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Prostate cancer progression and mortality: a review of diet and lifestyle factors

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Abstract

Purpose—To review and summarize evidence on the role of diet and lifestyle factors and prostate cancer progression, with a specific focus on habits after diagnosis and the risk of subsequent disease recurrence, progression, or death.

Methods—Given the well-documented heterogeneity of prostate cancer and the long survivorship of the majority of diagnoses, our goal was to summarize and describe modifiable risk factors for clinically relevant prostate cancer. We focused where possible on epidemiologic studies of post-diagnostic habits and prostate cancer progression, defined as recurrence (e.g., PSA risk, secondary treatment), metastasis, or death. Where data were limited, we also describe evidence on risk factors and indicators of prostate cancer aggressiveness at diagnosis.

Results—A variety of dietary and lifestyle factors appear to affect prostate cancer progression. Several generally widely recommended lifestyle factors such as not smoking, maintaining a healthy body weight, and regular vigorous physical exercise also appear to affect prostate cancer progression. Several dietary factors, such as tomato sauce/lycopene, cruciferous vegetables, healthy sources of vegetable fats, and coffee, may also have a role in reducing risk of prostate cancer progression.

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Compliance with ethical standards

The funding organizations had no role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; nor the preparation, review, or approval of the article. The authors are grateful to the participants and staff of the Health Professionals Follow-up Study and the Physicians' Health Study for their valuable contributions.

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Conclusion—Diet and lifestyle factors, in particular exercise and smoking cessation, may reduce the risk of prostate cancer progression and death. These promising findings warrant further investigation, as their overall impact might be large.

Keywords

Prostate cancer progression; Lethal prostate cancer; Diet; Lifestyle

Introduction

Prostate cancer is a heterogeneous disease with lethal and indolent phenotypes. A total of 221,000 men were estimated to receive a new diagnosis of prostate cancer in the USA in 2015, while 28,000 are predicted to die from the disease. With PSA screening, 5-, 10-, and 15-year survival approaches 100, 98, and 94 %, respectively. Thus, many men will live for several years after a diagnosis, and it is of public health interest to identify ways these men may minimize their risk of disease progression. Thus, in this review, we summarize evidence from epidemiologic studies (randomized controlled trials, and observational cohort and case control studies) on diet and lifestyle and the risk of prostate cancer progression; with an emphasis on reports that had data on post-diagnostic behaviors as exposures, or prostate cancer metastasis or death as outcomes. Where possible, emphasis was given to reports with prospective data collection. As corroborating evidence and as relevant, we summarize the associations between diet/lifestyle risk factors and aggressive prostate cancer at diagnosis (e.g., high grade or stage at diagnosis). These associations are summarized in Table 1.

We define prostate cancer progression as recurrence after therapy (i.e., prostate-specific antigen (PSA) rise after radical prostatectomy or radiation therapy), disease progression while on active surveillance, development of metastases, or death due to prostate cancer. Although we include PSA rise in the category of progression, it is important to recognize that most men with PSA rise after treatment for localized disease do not experience overt clinical progression or die from prostate cancer [1]. We also include development of metastases as part of the category “lethal prostate cancer,” because virtually all cases of prostate cancer death are preceded by metastases, particularly to bone. Reports were limited to those that were available as full-text articles in English in PubMed.

Lifestyle factors

Body mass index (BMI)

High body mass index (BMI, weight in kilograms divided by height in meters squared, kg/m^2) is strongly associated with increased risk of developing lethal prostate cancer, and increasing evidence suggests that obesity (either before or at the time of diagnosis) is associated with prostate cancer progression and prostate cancer-specific mortality, independent of lifestyle or clinical factors. For example, among 2546 men diagnosed with localized prostate cancer in the Physicians’ Health Study (PHS), a one-unit higher pre-diagnostic BMI was associated with approximately 10 % increase in the risk of prostate cancer-specific mortality and BMI of ≥30 kg/m^2 was associated with a nearly twofold increased risk of prostate cancer death, compared with normal weight [2]. A meta-analysis

