Diet and Lifestyle in Prostate Cancer

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Prostate cancer is the most commonly diagnosed non-skin cancer among men in the United States (US). In addition, three million men in the US are prostate cancer survivors. Given the large public health burden of prostate cancer, the identification of the factors associated with prostate cancer prevention could improve health and outcomes for men.

A variety of diet and lifestyle factors have been studied with respect to prostate cancer risk in large, prospective cohort studies. More recently, researchers have begun to study the association of diet and lifestyle with prostate cancer survival after diagnosis. Cohort studies are generally considered to be a higher level of evidence than case-control studies, which are susceptible to recall bias and selection bias. For this reason, we focus on results from prospective cohort studies when possible. The major cohort studies with results discussed in this chapter are summarized in Table 1.

In spite of this work, few modifiable risk factors have been firmly established as playing a role in prostate cancer. Among modifiable risk factors, smoking and obesity are consistently associated with higher risk specifically of advanced prostate cancer. There is also considerable evidence for a positive association between dairy intake and overall prostate cancer risk, and an inverse association between cooked tomato/lycopene intake and risk of advanced disease. Several other dietary factors consistently associated with risk in observational studies, including selenium and vitamin E, have been cast into doubt by results from clinical trials. Results for other well-studied dietary factors, including fat intake, red meat, fish, vitamin D, soy and phytoestrogens are mixed.

Migrant studies have found that moving from countries with low prostate cancer incidence to countries with high incidence increases the risk of prostate cancer over time. Among Japanese [1, 2] and Korean [3] immigrants to the US, Chinese immigrants to the US and Canada [4], and European immigrants to Australia [5] prostate cancer risk is much higher than that of their native counterparts, but still below that of white men born in the US, Canada, and Australia. This suggests that there are important environmental contributors to prostate cancer risk in addition to strong genetic factors.

The lack of well-established modifiable risk factors for prostate cancer compared to other common cancers is likely due to several possibilities. First, prostate cancer has among the highest heritability of all common cancers [6]; second, early life exposures may play an important role in risk, rather than mid- and later-life exposures assessed in most epidemiological

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Table 1 Overview of major prospective studies discussed in the chapter

Study name	Primary institution	Location	Design	Start–End dates	N male participants at baseline	Age at baseline; other entry criteria
Health Professionals Follow-up Study (HPFS)	Harvard University	U.S.	Observational cohort study	1986 to ongoing follow-up	51,529	40–75 years
Physicians' Health Study I and II (PHS)	Harvard University/ Brigham & Women's Hospital	U.S.	Randomized trials of cardiovascular disease and cancer prevention (PHS I: aspirin, beta-carotene; PHS II: Vitamins C, E, beta-carotene, multivitamin)	PHS I: 1982–1995 PHS II: 1997–2007 (Follow-up for prostate cancer through 2012)	PHS I: 22,071 PHS II: 14,642	PHS I: 40–84 PHS II: ≥50 years
NIH-AARP Diet and Health Study	National Cancer Institute (US)	U.S. (6 states, 2 metro areas)	Observational cohort study	1995/6 to ongoing follow-up	322,363	50–71 years
Prostate Cancer Prevention Trial (PCPT)	Southwest Oncology Group (SWOG)	U.S.	Randomized trial of prostate cancer prevention with finasteride	1993–2003	18,882	≥55 years; Normal DRE and PSA < 3 ng/ml at baseline
Selenium and Vitamin E Cancer Prevention Trial (SELECT)	Southwest Oncology Group (SWOG)	U.S.	Randomized trial of prostate cancer prevention with selenium and Vitamin E	2001/4–2008	35,533	≥50 years
European Prospective Investigation into Cancer and Nutrition (EPIC)	International Agency for Research on Cancer (IARC)-World Health Organization (WHO)	10 Western European countries	Observational cohort study	1992/9 to ongoing follow-up	153,427	35–74 years at most centers
VITamin D and OmegA-3 TriaL (VITAL)	Harvard University/ Brigham & Women's Hospital	U.S.	Randomized trial of cardiovascular disease and cancer prevention with vitamin D and omega-3 fatty acids	2010–2017	12,786	≥50 years

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)	National Cancer Institute (US) and National Institute for Health and Welfare of Finland	Finland	Randomized trial of lung cancer prevention with alpha-tocopherol and beta-carotene	1985–1993	29,133	50–69 years; current smokers
Cancer Prevention Study II Nutrition Study (CPS II)	American Cancer Society	U.S. (21 states)	Observational cohort study	1992/3 to ongoing follow-up	86,402	50–74 years, approximately
Multi-ethnic Cohort Study (MEC)	University of Hawaii and University of Southern California	U.S. (Hawaii & Los Angeles)	Observational cohort study	1993/6 to ongoing follow-up	96,810	45–75 years
VITamins and Lifestyle Study (VITAL)	University of Washington/ Fred Hutchinson Cancer Research Center	U.S. (Washington State)	Observational cohort study	2000/2 to ongoing follow-up	35,242	50–76 years

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studies. Finally, prostate-specific antigen (PSA) screening plays a critical role in prostate cancer detection and incidence rates, which has important implications for epidemiological studies. It is important to understand the impact of PSA screening on prostate cancer epidemiology, as screening must be considered in the interpretation of risk factor studies. We will briefly discuss this below, and we will then review current evidence on dietary and other lifestyle factors, including tobacco use, obesity, and physical activity. For each of these potential risk factors, we will discuss findings for both incidence and survival, if available. A summary of risk factors for prostate cancer is provided in Table 2.

Table 2 Summary of epidemiological evidence on diet and lifestyle in prostate cancer

Risk factor	Direction of effect[a]
Well-confirmed risk factors	
Height	↑
Probable relationship exists, based on substantial data	
Insulin-like growth factor 1	↑
Smoking	↑ (advanced disease)
Obesity/Body mass index	↑ (advanced disease)
Obesity/Body mass index	↓ (localized disease)
Physical activity (vigorous)	↓ (advanced disease)
Dairy intake	↑
Fish intake	↓ (advanced disease)
Lycopene/tomato intake	↓
Weak, if any, relationship exists, based on substantial data	
Total fat intake	–
Alpha-tocopherol supplements	–
Selenium supplements	–
Childhood/young adult body size	–
Inconsistent findings or limited study to date	
Long-chain marine fatty acid intake	–
Alpha-linolenic acid intake	↑
Red & processed meat intake	–
Calcium intake	↑
Vitamin D	↓ (advanced disease)
Soy/phytoestrogen intake	↓
Dietary vitamin E intake	↓ (advanced disease)
Dietary selenium intake	↓

[a]Arrows indicate direction of relationship: ↑: increase in risk; ↓: decrease in risk; —: no association

The Impact of PSA Screening on Epidemiological Studies of Prostate Cancer

Autopsy studies have shown that latent prostate cancer is quite common. A review of 19 studies of prostate cancer prevalence upon autopsy found that 29% of white men aged 60–69 and 36% aged 70–79 had undiagnosed prostate cancer at the time of death, with even higher prevalence among black men [7]. Screening by prostate specific antigen (PSA) allows for the detection of these lesions, many of which would never come to light clinically in the absence of screening. Thus, PSA screening has a great impact on incidence rates and the clinical presentation of prostate cancer in populations where it has been introduced.

