of all-cause mortality (HR, 0.73; 95% CI, 0.64–0.83; p<0.00001) and the risk of cancer-specific mortality (HR, 0.64; 95% CI, 0.53–0.77; p<0.00001) in advanced PCa patients treated with ADT.	[51]

PCa: prostate cancer, RP: radical prostatectomy, RT: radiation therapy, OR: odds ratio, CI: confidence interval, HR: hazard ratio, BCR: biochemical recurrence, pHR: pooled hazard ratio, RR: relative risk, PSA: prostate-specific antigen, ADT: androgen deprivation therapy.

was induced by the loss of tumor suppressor PTEN expression and further activation of the PI3K–AKT–mTOR signaling pathway. They also showed that the intracellular aggregation of cholesteryl ester was related to high-grade PCa [7]. One of the main cholesterol-mediated processes [3] by which statins suppress tumor growth involves particular cholesterol-abundant domains in the cell membrane referred to as lipid rafts [8]. These regions can ease membrane-initiated signaling episodes in cells *via* the compartmentalization of signaling routes, promoting tumor growth. Cell signaling routes involved PCa occurrence and progression, which could be impacted by lipid raft cholesterol distribution, include pathways related to the androgen receptor [9], the luteinizing hormone receptor [10], and the epidermal growth factor receptor (EGFR) [11]. Statins, *via* their effects on intracellular cholesterol balance, are considered to disturb lipid raft organization, hence interfering with these or other downstream intracellular signaling routes [12]. The treatment of PCa cells with cholesterol binders can interfere with EGFR signaling and disorganize lipid raft organization [11]. Other signaling routes involved in the occurrence of PCa and castration resistance, like IL 6 activated Janus kinase–signal transducer and activator of transcription 3 (JAK-STAT3) signaling, are influenced by lipid raft organization. Therefore, they are likely affected by lipid raft cholesterol levels [13]. As cholesterol is androgens' precursor, cholesterol levels could also influence the development of PCa through the androgen signaling pathway. Decreasing cholesterol levels using statins might lower PCa growth by decreasing intratumoral or serum androgen levels. However, the effect of statins on serum androgen levels remains unsure. Several investigations have proposed that statins can decrease serum testosterone [14-16]. However, these decreases were minimal or induced by statin doses higher than are generally utilized in the real world. Emerging evidence has suggested that intratumoral androgen levels are persistently high even when castrated androgen levels are attained in the sera of PCa men conceivably due to novel androgen synthesis in tumor cells [17-19]. Therefore, statins could diminish intratumoral androgen levels by decreasing intratumoral cholesterol levels.

As for non-cholesterol mediated pathways, change from HMG-CoA to mevalonate could be suppressed by statins. Mevalonate belongs to a class of isoprenoids that includes geranyl pyrophosphate and farnesyl pyrophosphate. Geranyl pyrophosphate and farnesyl pyrophosphate can ease the recruitment of signaling proteins like G proteins of the Ras and Rho superfamilies by engaging their connection to plasma membranes, where their signaling actions could enhance PCa cell viability and proliferation [20,21]. Therefore, statins might inhibit cancer cell proliferation by lowering mevalonate and downstream isoprenoids. Moreover, statins seem to directly promote apoptosis in tumor cells regardless of their effects on cholesterol levels [22]. For instance, statins were shown to suppress cyclin-dependent kinase 2 and induce cell cycle arrest [23] or trigger apoptosis-stimulating specific proteases [24]. Statins also possess direct antiangiogenic and anti-inflammatory features. They were also reported to suppress tumor growth and progression [22]. One study [25] of a group of patients receiving radical prostatectomy (RP) showed that statin takers were 69% less likely to display inflammation in their tumors than non-takers (p=0.047). Hoque et al [26] evaluated the action of statins on PCa cells and the elemental molecular mechanism of action. They found that antitumor function of statins was due to the promotion of growth arrest and cell apoptosis. The fundamental molecular mechanism of action of statins is arbitrated *via* RhoA inactivation, which successively promotes caspase enzymatic action with or without G1 cell cycle. Raittinen et al [27] elucidated atorvastatin's impact on serum and prostatic tissue steroidomic profiles and exposed new pathways for lowering androgen levels in men with PCa. Most serum and prostatic steroids, including dihydrotestosterone and testosterone, were not related to atorvastatin usage. Yet, they concluded that atorvastatin use was associated with an adrenal androgen decrease in the serum and likely in the prostate.