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of six studies in prostate cancer patients reported that a 5 kg/m^2 increase in BMI increased the risk of prostate cancer-specific mortality by 20 % and biochemical recurrence by 21 % [3]. A recent analysis found that compared with men who had stable weight, those whose weight increased by >2.2 kg from 5 years before to 1 year after surgery had a 94 % increased risk of prostate cancer recurrence after multivariate adjustment [4]. Also, men with higher BMI are more likely to have upstaged disease [5]. Weight gain after a diagnosis of prostate cancer is associated with an increased rate of biochemical recurrence and prostate cancer-specific mortality [6]. The proposed underlying biologic mechanisms involve the insulin/insulin-like growth factor axis [7] altered levels of sex hormones and adipokine signaling [8].

Physical activity

Accumulating evidence from prospective cohort studies of healthy individuals suggests that vigorous activity is associated with a reduced risk of lethal prostate cancer. Vigorous activity is defined as activities that cause sweating and increased heart and respiratory rate. These are typically activities with a metabolic equivalent task (MET) value greater than 6 and include jogging, biking, swimming, or bicycling. In a study of 2705 men with prostate cancer from the Health Professionals Follow-up Study (HPFS), men performing three or more hours per week of vigorous activity had a 61 % lower risk of dying from prostate cancer compared with men with less than 1 h of vigorous activity per week [9]. These findings were adjusted for a variety of potential confounding factors. These results were corroborated in a similar cohort of prostate cancer patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study, which demonstrated that men who walked three or more hours per week at a brisk pace (≥3 mph) had a 57 % lower risk of prostate cancer recurrence (mainly PSA rise) compared with men who walked less than three hours per week at an easy pace (<2 mph) [10]. The CaPSURE results are compelling, as there was less potential for reverse causation (i.e., a bias caused by men reducing their physical activity due to disease recurrence) since physical symptoms do not typically precede biochemical recurrence. These findings are further supported by results from a cohort of 4623 Swedish men with localized prostate cancer, which found that men who walked or biked ≥20 min/day versus <20 min/day had a statistically significant 36 % lower risk of prostate cancer-specific mortality [11].

While the exact mechanisms for the effect of vigorous activity on prostate cancer progression are unclear and understudied, multiple trials have shown that vigorous aerobic activity or weight training improves cardiorespiratory (heart–lung) function, muscle strength, fat and muscle mass, fatigue, anxiety, depression, and overall quality of life in men with prostate cancer. [12] Hypothesized mechanisms include changes in energy metabolism, inflammation, oxidative stress, immunity, and androgen receptor signaling pathways [13].

Smoking

Smoking increases risk of aggressive prostate cancer and prostate cancer-specific mortality. Several studies reported that smoking is associated with more aggressive disease at diagnosis. Smokers consistently have a higher risk of prostate cancer progression, including biochemical recurrence, metastasis, hormone-refractory prostate cancer, and prostate cancer-

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specific mortality [14, 15]. In the largest study to date, with 22 years of follow-up among 5366 men with prostate cancer, current smoking prior to diagnosis was associated with a 61 % increased risk of prostate cancer mortality and a 61 % increased risk of biochemical recurrence [14]. This study also found that men who reported smoking 10+ years ago had prostate cancer mortality risks similar to those who had never smoked [14]. Additionally, one recent analysis that looked exclusively at biochemical recurrence as an end point corroborated the early finding and reported a similar risk of biochemical recurrence for long-term quitters of ≥10 years compared with never smokers (HR 0.96, 95 % CI 0.68–1.37; $P = 0.84$) [15].

Dietary factors: protein

Eggs/choline

Few studies have examined whether egg consumption is associated with risk of prostate cancer or outcomes after prostate cancer diagnosis. A recent meta-analysis suggested no association with risk of prostate cancer (overall or prostate cancer-specific mortality) [16]. In the HPFS, men who consumed ≥2.5 eggs per week had a 1.8-fold increased risk of developing lethal prostate cancer compared with men who consumed <0.5 eggs per week [17]. That study also found no association between post-diagnostic consumption of eggs and risk of lethal prostate cancer. In contrast, in CaPSURE™, men who consumed the most eggs after prostate cancer diagnosis (~5.5 eggs per week) had a twofold increased risk of prostate cancer recurrence compared with men who consumed the least eggs (<0.5 eggs per week) [18]. However, this study did not have data on egg intake prior to diagnosis, and thus, it is possible that the increased risk observed reflected the men's egg consumption before diagnosis.

