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

Sam F. Peisch[1], **Erin L. Van Blarigan**[2,3], **June M. Chan**[2,3], **Meir J. Stampfer**[1,4,5], and **Stacey A. Kenfield**[2,4]

[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[2]Department of Urology, University of California-San Francisco, San Francisco, CA, USA

[3]Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, CA, USA

[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

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.

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

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-

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

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.

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

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,

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.

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.

Acknowledgments

References

1. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999; 281:1591–1597. [PubMed: 10235151]

2. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol. 2008; 9:1039–1047. [PubMed: 18835745]

3. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2011; 4:486–501. [PubMed: 21233290]

4. Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB, et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev Res (Phila). 2011; 4:544–551. [PubMed: 21325564]

5. Ploussard G, de la Taille A, Bayoud Y, Durand X, Terry S, Xylinas E, et al. The risk of upstaged disease increases with body mass index in low-risk prostate cancer patients eligible for active surveillance. Eur Urol. 2012; 61:356–362. [PubMed: 21803484]

6. Bonn SE, Wiklund F, Sjolander A, Szulkin R, Stattin P, Holmberg E, et al. Body mass index and weight change in men with prostate cancer: progression and mortality. Cancer Causes Control. 2014; 25:933–943. [PubMed: 24810654]

7. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol. 2013; 31:3069–3075. [PubMed: 23918942]

8. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med. 2010; 61:301–316. [PubMed: 19824817]

9. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol. 2011; 29:726–732. [PubMed: 21205749]

10. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res. 2011; 71:3889–3895. [PubMed: 21610110]

11. Bonn SE, Sjolander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al. Physical activity and survival among men diagnosed with prostate cancer. Cancer Epidemiol Biomark Prev. 2015; 24:57–64.

12. Baumann FT, Zopf EM, Bloch W. Clinical exercise interventions in prostate cancer patients—a systematic review of randomized controlled trials. Support Care Cancer. 2012; 20:221–233. [PubMed: 21989678]

13. Van Blarigan EL, Gerstenberger JP, Kenfield SA, Giovannucci EL, Stampfer MJ, Jones LW, et al. Physical activity and prostate tumor vessel morphology: data from the health professionals follow-up study. Cancer Prev Res (Phila). 2015; 8:962–967. [PubMed: 26276753]

14. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA. 2011; 305:2548–2555. [PubMed: 21693743]

15. Rieken M, Shariat SF, Kluth LA, Fajkovic H, Rink M, Karakiewicz PI, et al. Association of cigarette smoking and smoking cessation with biochemical recurrence of prostate cancer in patients treated with radical prostatectomy. Eur Urol. 2015; 68:949–956. [PubMed: 26050111]

16. Xie B, He H. No association between egg intake and prostate cancer risk: a meta-analysis. Asian Pac J Cancer Prev. 2012; 13:4677–4681. [PubMed: 23167401]

17. Richman EL, Kenfield SA, Stampfer MJ, Giovannucci EL, Chan JM. Egg, red meat, and poultry intake and risk of lethal prostate cancer in the prostate-specific antigen-era: incidence and survival. Cancer Prev Res (Phila). 2011; 4:2110–2121. [PubMed: 21930800]

18. Richman EL, Stampfer MJ, Paciorek A, Broering JM, Carroll PR, Chan JM. Intakes of meat, fish, poultry, and eggs and risk of prostate cancer progression. Am J Clin Nutr. 2010; 91:712–721. [PubMed: 20042525]

19. Richman EL, Kenfield SA, Stampfer MJ, Giovannucci EL, Zeisel SH, Willett WC, et al. Choline intake and risk of lethal prostate cancer: incidence and survival. Am J Clin Nutr. 2012; 96:855–863. [PubMed: 22952174]

20. Johansson M, Van Guelpen B, Vollset SE, Hultdin J, Bergh A, Key T, et al. One-carbon metabolism and prostate cancer risk: prospective investigation of seven circulating B vitamins and metabolites. Cancer Epidemiol Biomark Prev. 2009; 18:1538–1543.

21. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr. 2010; 92:1223–1233. [PubMed: 20844069]

22. Brasky TM, Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst. 2013; 105:1132–1141. [PubMed: 23843441]

23. Chan JM, Holick CN, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, et al. Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). Cancer Causes Control. 2006; 17:199–208. [PubMed: 16425098]

24. Galet C, Gollapudi K, Stepanian S, Byrd JB, Henning SM, Grogan T, et al. Effect of a low-fat fish oil diet on pro-inflammatory eicosanoids and cell-cycle progression score in men undergoing radical prostatectomy. Cancer Prev Res (Phila). 2014; 7:97–104. [PubMed: 24169960]

25. Sinha R, Park Y, Graubard BI, Leitzmann MF, Hollenbeck A, Schatzkin A, et al. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. Am J Epidemiol. 2009; 170:1165–1177. [PubMed: 19808637]

26. Alexander DD, Mink PJ, Cushing CA, Sceurman B. A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer. Nutr J. 2010; 9:50. [PubMed: 21044319]

27. Wilson KM, Kasperzyk JL, Rider JR, Kenfield S, van Dam RM, Stampfer MJ, et al. Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study. J Natl Cancer Inst. 2011; 103:876–884. [PubMed: 21586702]

28. Geybels MS, Neuhouser ML, Wright JL, Stott-Miller M, Stanford JL. Coffee and tea consumption in relation to prostate cancer prognosis. Cancer Causes Control. 2013; 24:1947–1954. [PubMed: 23907772]

29. Discacciati A, Orsini N, Wolk A. Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer—a dose–response meta-analysis. Ann Oncol. 2014; 25:584–591. [PubMed: 24276028]

30. Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. Pharmacol Res. 2007; 55:224–236. [PubMed: 17317210]

31. Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, et al. Prospective study of fruit and vegetable intake and risk of prostate cancer. J Natl Cancer Inst. 2007; 99:1200–1209. [PubMed: 17652276]

32. Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case–control study. Cancer Epidemiol Biomark Prev. 2000; 9:795–804.