2. Evidence on statin use and prostate cancer risk or prevention

Bonovas et al [28] performed a meta-analysis including several randomized clinical trials (RCTs) [29-34]. They reported an insignificant association between statin usage and overall PCa among either RCTs (pooled relative risk [RR], 1.06; 95% confidence interval [CI], 0.93–1.20) or observational investigations (high heterogeneity detected) (pooled RR, 0.89; 95% CI, 0.65–1.24). Furthermore, longstanding statin usage did not significantly influence the total PCa risk (pooled

RR, 0.93; 95% CI, 0.77–1.13). Nevertheless, the synthesis of applicable studies that particularly evaluated statin usage concerning advanced PCa indicated a protective relationship (pooled RR, 0.77; 95% CI, 0.64–0.93). Stranberg et al [32] investigated extended post-trial follow-up of an RCT of simvastatin or placebo in men with heart disease. They found that 227 and 248 incident cancers were reported in the simvastatin and placebo group, respectively (0.88; 95% CI, 0.73–1.05; p=0.150). The incidence of any malignancy type did not increase in the simvastatin group (55 and 51 PCas were diagnosed in the placebo and simvastatin groups, respectively). The Heart Protection Study Collaborative Group [33] performed an RCT including 20,536 patients aged 40 to 80 years with diabetes or vascular disease. The study found that the use of simvastatin did not reduce PCa (event ratio, 0.99; 95% CI, 0.79–1.25). Murtola et al [35] found that ever-usage of any statin was associated with a marginally elevated total PCa risk (odds ratio [OR], 1.07; 95% CI, 1.00–1.16). Nevertheless, none of these statins was related to the total PCa risk when analyzed individually. The risk of advanced PCa was reduced among the users of atorvastatin, simvastatin, and lovastatin (OR 0.61, 95% CI 0.37–0.98; OR 0.78, 95% CI 0.61–1.01; OR 0.61, 95% CI 0.43–0.85, individually). The risk was not affected in the users of other cholesterol medication groups. Kang et al [36] analyzed 143,870 males to evaluate the risk of kidney malignancy, bladder malignancy, and PCa developments, individually, during a 10-year follow-up (2004–2013). In their study, statins did not appear to be a predictive factor for the development of PCa (hazard ratio [HR], 1.01; 95% CI, 0.85–1.18; p=0.953). Kaye and Jick [37] studied the General Practice Research Database and reported that present statin usage was not related to a significantly modified PCa risk. However, untreated hyperlipidemia was related to a slightly elevated PCa risk (RR, 1.5; 95% CI, 1.1–2.0). Wang et al [38] reported that statin usage was associated with the decreased risks of both Gleason score (GS) low-grade PCa (<7) (HR, 0.85; 95% CI, 0.74–0.96) and high-grade PCa (≥7) (HR, 0.54; 95% CI, 0.42–0.69). This protective relationship was detected exclusively when statins were taken for a longer period (≥11 months) or a stronger dosage (≥121 daily doses). It was more prominent in men with PCa with a higher GS. Lipophilic agents (HR, 0.83; 95% CI, 0.72–0.95) might be more protective against PCa than hydrophilic agents (HR, 0.91; 95% CI, 0.63–1.33). Yu et al [39] analyzed 11,772 men with non-metastatic PCa (mean 4.4 years follow-up) and reported that post-diagnostic statin usage was associated with a lower possibility of PCa-specific death (HR, 0.76; 95% CI, 0.66–0.88) and overall death (HR, 0.86; 95% CI, 0.78–0.95). These reduced risks of PCa-specific death and overall death were more prominent in men who took statins before PCa diagnosis (HR 0.55, 95% CI 0.41–0.74; and HR 0.66; 95% CI 0.53–0.81, respectively), with lower impacts on men who started the therapy exclusively after PCa diagnosis (HR 0.82, 95% CI 0.71–0.96; and HR 0.91, 95% CI 0.82–1.01, respectively).