Eggs may increase risk of aggressive prostate cancer due to their choline content. One study found that men with the highest choline intake (~500 mg/day) had a 70 % increased risk of incident lethal prostate cancer compared with men with the lowest intake (~300 mg/day) [19]. A Swedish study also reported that men with the highest plasma levels of choline had a 46 % increased risk of prostate cancer compared with men with the lowest levels [20].

Fish

Studies in healthy individuals suggest that men who habitually consume more fish have lower risk of death from prostate cancer. A pooled analysis of four cohort studies reported a significant 63 % reduction in prostate cancer mortality among those with the highest intake of fish [21]. Other studies have reported no association between fish intake and risk of advanced or aggressive prostate cancer [21]. All together, the data suggest that fish intake, especially fish with high levels of omega-3 fatty acids such as salmon, sardines, mackerel, and herring, may reduce risk of clinically significant prostate cancer. Brasky et al. [22] reported that men with higher blood levels of long-chain omega-3 fatty acids (reflecting fish intake) had an increased risk of being diagnosed with prostate cancer. However, the cases in this study were early-stage cases detected by PSA screening. Because the non-aggressive, indolent form of prostate cancer is extremely common [1], PSA screening often detects cases that would never cause harm if undiagnosed. Men who eat more fish tend to be more

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health conscious and also tend to have more intense PSA screening, so this group is more likely to be diagnosed with prostate cancer. The Brasky study included only one man with advanced-stage disease and thus could not examine whether long-chain omega-3 levels in the blood were associated with risk of lethal prostate cancer.

Only two studies have examined post-diagnostic fish intake in relation to prostate cancer progression. In the first, an additional two servings of fish per week after diagnosis was associated with a 17 % lower risk of prostate cancer recurrence [23], and no association was observed in the second study [18]. A clinical trial among men scheduled for surgery for prostate cancer showed that fish oil intake for 4–6 weeks prior to the surgery inhibited prostate cancer tumor growth [24]. In addition, baseline data from a clinical trial of men on active surveillance reported that EPA (a long-chain omega-3 fatty acid) measured in the men's prostate tissue was associated with lower risk of prostate cancer progression [24]. Further studies are underway to clarify whether fish intake *after* diagnosis is associated with a lower risk of prostate cancer progression or death.

Poultry

Studies consistently report that skinless poultry intake is not associated with risk of developing aggressive prostate cancer [17], and two studies have reported that consuming skinless poultry after diagnosis is not associated with risk of prostate cancer progression. In contrast, men who reported consuming higher amounts of poultry *with skin* (about 3 servings/week) after prostate cancer diagnosis had a 2.26-fold increased risk of recurrence compared with men who consumed less (0 servings/week) [18]. Additionally, men who reported consuming the most poultry sandwiches (1.5 or more servings per week) had a non-statistically significant 55 % increased risk of developing metastases or dying from prostate cancer compared with men who consumed less than 0.5 servings of poultry sandwiches per week [18]. Given the lack of an association between skinless poultry and prostate cancer progression, this observation was most likely driven by processed luncheon meats made from poultry, and not sandwiches made with sliced pieces from whole skinless poultry.