The mix of indolent and aggressive disease in a given study population will depend on the time period of the study and the PSA screening practices in the population. This makes is difficult to compare relative risks for "total" prostate cancer across studies, as relative risks will reflect a weighted average of indolent and aggressive disease specific to the time and place in which the study was conducted. To deal with this, it is helpful to assess associations separately for fatal or advanced stage disease and localized disease, and/or to stratify results by pre-PSA and PSA time periods. Some studies also look at associations for high-grade and low-grade disease separately; however, changes in grading over time, along with between-pathologist differences in grading, introduce substantial misclassification into grade-based categorization in large cohort studies [8].

Dietary Factors and Prostate Cancer Risk and Survival

A western dietary pattern has long been suspected to contribute to prostate cancer risk based on ecologic studies that compared prostate cancer mortality rates around the world and migrant studies as discussed above. Early ecologic studies demonstrated the striking disparity in animal product and fat consumption between high-risk (US, Sweden) and low-risk (Japan, China) countries [9]. Such studies are quite limited, however, as they do not assess individual-level behaviors and subsequent disease outcomes and are unable to account for confounding elements.

Western dietary patterns are also implicated based on the strong evidence of positive associations of adult height and circulating insulin-like growth factor 1 (IGF-1) levels with prostate cancer risk. Both height and circulating IGF-1 levels reflect, in part, nutritional status.

Height. A systematic review found 22 out of 25 studies of height and prostate cancer incidence reported positive associations [10]. The dose-response meta-analysis found a significant 4% increase in risk of prostate cancer overall per 5 cm increase in height (95% CI 1.03–1.05). The same review found that four of five studies on height and risk of prostate cancer mortality reported positive associations. Results were consistent for non-advanced, advanced, and fatal disease. Two large pooled analyses [11, 12] found very similar results for associations of height with prostate cancer incidence as well as mortality.

Adult height partially reflects nutritional status in early life [13–15], which impact circulating growth factors and other hormones during childhood and puberty [16]. Although genetics plays a major role in determining height, [17], dietary factors are essential to reach the genetic potential. Total energy intake, protein, and dairy intake in childhood are all associated with greater attained height [18–20].

IGF-1. Total energy intake and protein intake are, in turn, positively associated with circulating IGF-1 in children and adults in observational studies [21, 22] and in feeding trials [23]. In addition, adult height is positively correlated with IGF-1. [24] IGF-1 is a major growth-regulating molecule, which is a potent mitogen that can also inhibit apoptosis. It is secreted mainly by the liver but is also produced in several other tissues, including the prostate, in response to growth hormone.

Adult levels of circulating IGF-1 have consistently been associated with increased risk of prostate cancer. A pooled analysis of data from 3700 cases and 5200 controls in 12 prospective cohort studies [25] found an odds ratio of 1.38 (95% CI 1.19–1.60, p-trend = <0.001) for prostate cancer comparing the top to bottom quintile of serum IGF1. The association was stronger for low-grade than for high-grade disease, but did not vary by stage of disease. Adjustment for various sex hormone levels also measured in 8 of the 12 studies did not affect the IGF-1 results. Results from a meta-analysis of 42 retrospective and prospective studies found a similar significant and positive association for IGF-1 and prostate cancer risk [26].

Evidence supporting associations of height and IGF-1 with prostate cancer is quite consistent across study populations. In combination with results from migrant studies and the large geographical variation in incidence rates of prostate cancer, this suggests that nutritional status plays some role, perhaps early in life, in the development of prostate cancer. A variety of specific dietary factors have been investigated in detail with respect to prostate cancer risk, including fat intake, meat intake, intake of fish and marine-derived long-chain fatty acids, dairy products and calcium, vitamin D, tomato and lycopene, soy and phytoestrogens, vitamin E, and selenium. Each is discussed in detail below.

Fat Intake

Driven by early ecologic studies, dietary fat intake has been of great interest in studies of diet and prostate cancer, as high fat intake, particularly from animal sources, is a major attribute of the western diet. However, a meta-analysis of 14 prospective cohort studies found no association

between total fat intake and risk of prostate cancer [27]. Intakes of saturated, polyunsaturated, and monounsaturated fats were also not associated with risk, and fat intakes were not associated with risk of advanced stage disease.

Several prospective studies have evaluated intake of specific fatty acids in relation to prostate cancer. In western diets, alpha-linolenic acid (ALA) is the principal dietary n-3 (or omega-3) fatty acid. Commonly consumed foods rich in ALA include: mayonnaise, vegetable oils, margarine, walnuts, cheese, beef, pork, and lamb. Several meta-analyses of ALA intake and prostate cancer have found no association with overall disease risk, though there appears to be significant heterogeneity between studies [28–30]. The Health Professionals Follow-up Study (HPFS) cohort found that ALA intake was not associated with overall prostate cancer risk but was associated with significantly increased risk of fatal prostate cancer [31]. This positive association between ALA intake and risk of lethal disease was observed among cases diagnosed prior to the advent of PSA screening (~1994), and not for cases diagnosed in the PSA-screening era [32]. Two other prospective studies of ALA intake did not find increased risks for more advanced prostate cancer; however, both were limited by low case numbers [33, 34], while a fourth prospective study did not examine associations specifically with advanced disease [35].

A pooled analysis [36] of individual-level data from seven prospective studies with measured blood levels of ALA found no association with overall prostate cancer risk. There was some suggestion of heterogeneity by stage of disease ($p = 0.032$), with no significant association for localized disease and a borderline significant *inverse* association for risk of advanced prostate cancer (OR 0.68, 95% CI 0.46–1.00); however, the number of advanced cases was low in the seven included studies. There was no suggestion of an association between blood ALA levels and risk of high- or low-grade disease. Overall it does not appear that ALA is an important risk factor for prostate cancer; however, the evidence in this area is unusually inconsistent across studies.

The role of long-chain n-3 fatty acids in prostate cancer has also been debated; see the section below on fish intake for discussion.

Survival. Fewer studies have examined the association between fat intake and survival among men with prostate cancer, but these studies are consistent in finding improved survival with increased vegetable fats and poorer survival with saturated and animal fats. In the Physicians' Health Study (PHS) men who consumed more saturated fat in place of carbohydrate in the post-diagnosis diet were at increased risk of cancer-specific and all-cause mortality [37]. Increased intake of vegetable fats after diagnosis was associated with lower risk of all-cause, but not cancer-specific, mortality. In HPFS, post-diagnosis vegetable fat intake was associated with significantly lower risk of both cancer-specific and all-cause mortality. Higher intakes of saturated and trans fats were positively associated with all-cause mortality [38]. A study of men diagnosed with prostate cancer in Sweden found that those reporting a higher intake of saturated fat at the time of diagnosis were at significantly greater risk of prostate cancer mortality [39]. To date, the literature has been consistent in showing that higher intakes of vegetable fats and lower intake of animal and saturated fats after diagnosis are associated with improved cancer-specific and overall survival.