3. Evidence on statin use and active surveillance for prostate cancer

Nyame et al [40] retrospectively studied men with active surveillance (2005–2015) and evaluated disease reallocation, progression to decisive curative therapy, and surveillance failure (the occurrence of either biochemical failure (BF) after curative treatment, metastasis, or PCa-specific death) among statin and non-statin users. They found no significant difference in the BF rate among patients who proceeded to definitive treatment when stratified by statin usage (p=0.890). Statin use duration was inversely related to adverse RP pathology in both univariate (OR, 0.99; 95% CI, 0.98–0.99; p=0.030) and multivariate analysis (OR, 0.98; 95% CI, 0.97–0.99; p=0.020).

4. Evidence on statin use and biochemical recurrence after definitive local therapy (radical prostatectomy or radiation therapy) for prostate cancer

High variability in the definition of BCR following therapy for localized PCa exists. Following RP, it is recommended to define BCR as an initial serum prostate-specific antigen (PSA) of ≥0.2 ng/mL, with a second confirmatory PSA level of ≥0.2 ng/mL. Regarding radiation therapy (RT), BCR is defined as three consecutive rises in PSA after a nadir has been reached, with the failure date being the midpoint between the nadir and the first of three consecutive increases [41].

Allott et al [42] studied the influence of post-RP statin usage on BCR in men with PCa who had never taken statins before RP. They revealed that post-RP statin usage was significantly related to 36% decreased BCR risk (HR, 0.64; 95% CI, 0.47–0.87; p=0.004). After adjusting for preoperative serum cholesterol levels,