Processed red meat

Processed red meat includes foods such as salami, bologna, sausage, bacon, and hot dogs. Several studies have reported a positive association between processed red meat consumption and risk of advanced or fatal prostate cancer [25], although others have reported no association [17, 26]. As with several other dietary factors, only two studies have examined the association between these foods after diagnosis and prostate cancer progression; both observed a nonsignificant increase in risk of 45 % (HR 1.45, 95 % CI 0.73–2.87; P trend = 0.08) [17] and 30 % (HR 1.30, 95 % CI 0.78–2.17, P trend = 0.18) [18]. Although firm data are lacking as to whether processed red meat increases risk of prostate cancer progression, substantial evidence shows that processed red meat increases the risk of other illnesses and all-cause mortality. The World Health Organization (WHO) recently classified processed meat as "carcinogenic to humans" (Group 1) and red meat as "probably carcinogenic to humans" (Group 2A), with special reference to the substantial evidence for a relation between red meat and increased risk of developing advanced prostate cancer.

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Dietary factors: plant products

Coffee

Multiple observational cohort studies have reported that pre-diagnostic coffee consumption is associated with a significant reduction in the risk of developing lethal prostate cancer [27] and experiencing recurrence or progression [28]. One study of 47,911 men observed a 60 % reduction in risk of lethal prostate cancer for men in the highest (≥6 cups per day) versus lowest categories of coffee consumption [27]. The results were similar for caffeinated and decaffeinated coffee. Those findings were supported by some, but not all, subsequent studies, as well as meta-analyses [29]. Several biologic mechanisms have been proposed, and many focused on the pronounced antioxidant effects of coffee, suggesting that this association is plausible. Though most studies have examined coffee consumption *before* prostate cancer diagnosis, one recent analysis by Geybels et al. [28] among men diagnosed with prostate cancer found that drinking ≥4 cups per day of coffee versus ≤1 cup/week was associated with a 59 % reduced risk of prostate cancer recurrence/progression (HR 0.41, 95 % CI 0.20–0.81; *P* for trend = 0.01). No studies to date have studied post-diagnostic coffee intake and risk of progression of prostate cancer.

Cruciferous vegetables

Commonly consumed cruciferous vegetables include: broccoli, cauliflower, cabbage, brussels sprouts, kale, mustard greens, and chard greens. Laboratory and animal studies suggest that metabolites of cruciferous vegetables, isothiocyanates, and indoles, may detoxify carcinogenic compounds, stop cancer cells from growing and dividing, and promote apoptosis [30]. As with tomato products, several studies have found that greater consumption of cruciferous vegetables is associated with a lower risk of developing aggressive prostate cancer [31, 32]. However, only one study has examined cruciferous vegetable intake after prostate cancer diagnosis. That study observed that men in the highest quartile of cruciferous vegetables intake (median ≥5.7 servings/day) after diagnosis of non-metastatic prostate cancer had 59 % lower risk of prostate cancer progression compared with men in the lowest quartile (median ≤1.4 servings/day), HR 0.41, 95 % CI 0.22–0.76, *P* value for trend = 0.003 [33].

Soy

Laboratory and animal studies suggest that isoflavones, found in soy products, inhibit prostate cancer cell growth, invasion, migration, and metastasis. Studies in Asian populations (with higher soy intake than Western populations) also tend to suggest that soy intake is inversely associated with risk of developing prostate cancer [34]. However, there is little data on the relation between soy consumption and risk of *lethal* prostate cancer or prostate cancer progression, in part due to the low intake of soy in Western populations, which have the largest observational studies with sufficient follow-up and high rates of aggressive prostate cancer. One study reported an inverse association between total legume intake and risk of advanced prostate cancer, and observed a suggestive protective effect of specifically soy intake [32]. In contrast, one small 2-year randomized controlled trial found no effect of a soy supplement on risk of prostate cancer progression among men with localized disease [35]. Additional research is needed, but available evidence does not

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strongly support the hypothesis that increasing soy intake will reduce prostate cancer progression; however, it may be beneficial if it replaces less healthful sources of protein, such as processed meat.

Tea

Several epidemiologic studies, mostly in Asian populations, suggest that tea consumption may possibly be associated with a reduced risk of prostate cancer [36, 37]. A recent meta-analysis of observational studies reported no overall association for tea consumption and prostate cancer, with a suggestive benefit seen only in case–control studies, which are prone to substantial bias [38]. Another meta-analysis found green (but not black) tea consumption to be beneficial, but again, the findings were dominated by less reliable case–control studies [39]. Small clinical trials of tea extracts have yielded promising initial results [40, 41], but further studies of tea, and especially trials of tea extracts, are warranted.