Meat Intake

Red meat and processed meat have both been intensively studied as possible risk factors for prostate cancer, as both are notable components of the western diet. However, meat intake does not appear to be associated with prostate cancer risk.

A meta-analysis of 11 prospective studies found a combined relative risk for extreme categories of red meat intake of 0.98 (95% CI 0.93–1.04) for total prostate cancer and 1.01 (95% CI 0.94–1.09) for advanced prostate cancer (8 studies) [40]. A recent pooled analysis of individual data from 15 cohort studies also found no

association between red meat intake and risk of total or fatal prostate cancer [41].

For processed meat, the meta-analysis of 11 prospective studies found a relative risk for extreme categories of intake of 1.05 (95% CI 0.99–1.12) for total prostate cancer and 1.10 (95% CI 0.95–1.27) for advanced cancer (8 studies) [40]. There was evidence of publication bias for processed meat studies, and risk estimates were weaker in more recent studies that adjusted for more potential confounders. The pooled analysis of 15 cohorts found a suggestion of a slight increase in risk of total prostate cancer for the highest category of processed meat intake, though there was no significant trend across categories (HR 1.04, 95% CI 1.01–1.08, p-trend = 0.29); there was no association for fatal disease [41]. Similarly, several more recent studies found no associations for red or processed meat. One paper found no evidence that red or processed meat was associated with risk total or advanced prostate cancer among African-Americans in the NIH-AARP Diet and Health Study [42]. A study [43] focused on the PSA screening era in the HPFS cohort also found no associations of meat intake with lethal prostate cancer. Finally, a study in the Netherlands found no association between low- or no meat consumption and risk of prostate cancer [44].

One possible mechanism by which red meat could raise the risk of cancer is through heterocyclic amines (HCA) formed during cooking [45–48]. HCAs are mutagenic compounds formed during cooking of muscle of meat and fish at high temperatures. Preference for doneness of red meat and calculated intakes of common HCAs have been studied with respect to prostate cancer in several prospective studies with mixed results. Three found no clear associations between doneness or HCA intake and risk of prostate cancer [47–49]. Three found positive associations between well done red meat [42, 45, 46, 50], as well as HCA intake [50], and risk of prostate cancer, including advanced disease. Overall, intakes of red and processed meat do not appear related to prostate cancer risk; however, well-done red meat and the associated carcinogens may play some role.

Survival. In a study of post-diagnosis meat intake and survival among men diagnosed with apparently localized prostate cancer, one study found suggestive but not statistically significant associations between intake of red meat and poultry and risk of lethal prostate cancer [43]. Another study found that a "Western dietary pattern", characterized by higher intakes of red and processed meats, high-fat dairy, and refined grains, was associated with increased risk of prostate cancer-specific and all-cause mortality [51]. Finally, a study [52] among men surgically treated for localized cancer found that lower intakes of red meat, particularly well-done red meat, and higher intakes of poultry and fish were associated with lower risk of PSA recurrence, independent of stage and grade of disease. Overall, it appears that lower intakes of red meat may be associated with improved survival, which is consistent with the findings on post-diagnosis fat intake and survival discussed above.

Fish Intake and Marine Fatty Acids

Populations with a high consumption of fish, for example in Japan and among Alaskan natives, have lower rates of prostate cancer than populations with western dietary patterns, where fish intake is generally lower [53–55]. Fish contain long-chain marine n-3 fatty acids (eicosapentaenoic acid, EPA, [20:5n-3] and docosahexaenoic acid, DHA, [22:6n-3]), which can modify inflammatory pathways and may therefore affect prostate cancer risk and progression [56]. Indeed, a study among men without cancer in the Prostate Cancer Prevention Trial (PCPT, a randomized trial of finasteride for prostate cancer prevention) found that men with higher serum levels of n-3 fatty acids had lower levels of prostatic inflammation [57].

However, the role of fish and long-chain fatty acids in prostate cancer has been debated due to reports from PCPT and The Selenium and Vitamin E Cancer Prevention Trial (SELECT) of significant *positive* associations between higher concentrations of serum long-chain n-3 fatty acids and risk of high-grade disease [58]. Neither

trial had enough advanced or fatal cases to study those outcomes separately.

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort found a positive association between serum EPA and risk of high-grade disease, consistent with PCPT and SELECT. However, they observed no association with advanced or fatal disease [59]. The PHS cohort [60] assessed whole blood fatty acid content and also found no association with advanced disease, and a significant inverse association with localized disease.

A pooled analysis of seven prospective studies [36], including all four discussed above, found a significantly increased risk of total prostate cancer with higher serum levels of both EPA and DHA. Risk was approximately 15% higher for men in the highest quintile of either fatty acid compared to men in the lowest quintile of that fatty acid. However, there was significant heterogeneity between studies ($p = 0.02$ for EPA, $p < 0.001$ for DHA). Thus there may be modest positive associations between blood levels of marine long-chain fatty acids and risk of total prostate cancer; however, it is unclear if these associations are causal, and the reason for heterogeneity across studies is unclear. Differences in PSA screening may explain some of the heterogeneity. The positive associations were stronger for cases diagnosed after 2000 than those diagnosed earlier. In addition, the vast majority of cases from the SELECT and PCPT trials were screen-detected, whereas the PHS, which found inverse associations, contained many cases diagnosed between 1982 and 1995, prior to the onset of widespread PSA screening in the US.

Multiple studies have examined questionnaire-assessed intake of fish and fish-derived long-chain fatty acids. A 2010 meta-analysis of fish intake found no association between fish consumption and incidence of total prostate cancer; for the highest versus lowest category of intake across 12 cohort studies the relative risk was 1.01 (95% CI 0.90–1.14) [61]. However, in four cohort studies of prostate cancer-specific mortality, fish intake was associated with a significantly lower risk (RR 0.37, 95% CI 0.18–0.74). A recent systematic review [62] of long-chain n-3 fatty acids found similar results, with no association for risk of overall prostate cancer, and an inverse association for prostate cancer mortality. Of seven studies investigating associations between long-chain n-3 fatty acid intake and prostate cancer-specific mortality, five found significant inverse associations and two found non-significant inverse associations. A study in Iceland, where there is a tradition of fish-oil consumption, found that fish oil consumption in later life was associated with a lower risk of advanced prostate cancer [63].

The recently completed VITAL trial [64] tested marine n-3 fatty acids (at a dose of 1 g per day, equal to about 4 servings/week of fish) in the primary prevention of cardiovascular disease and cancer among 12,786 men 50 years of age or older. Mean follow-up was 5.3 years. There was no difference in the incidence of prostate cancer (a predefined secondary outcome) between groups. (N = 411 total cases, RR = 1.15, 95% CI 0.94–1.39). However, low power and a relatively short follow-up time limit the conclusions that can be drawn from this null result.

Overall, current evidence is quite mixed regarding associations of serum fatty acid levels and fish intake with risk of disease by both grade and stage. Additional studies in cohorts with long-term follow-up are needed to draw conclusions about the role of fish, fish oil supplements, and specific long-chain omega-3 fatty acids in prostate cancer risk and progression.