33. Richman EL, Carroll PR, Chan JM. Vegetable and fruit intake after diagnosis and risk of prostate cancer progression. Int J Cancer. 2012; 131:201–210. [PubMed: 21823116]

34. Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis. Am J Clin Nutr. 2009; 89:1155–1163. [PubMed: 19211820]

35. Bosland MC, Kato I, Zeleniuch-Jacquotte A, Schmoll J, Enk Rueter E, Melamed J, et al. Effect of soy protein isolate supplementation on biochemical recurrence of prostate cancer after radical prostatectomy: a randomized trial. JAMA. 2013; 310:170–178. [PubMed: 23839751]

36. Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S. JPHC Study Group. Green tea consumption and prostate cancer risk in Japanese men: a prospective study. Am J Epidemiol. 2008; 167:71–77. [PubMed: 17906295]

37. Jian L, Lee AH, Binns CW. Tea and lycopene protect against prostate cancer. Asia Pac J Clin Nutr. 2007; 16(Suppl 1):453–457. [PubMed: 17392149]

38. Lin YW, Hu ZH, Wang X, Mao QQ, Qin J, Zheng XY, et al. Tea consumption and prostate cancer: an updated meta-analysis. World J Surg Oncol. 2014; 12:38. [PubMed: 24528523]

39. Zheng J, Yang B, Huang T, Yu Y, Yang J, Li D. Green tea and black tea consumption and prostate cancer risk: an exploratory meta-analysis of observational studies. Nutr Cancer. 2011; 63:663–672. [PubMed: 21667398]

40. Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. Eur Urol. 2008; 54:472–473. [PubMed: 18406041]

41. Henning SM, Wang P, Said JW, Huang M, Grogan T, Elashoff D, et al. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. Prostate. 2015; 75:550–559. [PubMed: 25545744]

42. Zu K, Mucci L, Rosner BA, Clinton SK, Loda M, Stampfer MJ, et al. Dietary lycopene, angiogenesis, and prostate cancer: a prospective study in the prostate-specific antigen era. J Natl Cancer Inst. 2014; 106(2):djt430.doi: 10.1093/jnci/djt430 [PubMed: 24463248]

43. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res. 1999; 59:1225–1230. [PubMed: 10096552]

44. Peters U, Leitzmann MF, Chatterjee N, Wang Y, Albanes D, Gelmann EP, et al. Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomark Prev. 2007; 16:962–968.

45. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst. 2002; 94:391–398. [PubMed: 11880478]

46. Haseen F, Cantwell MM, O'Sullivan JM, Murray LJ. Is there a benefit from lycopene supplementation in men with prostate cancer? A systematic review. Prostate Cancer Prostatic Dis. 2009; 12:325–332. [PubMed: 19901932]

47. Ansari MS, Gupta NP. A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. BJU Int. 2003; 92:375–378. (discussion 8). [PubMed: 12930422]

48. Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomark Prev. 2001; 10:861–868.

49. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr. 2015; 101:87–117. [PubMed: 25527754]

50. Song Y, Chavarro JE, Cao Y, Qiu W, Mucci L, Sesso HD, et al. Whole milk intake is associated with prostate cancer-specific mortality among U.S. male physicians. J Nutr. 2013; 143:189–196. [PubMed: 23256145]

51. Pettersson A, Kasperzyk JL, Kenfield SA, Richman EL, Chan JM, Willett WC, et al. Milk and dairy consumption among men with prostate cancer and risk of metastases and prostate cancer death. Cancer Epidemiol Biomark Prev. 2012; 21:428–436.

52. Chavarro JE, Stampfer MJ, Li H, Campos H, Kurth T, Ma J. A prospective study of polyunsaturated fatty acid levels in blood and prostate cancer risk. Cancer Epidemiol Biomark Prev. 2007; 16:1364–1370.

53. Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, et al. A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomark Prev. 2003; 12:64–67.

54. Park SY, Wilkens LR, Henning SM, Le Marchand L, Gao K, Goodman MT, et al. Circulating fatty acids and prostate cancer risk in a nested case–control study: the multiethnic cohort. Cancer Causes Control. 2009; 20:211–223. [PubMed: 18821021]

55. Fradet Y, Meyer F, Bairati I, Shadmani R, Moore L. Dietary fat and prostate cancer progression and survival. Eur Urol. 1999; 35:388–391. [PubMed: 10325493]

56. Epstein MM, Kasperzyk JL, Mucci LA, Giovannucci E, Price A, Wolk A, et al. Dietary fatty acid intake and prostate cancer survival in Orebro County, Sweden. Am J Epidemiol. 2012; 176:240–252. [PubMed: 22781428]

57. Richman EL, Kenfield SA, Chavarro JE, Stampfer MJ, Giovannucci EL, Willett WC, et al. Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. JAMA Intern Med. 2013; 173:1318–1326. [PubMed: 23752662]

58. Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, Mac-Fadyen J, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2012; 308:1871–1880. [PubMed: 23162860]

59. Kristal AR, Darke AK, Morris JS, Tangen CM, Goodman PJ, Thompson IM, et al. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. J Natl Cancer Inst. 2014; 106(3):djt456.doi: 10.1093/jnci/djt456 [PubMed: 24563519]

60. Kenfield SA, Van Blarigan EL, DuPre N, Stampfer MJ, Giovannucci EL, Chan JM. Selenium supplementation and prostate cancer mortality. J Natl Cancer Inst. 2015; 107:360. [PubMed: 25505227]

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