Tomatoes/lycopene

Tomatoes are rich in the antioxidant nutrient, lycopene, which may inhibit prostate cancer growth and metastases [42]. Cooking tomatoes and consuming them with oil increases absorption. Studies examining intake of tomato products, such as tomato sauce, or circulating lycopene levels strongly suggest that these foods/nutrients are associated with a reduced risk of developing aggressive prostate cancer [43]. Though some studies have reported no association [44], they were conducted during the PSA era in heavily screened populations, which likely undermined the ability to see a protective association. Evidence for this conclusion is bolstered by the fact that a study conducted by Giovannucci et al. [45], reported that the inverse association between tomato sauce and prostate cancer incidence was statistically significant among men diagnosed during the pre-PSA era (1986–1992), while the association was substantially weaker among those diagnosed during the PSA era (1992–1998). Notably, in this same study using the combined data from 1986 to 1998, men who consumed ≥2 servings per week of tomato sauce compared to <1 serving per month had a 66 % decreased risk of meta-static prostate cancer [45]. Most recently, in an updated analysis from the HPFS, healthy men who consumed the most lycopene were reported to have a 28 % lower risk of developing lethal prostate cancer compared with men who consumed the least [42]. Moreover, in that study, lycopene intake from tomato products prior to diagnosis was associated with large, more regularly shaped blood vessels in men's prostate tumors, which indicates better prognosis. Such an observation supports the conclusion that tomato products have a biologic effect on the prostate microenvironment and may reduce risk of developing aggressive prostate cancer.

Although studies have linked cooked tomatoes or tomato-based products (e.g., tomato sauce) with reduced risk of *developing* lethal prostate cancer among healthy men, it is not known whether these foods are beneficial for men after they have been diagnosed with prostate cancer. Only two studies have examined consumption of tomato products in relation to prostate cancer progression, and the results were inconsistent, with one study suggesting a benefit [23] and the other reporting no association [46]. Two randomized controlled trials have reported that lycopene supplementation lowers PSA levels in men with prostate cancer [47, 48]. In the first, conducted by Kucuk et al. twenty-six men with newly diagnosed,

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clinically localized prostate cancer were randomly assigned to receive 15 mg of lycopene (n = 15) twice daily or no supplementation (n = 11) for 3 weeks before radical prostatectomy. Plasma prostate-specific antigen levels decreased by 18 % in the intervention group, whereas they increased by 14 % in the control group (P = 0.25). The second trial undertaken by Ansari et al. [47] randomized 54 men diagnosed with histologically confirmed metastatic prostate cancer to orchiectomy alone or orchiectomy plus 2 mg lycopene/day, which was administered on the day of orchiectomy. After 2 years, eleven (40 %) patients in the orchiectomy group and twenty-one (78 %) in the orchiectomy + lycopene group had a complete PSA response (P < 0.05), with a partial response in nine (33 %) and four (15 %), and progression in seven (25 %) and two (7 %), comparatively (P < 0.05) [47]. These provocative pilot results warrant follow-up confirmation in a larger study with longer follow-up and end points of disease progression or death.

Dietary factors: dairy/calcium, dietary fats, and supplements

Dairy/calcium

Several studies have reported that high intakes of calcium (*above* the recommended dietary allowance of ~1000 mg/day) or dairy products are associated with increased risk of *developing* prostate cancer [49]. Data on post-diagnostic calcium and dairy intake are limited. However, among men diagnosed with non-metastatic prostate cancer in the PHS, men who consumed >1 serving/day of whole milk had a significantly increased risk of disease progression to fatal prostate cancer compared with men who drank <0.5 servings/day (HR 2.17, 95 % CI 1.34–3.51, P trend ≤0.001 [50]. Similar findings were reported in a similar cohort of men in the HPFS [51]. In contrast, consumption of *low-fat* dairy foods has not been consistently linked to adverse outcomes after a prostate cancer diagnosis, though data are limited [49, 51].