post-RP statin usage was still related to a reduced BCR risk. In a secondary investigation, this protective relationship was pronounced in non-Afro-American patients (HR, 0.49; 95% CI, 0.32–0.75; p=0.001), but not in Afro-American patients (HR, 0.82; 95% CI, 0.53–1.28; p=0.384) after stratification by race. Jeong et al [43] investigated the efficacy of adjuvant atorvastatin in men with PCa after RP in a double-blind RCT. Among the PCa patients with high-risk pathologic features after RP, 1-year adjuvant atorvastatin usage was not associated with a lower risk of BCR compared to that for placebo (HR, 0.96; 95% CI, 0.58–1.60). Scosyrev et al [44] executed a meta-analysis (5 based on RP and 3 based on RT series). They reported that the pooled HR (pHR) estimates for BCR risk in statin takers *vs.* never-takers were 0.91 (95% CI, 0.72–1.13) for the overall investigations, 1.02 (95% CI, 0.80–1.29) for the RP studies, and 0.71 (95% CI, 0.44–1.16) for the RT studies. However, there were considerable disagreements in the reported findings and conclusions between the individual studies. Chao et al [45] analyzed 1,200 men with PCa who underwent RP for BCR with a follow-up for up to 5 years (a single PSA assessment of >0.2 ng/mL) and clinical progression (diagnosis of metastasis or PCa-specific mortality). Of these men, 37% and 56% used statins preoperatively and postoperatively, respectively. They reported that neither pre- nor postoperative statin usage was affiliated with disease progression (HR 0.63, 95% CI 0.31–1.27 and HR 1.20, 95% CI 0.63–2.30, respectively) or BCR (HR 1.00, 95% CI 0.72–1.39 and HR 1.05, 95% CI 0.76–1.46, respectively). An unclear dose–response relationship was revealed for the duration of usage. Meijer et al [46] investigated whether statin usage could decrease the incidence of advanced PCa in males with high PSA levels (≥4.0 ng/mL) and whether statin usage could reduce post-RP BCR risk. Of their subjects, 72% were confirmed to have PCa. At the time of PCa diagnosis, 23% had taken statins compared to 19% in the non-PCa men (p=0.100). There was an insignificant difference in statin use between the different risk groups. No association was proven between post-RP BCR risk and statin use in the total subjects (p=0.200), the intermediate-risk group (p=0.630), or the high-risk group (p=0.140). Raval et al [47] performed a meta-analysis and reported that statin usage was associated with a 21% decrease in BCR risk in patients who underwent RT (pHR, 0.79; 95% CI, 0.65–0.95; p=0.010; 10 studies; I^2=54%). However, statin usage was not related to BCR among patients who underwent RP (pHR, 0.94; 95% CI, 0.81–1.09; p=0.430; 15studies; I^2=65%). Otherwise, statin usage was associated with 22% decrease in metastasis possibility (pHR, 0.78; 95% CI, 0.68–0.87; p=0.001; 6 studies; I^2=0%) and a 24% decrease in the risk of both cancer-specific death (pHR, 0.76; 95% CI, 0.64–0.89; p=0.0007; 5 studies; I^2=40%) and overall death (pHR, 0.76; 95% CI, 0.63–0.91; p=0.004; 6 studies; I^2=71%). Huynh et al [48] evaluated 1,581 patients undergoing RP or RT and the effect of statin usage on overall BF and the time to BF after initial treatment for localized PCa. When classified by statin usage, BF overall and within first, third, and fifth year did not differ significantly. A shorter time to BF was shown in men taking statins (1.8±1.9 y *vs.* 2.4±2.6 y; p=0.016). This finding remained in the multivariate investigation, wherein statin usage was not associated with BF, although it was related to a shorter time to BF.

5. Evidence for the effect of statin usage and clinical outcomes in advanced prostate cancer and the effect of statin use alone or combination with other drugs on prostate cancer

Platz et al [49] evaluated the relationship between statin usage and overall and advanced PCa in 34,989 American males who had no tumor in 1990 and were tracked until 2002. The age-standardized incidences of advanced PCa was 89 and 38 per 100,000 person-years in never or past-takers and current statin takers, respectively. The adjusted RR was 0.51 (95% CI, 0.30–0.86) for advanced disease and 0.39 (95% CI, 0.19–0.77) for lethal or metastatic disease among current statin users compared to non-current users. These significant associations were retained after adjusting for PSA screening record (advanced case: RR 0.57, 95% CI 0.30–1.11; lethal or metastatic case: RR 0.35, 95% CI 0.14–0.92). The risk of advanced PCa was lower with longer statin usage (p=0.003). Compared to never use, the RR was 0.60 for <5 years of use (95% CI, 0.35–1.03) and 0.26 for ≥5 years of use (95% CI, 0.08–0.83). No affiliation was shown between total PCa risk and statin usage (RR, 0.96; 95% CI, 0.85–1.09). Peltomaa et al [50] evaluated the effect of statins on PCa prognosis among patients managed with androgen deprivation therapy (ADT). Post-ADT statin usage was related to a reduced risk of PSA relapse (HR, 0.73; 95% CI, 0.65–0.82) and PCa-specific mortality (HR, 0.82; 95% CI, 0.69–0.96).

However, statin usage with a one-year lag (HR, 0.89; 95% CI, 0.76–1.04), pre-ADT statin usage (HR, 1.12; 95% CI, 0.96–1.31), and stain usage in the first year of ADT (HR, 1.02; 95% CI, 0.85-1.24) were not associated with PCa mortality, indicating no dose dependency. Yang et al [51] investigated the impact of statin usage on the outcomes of men with advanced PCa treated with abiraterone/enzalutamide or ADT. They found that statin usage significantly lowered the risk of overall death (HR, 0.73; 95% CI, 0.64–0.83; p<0.00001) and the risk of PCa-specific mortality (HR, 0.64; 95% CI, 0.53–0.77; p<0.00001) in men with advanced PCa undergoing ADT. However, these findings provided no credible evidence for men with metastatic castration-resistant PCa (mCRPC) treated with enzalutamide/abiraterone since related investigations are scarce with inconsistent results.