Dairy Products and Calcium

Dairy products, in addition to containing a substantial amount of animal fat, are the most common dietary sources of calcium and vitamin D, all of which have been implicated in prostate cancer risk. The strong correlation between dairy foods and these nutrients create challenges in trying to disentangle their independent effects. A meta-analysis conducted as a part of the AICR/WCRF Continuous Update Project found a statistically significant increased risk of total prostate cancer with higher intakes of dairy products and dietary calcium (i.e. from foods, not supplements) [10]. The combined estimate across 15

cohort studies found a 7% increased risk per 400 g of dairy products per day (95% CI 2–12%) and 5% increased risk per 400 mg of dietary calcium (95% CI 2–9%). Intakes of milk, cheese, and total calcium (i.e. foods plus supplements) were also positively associated with risk. There was evidence of non-linear associations for calcium (from foods alone and total intake), with positive associations more pronounced at very high intakes (>1500 mg/day).

Associations according to stage of disease were less clear, with significant positive associations for non-advanced disease but not for advanced disease for both dairy and dietary calcium. However, across five studies of fatal cancer, the association with dairy was an 11% increased risk per 400 g per day (95% CI −8% to 33%), quite similar to the risk estimate for overall prostate cancer, but with lower power and a wide confidence interval.

Estimates for total calcium were somewhat weaker than for dietary calcium, suggesting that some other component of dairy, rather than calcium itself, is driving the dietary calcium estimates. However, interpretation of this, too, is complicated, as the only two studies that examined total calcium and fatal prostate cancer found a significantly increased risk (RR 1.11, 95% CI 1.02–1.21). In addition, there was significant heterogeneity for the total calcium estimate based on study follow-up time, with a non-significant association with total prostate cancer in six studies with less than 10 years of follow-up, but a significant positive association in three studies with 10 or more years of follow-up. This heterogeneity by follow-up time is supported by a report from the HPFS [65], which found a significant association between total calcium intake 12–16 years prior to diagnosis of advanced prostate cancer, but not for shorter time periods between intake and diagnosis. This suggests that calcium may play a role early in the carcinogenesis process.

Possible mechanisms linking dairy or calcium and prostate cancer risk include the down-regulating effect of high calcium intake on vitamin D levels [66] and the positive association between dairy and IGF-1 levels [67]. The positive association observed for low-fat or skim milk argues against dairy fat playing an important role in the association.

Interestingly, the HPFS cohort also found a positive association between phosphorus intake and risk of total, lethal, and high-grade prostate cancer, independent of the association with calcium [65]. In contrast to the pattern observed for calcium, the phosphorus association was strongest for intakes shortly before the time of diagnosis (0–4 years). Phosphorus, like calcium, is concentrated in dairy, but is more widespread in other foods than is calcium. Fewer studies have examined phosphorus than calcium, particularly with respect to advanced or fatal disease, but this should be explored in other studies. High phosphorus intake increases parathyroid hormone, which promotes bone remodeling [68]. Prostate cancer preferentially metastasizes to bone and is more likely to spread to bone with higher remodeling activity [69, 70].

Overall, there is substantial evidence that dairy intake is associated with increased prostate cancer risk; however, the role of calcium, phosphorus, or other specific components is less clear.

Survival. There have been three studies of post-diagnosis dairy intake and prostate cancer survival among men diagnosed with apparently localized disease. HPFS and a Swedish study both found that higher post-diagnosis intake of whole milk was associated with worse survival [71, 72], while higher intake of low-fat dairy was associated with improved survival that was statistically significant in HPFS and suggestive in the Swedish population. On the other hand, PHS reported that intake of total dairy, including both high- and low-fat dairy foods, was associated with increased risk of all-cause and prostate cancer-specific mortality [73]. Thus, evidence has consistently shown that high-fat dairy after diagnosis is associated with worse survival, whereas the role of low-fat dairy is uncertain.

Vitamin D

Vitamin D, which is an important regulator of calcium homeostasis, has also been considered as

a prostate cancer risk factor. The main source of vitamin D is endogenous production in the skin resulting from sun exposure, and diet is a secondary source. Dihydroxyvitamin D [1,25$(OH)_2$D] is a steroid hormone involved in regulating differentiation and proliferation of many cell types, including prostate epithelial cells, which express functional vitamin D receptors. 1,25$(OH)_2$D is the most biologically active form, whereas hydroxyvitamin D [25(OH)D] is found in much higher concentrations in blood and better reflects sun and dietary exposure, as its levels are less strictly regulated by the body.

A meta-analysis of circulating 25(OH)D levels in 14 prospective nested case-control studies found no association with total prostate cancer risk (OR 1.04, 95% CI 0.99–1.10) [74]. In six studies of aggressive prostate cancer, defined as a mix of high grade and advanced stage, there was also no association (OR 0.98, 95% CI 0.84, 1.15); however, there was evidence of heterogeneity between studies. A similar null association was found in another meta-analysis [75]. A consortium of cohort studies with 518 fatal cases and 2986 controls similarly found no association between 25(OH)D and risk of fatal prostate cancer. However, there was evidence that the 25(OH)D association may be modified by genetic variation in several vitamin D-related genes [76].

Five large studies published after these meta-analyses have had mixed results. The PCPT [77] found no association overall, but a significant inverse association between 25(OH)D and high-grade cancer. Conversely, a Swedish study [78] found a suggestive positive association with total prostate cancer, and the ATBC study [79], a cohort of Finnish smokers, found a significantly increased risk of total and aggressive (stage 3 or 4 or Gleason grade 8+) disease. Finally, the SELECT [80] trial reported a U-shaped relationship between circulating Vitamin D and risk of total prostate cancer, with significantly lower risk in the middle quintile relative to the lowest quintile and no difference in risk between the highest and lowest quintiles.

The recently completed VITAL trial [81] tested vitamin D3 (cholecalciferol) at a dose of 2000 IU per day (together with fish oil) in the primary prevention of cardiovascular disease and cancer among 12,786 men 50 years of age or older with mean follow-up of 5.3 years. There was no association between vitamin D supplementation and prostate cancer incidence (N = 411 total events, RR 0.88 (0.72–1.07)). However, as with the VITAL results for fish oil supplements, the limited power and short follow-up time of the trial limit how informative this null result is.

1,25$(OH)_2$D has been less studied than 25(OH)D. However, a meta-analysis of seven prospective studies of 1,25$(OH)_2$D found no association with total prostate cancer (OR 1.00, 95% CI 0.87–1.14). Only two studies have looked at 1,25$(OH)_2$D and risk of aggressive disease (both based on high grade, or advanced stage, or prostate cancer death) with a suggestive combined odds ratio of 0.86 (95% CI 0.72–1.02) [82].

Survival. In spite of the null findings for associations between vitamin D and incidence of total or aggressive disease, there is some evidence that vitamin D plays a role in prostate cancer progression. Several studies have found inverse associations between 25(OH)D and survival among prostate cancer patients [83–86], though others have not [79, 87]. In addition, genetic variants in the vitamin D pathway are associated with risk of recurrence or progression and prostate cancer-specific mortality [76, 85, 88]. Genetic variants in the vitamin D receptor were associated with Gleason score in some studies [89, 90], and high expression of the vitamin D receptor protein in prostate cancer tissue was associated with lower risk of prostate cancer mortality among men with prostate cancer in the HPFS and PHS cohorts, with adjustment for PSA at diagnosis, Gleason grade, and stage [91].