Dietary fats

Studies consistently show that replacing saturated fat with unsaturated fat is beneficial for overall health. Additionally, several studies have reported that saturated fat intake is associated with an increased risk of developing advanced or fatal prostate cancer, while long-chain omega-3 fatty acids (such as those found in fatty fish, see section on Fish) are associated with lower risk [52, 53], although not all studies are consistent [54]. The data on dietary fat *after* prostate cancer diagnosis are sparse, but reasonably consistent in indicating that fat from mammal origins (e.g., meat, high-fat dairy) may increase risk of prostate cancer mortality [55, 56]. Additionally, one study reported that consuming high amounts of fat from vegetable sources (e.g., olive oil, nuts) after diagnosis of non-metastatic prostate cancer was associated with lower risk of developing lethal disease [57]. Replacing 10 % of energy intake from carbohydrate with vegetable fat was associated with a lower risk of lethal prostate cancer (HR 0.71, 95 % CI 0.51–0.98, P trend = 0.04). Given the strong evidence that these foods lower risk of cardiovascular disease and diabetes, we recommend that men (with or without prostate cancer) replace foods high in saturated fat with healthy sources of vegetable fats, especially olive oil and nuts, which are proven to have cardiovascular and other benefits.

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Supplements

Available evidence suggests that a regular multivitamin is safe and may be beneficial. The Physicians' Health Study randomized trial of a regular multivitamin supplement demonstrated a modest (8 %) but statistically significant reduction in total cancer incidence in men; the subgroup of men with a baseline history of cancer had a 27 % reduction in total cancer during the study [58]. However, at this time, there is no strong evidence that any single supplement may offer protection against prostate cancer (neither the development of prostate cancer nor its progression). The Selenium and Vitamin E Cancer Prevention Trial (SELECT) observed no effect of 200 μg/day of selenium versus placebo on risk of screen-detected incident prostate cancer. However, in a secondary analysis among men with high levels of selenium at baseline in SELECT, men randomized to selenium had a 91 % increased risk of high-grade prostate cancer compared to placebo ($P = 0.007$) [59]. Recently, our group was the first to examine selenium supplementation after diagnosis in relation to prostate cancer mortality. In that analysis, men who reported consuming 140+ μg/day of selenium after diagnosis had a 2.6-fold increased risk of prostate cancer mortality [60]. One potential exception to avoidance of single nutrient supplements is vitamin D. Many men are vitamin D deficient, especially older men, those with less sun exposure or who live in northern latitudes (vitamin D is produced in the body when the skin is exposed to sunlight), and men with heavily pigmented skin. Vitamin D levels should be checked before taking supplemental vitamin D.

Conclusion

A variety of dietary and lifestyle factors appear to affect prostate cancer progression, though data are sparse. Several widely recommended lifestyle behaviors such as not smoking, maintaining a healthy body weight, and exercising vigorously on a regular basis appear to lower risk of prostate cancer progression. Additionally, preliminary data suggest that several dietary factors may also have a role in reducing risk of prostate cancer progression. These promising findings warrant further investigation, as the overall impact might be large.

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Table 1

Selected risk factors and risk of prostate cancer progression

Increased risk	Decreased risk
BMI****	Physical activity****
Smoking****	Fish**
Dairy/calcium**	Tomatoes/lycopene**
Processed red meat *	Vegetable fat**
Eggs/choline *	Cruciferous vegetables**
Poultry (w/skin) *	Coffee *
Animal fat/saturated fat *	Soy *
Selenium supplementation *	Tea *

2–3 asterisks indicate a strength of evidence in between 1 asterisk and 4 asterisks

* Number of asterisks indicates our assessment of the strength of the evidence, not the magnitude of effect. The greater the number of asterisk for a specific factor, the greater our confidence in the association. One asterisk means that the association is supported by at least one well-designed observational cohort study and that the magnitude is likely clinically meaningful. Four asterisks mean that we are confident that the studies performed are least likely to be biased and that the relationship between the risk factor and outcomes among men with prostate cancer is most likely real