Jiménez-Vacas et al [52] evaluated the presumed *in vivo* relationship between statins and/or metformin treatment and the core tumor and clinical factors. They also assessed the direct effects of different statins (atorvastatin, lovastatin, and simvastatin), biguanides (metformin, phenformin, and buformin), and their combination. The combination of statins and metformin *in vivo* was associated with a lower GS and longer BCR-free survival. Furthermore, statins and biguanides showed strong antitumor effects on PCa cells. These actions were mediated *via* the modulation of molecular mediators and key metabolic and oncogenic signaling pathways. Tan et al [53] have quantified individual and synergistic effects of statin and metformin usage among high-risk PCa patients. Statin-only or combined with metformin was significantly related to decreased PCa-specific death (HR 0.80, 95% CI 0.69–0.92 and HR 0.64, 95% CI 0.51–0.81, respectively) and overall death (HR 0.89, 95% CI 0.83–0.96 and HR 0.75, 95% CI 0.67–0.83, respectively). These impacts were more prominent in post-diagnostic takers, where the combined usage of statins and metformin was related to a 32% decrease in overall death (95% CI, 0.57–0.80) and a 54% decrease in PCa-specific death (95% CI, 0.30–0.69). However, an insignificant relationship between metformin usage only was shown with either PCa-specific death or all-cause death.

EFFECT OF OMEGA-3 ON PROSTATE CANCER

Omega-3s are polyunsaturated fatty acids (PUFAs) containing a double bond at carbon number 3 in the omega naming system [54]. They are proven to be anti-inflammatory substances against cardiovascular diseases and malignancies. They also play a nutrigenetic role by interacting with genes involved in inflammation and cancers [55]. Omega-3s include long-chain α-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Recent epidemiological investigations have proven that continuous oily fish intake was associated with decreased PCa risk. PUFAs, both ω-3 and omega-6 fatty acid (ω-6), are changed to eicosanoids (*e.g.*, thromboxanes and prostaglandins) in the body. These compounds are commonly engaged in cell growth and differentiation, anti-inflammatory process, and immune modulation [56]. ALA is believed to be a fundamental fatty acid and must be obtained by the consumption of food or supplements because it cannot be synthesized by the body. Nevertheless, edible intake is not considered essential for health as DHA and EPA are made from ALA in the body [57]. Omega-3s can also be obtained from ALA containing plant oils such as walnuts, flaxseed, or canola [58]. Omega-3s are integrated into various parts of the body. For instance, DHA is a core element for all cell membranes [59]. EPA and DHA are metabolites, which can act as lipid mediators expected to be efficient in treating or preventing some disorders [60]. Several clinical findings are summarized in Table 2.

1. Mechanism and effects of omega-3 on prostate cancer

The mechanism by which ω-3 prevents carcinogenesis involves the suppressive effect on arachidonic acid synthesized eicosanoids [61]. Eicosanoids extracted from arachidonic acid exert pro-inflammatory activity while ω-3 derived eicosanoids exert anti-inflammatory activity, thus preventing PCa. In eicosanoid synthesis, cyclooxygenase-2 (COX-2) acts as a core enzyme. Investigations have revealed that there is an overproduction of COX-2 in PCa [62,63]. Eicosanoids derived from ω-3s have a suppressive effect on COX-2 overproduction, thus preventing PCa. Hedelin et al [64] found a meaningful relationship between the use of salmon-type fish abundant in omega-3 unsaturated fats and a genetic