Thus, while vitamin D exposure does not seem to be associated with lower risk of prostate cancer incidence, several lines of evidence suggest that the vitamin D pathway may play a role in prostate cancer progression.

Lycopene and Tomatoes

Tomatoes and lycopene, a carotenoid consumed mainly from tomato products, have been the

focus of many studies due to early reports of a significant inverse association between intake and risk of prostate cancer [92]. A meta-analysis [93] found significant inverse associations between both questionnaire-assessed lycopene intake and circulating lycopene levels and risk of prostate cancer. Across 16 case-control and 9 prospective studies, men with the highest lycopene intake had a 12% lower risk of prostate cancer compared to men with the lowest intakes (95% CI 0.78–0.98, p = 0.02).

A pooled analysis of data from 15 prospective studies found no association between circulating lycopene levels and risk of overall prostate cancer (OR 0.97, 95% CI 0.86–1.08 for top versus bottom quintile). However, there was significant heterogeneity by stage, with higher lycopene associated with lower risk of advanced, but not localized disease. Men in the highest quintile of circulating lycopene had a HR of 0.65 (95% CI 0.46–0.91, p-trend = 0.03) for advanced stage or fatal prostate cancer compared to men in the lowest quintile.

These findings are in agreement with those from the HPFS cohort [94] based on lycopene intake assessed by questionnaire, which found a stronger inverse association with lethal cancer (death or distant metastatic disease) than for total prostate cancer. The HR for lethal cancer was 0.72 (95% CI 0.56–0.94, p-trend = 0.04) for the highest versus lowest quintile. This inverse association with lethal cancer was stronger among a sub-cohort of men who received PSA tests (HR 0.47, 95% CI 0.29–0.75, p-trend = 0.009), suggesting the association is not related to differences in screening or detection.

Cooked or processed tomato products, such as tomato sauce, tomato soup, and ketchup, offer more readily bioavailable sources of lycopene than fresh tomatoes [95]. Accordingly, some epidemiologic studies have found significant inverse effects for tomato sauce while reporting weaker results for raw tomato intake and no significant influence for tomato juice [96]. The correlation between dietary estimates of lycopene based on food frequency questionnaires and circulating levels measured in blood are relatively low, ranging from 0 to 0.47 [96]. A clinical trial found that men assigned to consume one serving per day of either tomato sauce, tomato juice, or tomato soup for at least 2 weeks had significant increases in both plasma and prostatic lycopene levels [97].

Experimental studies suggest that lycopene can inhibit angiogenesis, perhaps through regulation of vascular endothelial growth factor (VEGF) and the PI3K-Akt and ERK/p38 signaling pathways [98–101]. Interestingly, three measures of tumor angiogenesis—microvessel diameter and area and irregularity of the vessel lumen—were all associated with lycopene intake such that those with higher intakes had more favorable angiogenesis markers [94]. These angiogenesis markers are associated with risk of lethal disease independent of grade [102]. Overall, there is fairly consistent evidence that lycopene is associated with lower risk of advanced or fatal prostate cancers, and experimental evidence supports this observation.

Survival. Among men diagnosed with aggressive prostate cancers in the American Cancer Society's Cancer Prevention Study II Nutrition Cohort (CPS II), high lycopene intake before and after diagnosis was consistently associated with improved survival; however, there was no association between lycopene intake and survival when all prostate cancer cases were included [103].

Soy/Phytoestrogens

Traditional Asian diets are notably high in phytoestrogens, chiefly from soy-based foods. Intakes of soy and phytoestrogens are low in the typical western diet. Because there are stark differences in incidence of prostate cancer between Asian and western countries, these foods and compounds have been of interest with respect to prostate cancer risk.

Dietary phytoestrogens, naturally occurring constituents of plants, are divided into two main categories: lignans and isoflavonoids. Lignans occur in whole-grain bread, seeds, berries, vegetables, and tea, while the main source of isoflavonoids is soy beans and soy products. The primary isoflavones in soy are genistein and daidzein.

Animal studies have suggested that phytoestrogens may play a role in prostate cancer initiation and progression through estrogenic effects, inhibition of angiogenesis, antioxidant activity, stimulation of apoptosis, and inhibition of cell growth [104–108].

A meta-analysis [109] of 16 studies of soy intake and total prostate cancer risk found a significant inverse association, with a relative risk of 0.70 (95% CI 0.58–0.85) for the highest versus lowest intakes. The association was stronger for unfermented soy foods (including soy milk, tofu, and soybeans) and was not significant for fermented soy foods (miso and natto). In addition, the inverse association was more pronounced among the nine case-control studies than in the seven prospective cohort studies. In four prospective studies that examined risk of advanced disease specifically there was no association with soy intake. The meta-analysis also included nine studies of circulating genistein and seven of circulating daidzein and found no association between these isoflavones and prostate cancer risk.

Another meta-analysis of questionnaire-assessed phytoestrogen intakes [110] found a significant inverse association with total prostate cancer risk in 18 case-control studies (RR for highest versus lowest category 0.69, 95% CI 0.57–0.81) and a borderline significant inverse association in 11 cohorts studies (RR 0.87, 95% CI 0.89–1.00). However, there was a suggestion of publication bias. In addition, the borderline significant association in prospective studies suggests that selection and/or recall bias may explain some of the results seen in the case-control studies.

The Multiethnic Cohort Study (MEC) [111], conducted among men in Hawaii and California, was the largest study included in both meta-analyses. There was a suggestion of an inverse association between soy foods and overall prostate cancer risk (HR 0.90, 95% CI 0.80–1.01, p-trend = 0.20 for the highest versus lowest tertile), and a borderline significant association for high-grade or nonlocalized prostate (HR 0.78, 95% CI 0.62–0.98, p-trend = 0.05). There was no inverse association between soy food and prostate cancer risk among the Japanese-American men in the study, who had higher soy intakes than the white, Latino, and African-American men. Two cohort studies in Japan that involved study populations with much higher soy intake than in MEC found suggestive, but not statistically significant, inverse associations with prostate cancer [112, 113].

Overall, weak inverse associations have been observed between soy and isoflavone intake; however, the lack of association for circulating isoflavone levels, along with the weaker results among prospective studies and among populations with higher soy intake suggest that the observed associations may be due to bias (selection bias, recall bias, confounding) rather than an underlying causal association. Additional prospective cohort studies are needed in populations with high soy intake to determine whether there is, in fact, an inverse association with disease risk.

Survival. One clinical trial [114] of soy protein supplementation and biochemical recurrence enrolled 177 men at high risk of recurrence following radical prostatectomy and randomized them to a daily soy protein isolate supplement versus placebo. Treatment lasted up to two years. The trial was stopped early due to a lack of treatment effect. It should be noted that adding soy protein isolate to an overall western dietary pattern has different nutritional effects than substituting soy foods for other foods in the diet, which is what was studied in the epidemiological studies of prostate cancer incidence discussed above. The association between soy food or isoflavone intake and long-term survival among men with prostate cancer has not been studied.

Vitamin E and Alpha-tocopherol

Vitamin E refers to a group of fat-soluble compounds, including tocopherols and tocotrienols, which have antioxidant and pro-immune properties. Gamma-tocopherol is the most common tocopherol in the US diet, but plasma levels of alpha-tocopherol are higher than those of gamma-tocopherol [115]. Alpha-tocopherol is the

biologically most active form, and current dietary recommendations for vitamin E in the US are based on alpha-tocopherol alone. Possible anti-carcinogenic actions of vitamin E include its ability to reduce DNA damage and inhibit malignant cellular transformation [116, 117]. In experimental models, derivatives of vitamin E inhibit growth, induce apoptosis, and enhance therapeutic effects in human prostate cancer cells [118, 119].

Interest in Vitamin E with respect to prostate cancer was driven by secondary results of the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study [120]. ATBC was a randomized trial of lung cancer prevention among male smokers in Finland. While alpha-tocopherol supplementation had no effect on lung cancer risk, men given alpha-tocopherol had a 32% reduction in prostate cancer risk compared to placebo [121]. Several years earlier, a large trial of a multi-nutrient supplement in Linxian, China found that vitamin E (in combination with selenium and beta-carotene) reduced overall cancer mortality [122]. These results, along with laboratory evidence and some epidemiologic support, motivated two trials of vitamin E supplementation on the risk of prostate cancer, SELECT and the Physicians' Health Study II (PHS II).

SELECT was a trial of selenium and vitamin E supplementation and prostate cancer risk, conducted among 35,533 men from the US, Canada, and Puerto Rico. The study was planned for 7–12 years but was stopped early due to a lack of efficacy for risk reduction [123]. The initial report, based on an average of 5.5 years of treatment, found a non-significant suggestion of *increased* prostate cancer risk among men receiving 400 IU/day of alpha-tocopherol. With additional follow-up time, the vitamin E group was found to have a significantly increased risk of prostate cancer (RR 1.17, 99% CI 1.004–1.36, $p = 0.008$, among 1149 cases) [124]. Interestingly, there was not a statistically significant increased risk of prostate cancer in the vitamin E and selenium combination group (HR 1.05, 95% CI 0.89–1.22), suggesting the two may interact. In fact, SELECT was designed as a four-group trial rather than a factorial trial based on the hypothesis that the two agents, both of which have antioxidant activity, may interact [125].

PHS II, conducted contemporaneously with SELECT, was a randomized trial of vitamin E and vitamin C supplement use and prostate cancer risk among 14,642 US physicians. With a median of 8 years of follow-up, there was no effect of 400 IU of vitamin E taken every other day on incidence of prostate cancer (HR 0.97, 95% CI 0.85–1.09) [126]. PHS II was a factorial design, so the vitamin E estimate was made across groups of vitamin C supplement use; however, there was no suggestion of an interaction between vitamin E and vitamin C supplementation.

Together, the SELECT and PHS II results suggest that vitamin E supplement use is at best ineffective and possibly harmful with respect to prostate cancer risk. This is in contrast to the ATBC findings that spurred these trials. Of note, all men in the ATBC trial were smokers, and the prostate cancers were diagnosed prior to the advent of PSA screening, and thus were generally aggressive. The SELECT and PHS II trials were done in the PSA screening era and could not specifically study advanced or fatal prostate cancers. Of 2279 prostate cancers diagnosed in SELECT through July 2011, only nine were diagnosed with stage T3 disease, three with N1 disease, and 13 with metastatic disease. Even the ability to study high-grade cancer was limited, with 613 (27%) cases grade 7 and above, only 134 of which were grade 8–10 [124]. In addition, only 8% of men in SELECT and 4% of men in PHS II were current smokers, so neither trial could address the effect of vitamin E specifically among smokers.

Interestingly, epidemiological studies of vitamin E and prostate cancer risk have tended to support the ATBC results, with generally null associations for overall prostate cancer, but inverse associations for advanced disease and among smokers. In the VITamins And Lifestyle (VITAL) study, a cohort study in Washington state designed specifically to examine supplement use and cancer risk, intake of supplemental vitamin E over 10 years was not associated with overall prostate cancer risk, but was associated

with a reduced risk of advanced prostate cancer (n = 123; HR 0.43, 95% CI 0.19–1.0 for average intake ≥400 IU/day vs. none) [127]. Other epidemiological studies have similarly found a protective association limited to ever smokers, including a prospective study of dietary vitamin E intake [128], and a study of vitamin E supplementation and lethal prostate cancer risk [129].

A pooled analysis of 13 prospective studies of blood alpha-tocopherol and prostate cancer risk found significant inverse associations overall and for advanced prostate cancer (regionally invasive, distant metastatic, or fatal cancer), with an odds ratio for advanced disease of 0.74 (95% CI 0.59–0.92; p-trend = 0.001) for the highest versus lowest quintile, based on 1226 advanced cases [130]. There was significant heterogeneity by disease aggressiveness, with no association for non-advanced disease. In addition, there was no association among never smokers (OR 0.99, 95% CI 0.82–1.18), and significant inverse associations for former and current smokers (OR 0.84, 95% CI 0.72–0.97 for former; OR 0.82, 95% CI 0.73–0.93 for current), although the p-value for heterogeneity by smoking was not statistically significant.

Overall, use of vitamin E supplements for prostate cancer prevention is not supported; however, diets higher in alpha-tocopherol appear to be associated with lower risk of advanced disease, particularly among smokers. The underlying mechanisms for this association among smokers are unclear.

Selenium

The trace element selenium is not itself an antioxidant, but it is an essential element for the antioxidant enzyme glutathione peroxidase. It is also required for the function of other selenoproteins involved in exerting anti-tumor effects, including apoptosis and inhibition of cellular proliferation [131–133]. Dietary intake of selenium depends on the selenium content of soil in which foods are grown, which varies greatly by geography. Ecologic studies have suggested an inverse association between selenium soil content and prostate cancer incidence [134]. Because selenium contents in specific foods vary based on the selenium content of the soil, epidemiological studies of selenium must be based on biological sampling, primarily measuring selenium levels in blood or toenails, rather than questionnaire-based diet assessments. Since the activity of some selenoenzymes plateau with higher selenium level [135], the chemopreventive effect of supplemental selenium is expected to be greatest in populations with low baseline selenium exposure, with little marginal effect among selenium-replete populations [136].

Like vitamin E, selenium was tested in the SELECT trial based on secondary results of other randomized trials. The Nutritional Prevention of Cancer Trial, designed to study the effect of selenium supplementation on non-melanoma skin cancer recurrence, found a 63% reduction in prostate cancer risk among men taking selenium supplements [137]. With additional follow-up time, the protective effect was seen only among men with low baseline levels of PSA or selenium [136]. Another trial of selenium (with vitamin E and beta-carotene) in Linxian, China found a reduction in total cancer mortality in China [122].

As discussed above, the SELECT trial was stopped early due to lack of efficacy of the supplements [123]. With additional follow-up, there was still no association between selenium and prostate cancer risk (RR 1.09, 99% CI 0.93–1.27) [124]. In addition, baseline selenium status (measured in toenails) was not associated with prostate cancer risk among men in the trial, and baseline status did not modify the association between selenium supplementation and risk [138]. As with vitamin E, conclusions about selenium drawn from SELECT are limited by the small number of advanced and high-grade cases.