Table 2. Clinical studies conducted on ω-3 and PCa

PCa stage	Findings with significance	Reference
Evaluating PCa risk or PCa prevention	DHA was positively associated with high-grade disease (quartile 4 *vs*. 1: OR, 2.50; 95% CI, 1.34–4.65).	[70]
	TFA 18:1 and TFA 18:2 were linearly and inversely associated with the risk of high-grade PCa (quartile 4 *vs*. 1: 1) TFA 18:1: OR 0.55, 95% CI 0.30–0.98; 2) TFA 18:2: OR 0.48, 95% CI, 0.27–0.84).	[70]
	Compared to men in the lowest quartiles of long-chain ω-3 level, men in the highest quartile had an increased risk for low-grade (HR, 1.44; 95% CI, 1.08–1.93), high-grade (HR, 1.71; 95% CI, 1.00–2.94), and total PCa (HR, 1.43; 95% CI, 1.09–1.88).	[71]
	Higher linoleic acid (ω-6) was associated with the reduced risk of low-grade (HR, 0.75; 95% CI, 0.56–0.99) and total PCa (HR, 0.77; 95% CI, 0.59–1.01).	[71]
	Blood levels of DHA correlated significantly with an increased risk of total (RR, 1.16; 95% CI, 1.03–1.31), low-grade (RR, 1.20; 95% CI, 1.04–1.38), and advanced PCa (RR, 1.48; 95% CI, 1.10–1.99).	[71]
	A negative association was noted between high serum levels of ω-3 including DPA and total PCa risk (RR, 0.756; 95% CI, 0.599–0.955; p=0.019).	[72]
	A positive association was seen between high blood levels of fish oil components, EPA and DHA, and high-grade prostate tumor incidence (RR, 1.381; 95% CI, 1.050–1.817; p=0.021).	[72]
	High blood levels of DPA had a significant negative association with total PCa risk.	[74]
	A high intake of salted or smoked fish was associated with a 2-fold increased risk of advanced PCa both in early life (95% CI, 1.08–3.62) and later life (95% CI, 1.04–5.00). Men consuming fish oil in later life had a lower risk of advanced PCa (HR, 0.43; 95% CI, 0.19–0.95).	[75]
Active surveillance	Patients with ω-3 supplementation and higher initial vitamin D levels were twice as likely to have a decreasing PSA trend (OR, 2.04; 95% CI, 1.04–4.01; p=0.040).	[83]

PCa: prostate cancer, DHA: docosahexaenoic acid, OR: odds ratio, CI: confidence interval, TFA: trans-fatty acid, HR: hazard ratio, ω-6: omega-6 fatty acid, RR: relative risk, ω-3: omega-3 fatty acid, DPA: docosapentaenoic acid, EPA: eicosapentaenoic acid, PSA: prostate-specific antigen.

variation of COX-2 in establishing PCa risk. Among homozygotes or heterozygotes of the variant allele of +6365T/C SNP in COX-2, large salmon fish intake was associated with a prominent PCa risk decrease, although there was an insignificant association between fish intake and tumor potentiality in wild-type allele carriers [65].

It is possible that some metabolic statuses favoring the aggregation of long-chain ω-3 (LCn3) in plasma phospholipids has an additional promoting impact on PCa. For instance, estrogen function has been linked to an increased risk of advanced PCa, indicating a role of estrogen receptor-alpha in PCa progression [66,67].

A recent study [68] reported the mechanisms underlying tumor lymph node (LN) metastasis. It was found that LN metastasis mandates tumor cells to go through a metabolic change toward fatty acid oxidation (FAO). In LN-metastatic tumors, selectively activated transcriptional coactivator yes-associated protein (YAP) leads to the upregulation of genes in the FAO signaling route. The genetic ablation of YAP or pharmacological suppression of FAO could inhibit LN metastasis in mice. These findings are consistent with our perspective on ω-3 discussed above.