A recent Mendelian randomization study [139] among over 70,000 men in the PRACTICAL consortium used a gene score based on 11 SNPs that predict circulating selenium levels as a non-confounded proxy for selenium status to investigate whether selenium might be causally related to prostate cancer risk. The results were similar to SELECT, with no association with overall prostate cancer risk. There was a non-significant

suggestion of increased risk of aggressive disease (OR = 1.21, 95% CI 0.98–1.49). However, the genetic instrument, while very significantly associated with circulating selenium levels ($p < 5 \times 10^{-8}$), explained only 2.5–5% of variation in these levels, limiting how informative this study is for shedding light on the true association between circulating selenium and prostate cancer risk.

In contrast to the SELECT results, observational studies of selenium and prostate cancer risk have been quite consistent in finding inverse associations. A recent pooled analysis [140] of individual-level data from 15 prospective studies found that nail selenium levels were associated with lower risk of total and aggressive prostate cancer, while blood levels were associated with lower risk of aggressive disease. For aggressive prostate cancer, the OR for men in the highest versus lowest quintile of nail selenium was 0.18 (95% CI 0.11–0.31), and for blood selenium was 0.43 (95% CI 0.21–0.87). A recent report from a Danish cohort [141] also found an inverse association between plasma selenium and risk of high-grade prostate cancer (HR 0.77, 95% CI 0.64–0·94, p-trend = 0.009) but no association with total or advanced stage disease. Two recent meta-analyses of blood selenium [142] and toenail selenium [143] also found significant inverse associations.

These results are unusually consistent and strong among studies of dietary factors and prostate cancer risk. Because selenium status depends on the geographical source of foods in the diet rather than the selection of specific foods, it is difficult to imagine how confounding by other aspects of a healthy diet or lifestyle could explain the magnitude of the results from observational studies. The results of the SELECT trial do not support the use of selenium supplements for the prevention of prostate cancer in middle-aged and older men. However, the association between selenium and prostate cancer risk and survival is still not completely clear.

Survival. A study in HPFS found that use of selenium supplements of 140 mcg/day was associated with significantly increased risk of prostate cancer mortality among men diagnosed with localized prostate cancer. The association was independent of pre-diagnosis supplement use, use of other supplements, and stage and grade of disease at diagnosis [144]. The authors suggest the possibility of a U-shaped relationship between selenium status and cancer incidence and progression, with adverse effects at very low and very high levels.

Other Lifestyle Factors

Tobacco

Although strongly linked to a number of cancers, cigarette smoking does not appear to be associated with overall prostate cancer incidence. A meta-analysis [145] of 15 studies prior to 1995 (i.e., the pre-PSA era), found a pooled relative risk for current smoking and risk of prostate cancer of 1.06 (95% CI 0.98–1.15). For 18 studies completed after 1995 (the PSA screening era), there was a significant inverse association with current smoking (RR 0.84, 95% CI 0.79–0.89). This likely reflects the fact that current smokers are less likely to undergo PSA screening and are therefore not as likely as non-smokers to be diagnosed with prostate cancer. This heterogeneity by time period highlights the importance of accounting for PSA screening in studies of prostate cancer incidence. A previous meta-analysis [146] similarly found no association between current smoking and prostate cancer incidence; however, it did show a positive association with risk among the heaviest smokers measured by cigarettes per day or pack-years.

In contrast to the lack of association for overall prostate cancer, a positive association between smoking and prostate cancer mortality has been documented consistently, as noted by the Surgeon General's 2014 report [147]. A meta-analysis of 21 prospective cohort studies of smoking and prostate cancer mortality found that current cigarette smoking was associated with a 24% increased risk of fatal disease (95% CI 18–31%), with little evidence of heterogeneity between studies [145]. There was a significant dose-response relationship between number of

cigarettes smoked per day and mortality. There was a suggestion of increased risk for former smoking and subsequent prostate cancer mortality, with a 6% increase in risk (95% CI 0–13%). In the HPFS cohort smokers who had quit less than 10 years previously were at increased risk of fatal prostate cancer (HR 1.73, 95% CI 1.00–3.01), but that longer-term former smokers were not at significantly increased risk (HR 1.04, 95% CI 0.66–1.64). Thus smoking is consistently observed to be associated with risk of advanced or fatal prostate cancer and appears to play a role in disease progression, in spite of its lack of association with overall incidence.

Survival. In line with findings on incidence of lethal disease, studies of smoking and survival among prostate cancer patients suggests that smoking is associated with increased prostate cancer-specific mortality as well as total mortality [148–154]. A pooled analysis of five prospective cohort studies found that current smoking was associated with a 40% higher risk of prostate cancer mortality (95% CI 20–70%) among prostate cancer patients [155]. A meta-analysis of 28 studies including both population-based and clinically-based study populations with varying treatments found that current smokers at treatment have worse overall mortality (HR 1.96, 95% CI 1.69–2.28), prostate cancer-specific mortality (HR 1.79, 95% CI 1.47–2.20), and recurrence-free survival (HR 1.48, 95% CI 1.28–1.72) than never smokers. Virtually all of the included studies adjusted for age at diagnosis, stage, and grade, and associations were similar across studies judged at high or low risk of bias. Another meta-analysis [156] among patients with localized prostate cancer undergoing primary radical prostatectomy or radiotherapy found very similar results.

Obesity

Because obesity can influence endogenous levels of sex hormones [157, 158], as well as the insulin/IGF axis, both of which are relevant to prostate cancer, it has been studied in many epidemiologic studies. Body mass index (BMI), measured as height (m)/weight $(kg)^2$ is the most commonly used measure of obesity in these studies. At the population level, BMI is highly correlated with other measures of adiposity and is uncorrelated with height [159, 160]; it is strongly predictive of mortality [161]. However, it does not perform well in the very elderly, when high BMI may begin to reflect lean body mass rather than adiposity [162].

The association between BMI and total prostate cancer incidence is somewhat inconsistent. A meta-analysis of 27 studies found a borderline significant combined relative risk of 1.03 (95% CI 1.00–1.07, p = 0.11) per 5 unit increase in BMI [163]. However, BMI is consistently associated with a lower risk of localized disease but an increased risk of advanced disease. Because of this heterogeneity by stage, the association between BMI and total prostate cancer varies across populations depending on PSA screening and the case mix found in that time and place. A meta-analysis of 13 prospective studies [164] found a relative risk per 5 unit increase in BMI of 0.94 (95% CI 0.91–0.97) for localized prostate cancer, and 1.09 (95% CI 1.02–1.16) for advanced prostate cancer. (The definitions of localized and advanced were a mix of advanced stage and high-grade, depending on the original studies.)