2. Evidence on omega-3 use and prostate cancer risk or prevention

Circumstantial factors seem to be involved in the occurrence of hormone-dependent malignancies like PCa. The effect of dietary fat consumption on PCa has diversely been investigated. However, no precise conclusion has been reached yet. Preclinical studies have indicated the protective effect of ω-3s on tumor progression. From a comprehensive review of epidemiologic data, Terry et al [69] concluded that with a general paucity of research that includes essential measurements like consumed fish type and tissue ω-3 concentrations, there is scarce evidence to confirm that an association exists between human cancer and marine fatty acid consumption. Brasky et al [70] examined the relationships between the 7-year prevalence of PCa and phospholipid fatty acids and in a nested case-control investigation of subjects in the Prostate Cancer Prevention Trial. No fatty acids were related to low-grade PCa risk. DHA was positively related to high-grade PCa (OR, 2.50; 95% CI, 1.34–4.65). Trans-fatty acid (TFA) 18:1 and TFA 18:2 were inversely and linearly correlated with high-grade PCa risk (TFA 18:1: OR 0.55, 95% CI 0.30–0.98; TFA 18:2: OR 0.48, 95% CI 0.27–0.84).

Another research study done by the same group [71] has evaluated relationships between PCa risk and plasma phospholipid fatty acids among subjects in the Selenium and Vitamin E Cancer Prevention Trial. Compared to subjects in the bottom quartiles of LCn3, the participants in the top quartile had higher possibilities of low-grade PCa (HR, 1.44; 95% CI, 1.08–1.93), high-grade PCa (HR, 1.71; 95% CI, 1.00–2.94), and overall PCa (HR, 1.43; 95% CI, 1.09–1.88). Elevated linoleic acid (ω-6) was related to decreased risks of low-grade PCa (HR, 0.75; 95% CI, 0.56–0.99) and overall PCa (HR, 0.77; 95% CI, 0.59–1.01). They also found that blood levels of DHA, but not EPA, were significantly related to an elevated possibility of low-grade PCa (RR, 1.20; 95% CI, 1.04–1.38), advanced PCa (RR, 1.48; 95% CI, 1.10–1.99), and total PCa (RR, 1.16; 95% CI, 1.03–1.31) comparing the lower and upper quantiles. From their analysis, they suggested the possibility that this relationship might be causal. The authors suggested that typical advice for raising LCn3 consumption should consider its possible harm.

Chua et al [72] systematically analyzed the association between PCa risk and serum level long chain ω-3 in human epidemiological studies. A significant inverse association was revealed between total PCa risk and high serum ω-3 levels including docosapentaenoic acid (DPA) (RR, 0.756; 95% CI, 0.599–0.955; p=0.019). Correspondingly, a positive relationship between high serum levels of EPA and DHA and high-grade PCa incidence (RR, 1.381; 95% CI, 1.050–1.817; p=0.021) was reported. Hanson et al [73] studied the relationships between LCn3, ALA, ω-6, and total PUFA intake with cancer risk. Increasing LCn3 was shown to slightly elevate PCa risk (low quality evidence). However, its impacts on PCa mortality were imprecise (very low-quality evidence, 5 mortalities). Seven studies (38,525 men, mean period 51 months, mean dose 1.2 g/d LCn3) showed 1,021 confirmed PCa cases, revealing an elevated PCa risk in males with elevated LCn3 intake (RR, 1.10; 95% CI, 0.97–1.24; I^2=0%; 334 needed to treat to cause additional harm). This superficial increase in PCa risk was reliable in overall sensitivity analysis. However, the risk probability was not supported by the PSA data shown in a single large study (25% reduction, mean difference: -0.13 ng/mL; 95% CI, -0.25 to 0.01; 1,622 men). PSA elevation was reported in 12 of 62 subjects in another study (RR, 0.47; 95% CI, 0.16–1.40), also refuting the suggested LCn3 harm. Sorongon-Legaspi et al [74] showed a non-significant relationship of the overall effect estimates for total, high-grade, or advanced PCa. High serum ALA levels had a non-significant positive relationship with total PCa risk. High serum DPA levels had a significant negative relationship with total PCa risk. Particular ω-3s in fish oil, DHA, and EPA, were positively associated with high-grade PCa risk exclusively after adjusting for inter-study inconsistency. Torfadottir et al [75] explored fish consumption, particularly in adolescence and midlife, and evaluated the effect of smoked or salted fish and fish oil intake on PCa risk in a prospective cohort investigation. Large fish intake in early- and midlife was not related to total or advanced PCa risk. The large consumption of smoked or salted fish was related to a two-fold elevation in advanced PCa risk in early (95% CI, 1.08–3.62) and in later life (95% CI, 1.04–5.00). Males taking fish oil in later life had a lower risk of advanced PCa (HR, 0.43; 95% CI, 0.19–0.95). However, no such relationship was revealed for early- or midlife intake. Aucoin et al [76] evaluated the efficacy and safety of fish-derived ω-3 on the occurrence and progression of PCa through a systemic review of 44 studies. Interventional research using fish oil supplementations in PCa men revealed no impact on PSA concentrations. However, two studies reported decreases of inflammatory markers and other cancer markers. A small number of mild side effects have been reported. The results of case-control and cohort research evaluating the relationship between PCa risk and dietary fish consumption are equivocal. Cohort studies evaluating PCa-specific mortality have proposed a relationship between the reduced risk of PCa-specific death and higher fish consumption. Zuniga et al [77] implemented a questionnaire study of 7,989 Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) participants and reported that multivitamin and ω-3 use was common (in 40% and 24% of patients, respectively). The study discussed a vitamin D and ω-3 trial. It revealed no significant reduction in death from PCa in those treated with ω-3 (HR, 1.15; 95% CI, 0.94–1.39) or vitamin D (HR, 0.88; 95% CI, 0.72–1.07) for a median of 5.3 years compared to placebo. Several meta-analyses [78-82] on the consumption of ω-3 and PCa have been published. Some meta-analyses reported statistically meaningful results for the relationship between PCa and ω-3 consumption. One meta-analysis [79] revealed that LCn3 consumption increased PCa risk (RR, 1.14; 95% CI, 1.01–1.28), while the other

two studies [79,80] revealed a protective effect of ω-3 consumption on PCa. One study [81] reported a marginally insignificant relationship between PCa and high fish intake (p=0.05).

3. Evidence on omega-3 use and various stages of prostate cancer

Campbell et al [83] evaluated the effect of targeted serum vitamin-D levels and the omega-6:3 fatty-acid ratio on PSA concentration in PCa patients supervised with active surveillance that included nutritional intervention and vitamin supplements. They found that men with higher initial vitamin D concentrations were more likely to show a decreasing PSA tendency (OR, 2.04; 95% CI, 1.04–4.01; p=0.040). Fifty-five of 68 men with subsequent biopsies showed no disease progression. They concluded that nutritional intervention with ω-3 and vitamin D supplementation might benefit patients in active surveillance for PCa. Liang et al [84] reported that ω-3 intake combined with castration could cause greater MycCap tumor (grown subcutaneously in mice) regression than the ω-6 diet (p=0.003) and also significantly delay the time to CRPC (p=0.006). Similarly, ω-3 intake meaningfully slowed the progression of demonstrated castrate-resistant MycCaP tumors (p=0.003). Dietary ω-3 reduced CRPC occurrence and progression in an immunocompetent mouse model with suppressive effects on M2-like macrophage activity.

CONCLUSIONS

Albeit evidence that statin and ω-3 are effective in preventing PCa has been continuously accumulated, it has not reached the level of recommendations in guidelines. Nevertheless, it is expected that the time will soon come when we can confirm a clear effect on PCa prevention or PCa progression reduction through accumulating evidence. There will be abundant hopeful situations in which the use of statins or ω-3s can be commonly considered in real clinical practice consistent with the objectives in the era of precision medicine.

Conflict of Interest

The authors have nothing to disclose.

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