The AICR/WCRF Continuous Update Project report on prostate cancer [10] concluded that greater body fatness is a "probable" cause of advanced prostate cancer. Their meta-analysis of 23 studies of advanced cancer found a relative risk per 5 unit increase in BMI of 1.08 (95% CI 1.04–1.12). For 12 studies of prostate cancer mortality, the combined relative risk per 5 unit increase in BMI was 1.11 (95% CI 1.06–1.17). These results are consistent with more recently published results from the large European EPIC cohort [165], which found a hazard ratio for fatal prostate cancer of 1.14 (95% CI 1.02–1.27) per five unit increase in BMI. Two recent meta-analyses [164, 166] also found similar magnitudes of association with prostate cancer mortality, as did a pooled analysis of 57 prospective studies [167] from Europe, Japan, and the USA, comprising 1242 prostate cancer deaths.

The NIH-AARP cohort [168], which includes over 150,000 U.S. men, studied BMI trajectories from early adulthood onward. The BMI trajectories were not associated with total prostate cancer incidence. However, among never-smokers, BMI trajectories that resulted in obesity during adulthood were associated with a twofold increased risk of fatal prostate cancer compared to men who maintained a healthy BMI. These results highlight the importance of accounting for smoking in studies of obesity due to the strong inverse association between smoking and body weight and the positive association between smoking and prostate cancer survival.

Survival. Higher BMI is fairly consistently associated with poorer outcomes among men diagnosed with prostate cancer. In a meta-analysis of six studies of survival after prostate cancer diagnosis, the relative risk of prostate cancer mortality was 1.20 (95% CI 0.99–1.46) for a five unit increase in BMI around the time of diagnosis or treatment [164]. There was significant heterogeneity in this estimate due to the inclusion of the largest study, which found a non-significant inverse association with mortality based on 4 years of follow-up. Two studies among men with prostate cancer in Sweden published after the meta-analysis found significantly increased risks of prostate cancer-specific mortality with higher BMI [169, 170]. In 16 studies of biochemical recurrence after treatment, a five unit increase in BMI was associated with a relative risk of 1.21 (95% CI 1.11–1.31) [164].

Body Size in Early Life

Childhood obesity is inconsistently associated with adult prostate cancer risk. Four studies have examined pre-puberty body size (8–10 years) [171–174], with two reporting inverse associations, including for advanced disease [172, 173], while two others found no associations [171, 174]. One of these studies was from HPFS [174], which was an update of a previous report from this cohort [175], which found significant inverse associations between obesity at age 10 and risk of advanced and metastatic disease. However, this association was no longer observed with 16 additional years of follow-up. It is possible that childhood body size influences risk of prostate cancer less among older men. One study of body size at the time of puberty also found no association with prostate cancer risk [176].

The HPFS found an inverse association between BMI at age 21 and risk of advanced and lethal (death or distant metastasis) prostate cancer, independent of later life and earlier life body size [174]. Two other studies found similar inverse associations with advanced [172] or fatal [177] disease; however, other studies have found no associations [178–181]. A review of studies on total prostate cancer incidence suggested no relationship or a weak positive relationship [182].

Adiposity is known to increase estrogen and decrease androgen serum concentrations in men [157]. Hence, a childhood or early adult hormonal milieu characterized by low exposure to the stimulating effect of androgens on the prostate might protect against the disease. However, overall there is no consistent association between childhood and young adult body size and prostate cancer risk.

Weight Change

A meta-analysis of adult weight gain, from around age 18 to 25 until study entry in mid or late life and risk of prostate cancer found no clear association with overall risk [183]. Among eight prospective studies, the combined relative risk for the highest versus lowest weight gain category was 0.98 (95% CI 0.91–1.06). A dose-response meta-analysis of four studies also found no association, but there was a suggestion of an inverse association for localized disease (RR 0.96 for 5 kg weight gain, 95% CI 0.92–1.00) and a suggestion of a positive association for advanced disease at diagnosis (RR 1.04 for 5 kg weight gain, 95% CI 0.99–1.09). In line with these suggestive findings, several cohort studies have found significant positive associations between adult weight gain and prostate cancer mortality [181, 184, 185].

Given that obesity itself is associated with increased risk of advanced and fatal prostate cancer, it is difficult to separate the effect of weight gain during adulthood from the effect of obesity. The large NIH-AARP study [168] discussed above found a similar increase in risk of fatal prostate cancer among never smokers for all weight change trajectories ending in obesity, regardless of the specific timing of the weight gain. A study [186] among men diagnosed with localized prostate cancer in the HPFS cohort found that weight gain from age 21 to the time of diagnosis was associated with worse survival among never smoking men, whereas BMI itself at the time of diagnosis was not associated with survival.

Four studies have examined short-term weight gain around the time of prostate cancer diagnosis. Two studies used mortality as the outcome. One [169] found a significantly increased risk of prostate cancer-specific mortality for weight gain of >5% compared to stable weight in the 5–10 years after diagnosis of localized prostate cancer, and a significantly increased risk of total mortality for weight loss of >5%. Another [186] found no association between weight change in the 4 or 8 years prior to diagnosis and prostate cancer mortality among men diagnosed with localized disease. Two other studies among men treated with prostatectomy reported that weight gain in the year before surgery [187] or from 1 year before to 5 years after surgery [188] were associated with increased risk of biochemical recurrence. Additional studies of the role of weight changes before and after diagnosis and prostate cancer survival are needed.

Physical Activity

Physical activity is associated with reduced risk of several types of cancer. Multiple biological mechanisms for this have been proposed, including enhanced immune system function [189], changes in the endogenous hormonal milieu [190–192], reduction in inflammation [193–196], and reduced obesity [197]. Both obesity and metabolic syndrome have been associated with increased risk of advanced prostate cancer and worse prostate cancer-specific survival and response to hormonal therapy [198], so the positive systemic effects of exercise may impact prostate cancer risk and survival.

Physical activity has not been associated with overall prostate cancer risk. A meta-analysis [199] of 27 cohort studies and 23 case-control studies found a summary relative risk of 0.99 (95% CI 0.94–1.04) comparing the highest versus lowest categories of activity. Interestingly, a population-based Norwegian cohort study [200], which also found no association between higher levels of activity and risk of overall prostate cancer, did report a positive association between sitting time and risk. Men who reported sitting for 8 or more hours per day had a 22% (95% CI 5–42%) increased risk of prostate cancer compared to those who reported less than 8 h/day of sitting time.

Results on the association between physical activity and risk of advanced or fatal disease are mixed. Two prospective cohort studies, HPFS [201] and the CPS II [202], found inverse associations between higher levels of recreational physical activity and the risk of advanced or fatal disease, independent of BMI. However, four other cohorts, EPIC [203], the NIH-AARP Diet and Health Study [204], the Swedish National March Cohort [205], and PHS [206] found no associations between greater activity and risk of disease by stage or grade. Overall, a meta-analysis [199] of 10 cohort studies found no association between pre-diagnosis physical activity and prostate cancer mortality, with a relative risk of 0.93 (95% CI 0.81–1.08) for the highest versus lowest categories of activity.

The assessment of long-term physical activity levels is challenging. Study participants are often asked to report on the type, intensity, and duration of their average physical activity, both currently and in the past. The resulting misclassification may be responsible for the weak and often nonsignificant findings. Subgroups less prone to measurement error, such as, men who engage in a consistent program of vigorous activity, may offer the best chance of detecting a relationship between exercise and prostate can-

cer if one exists. The HPFS analysis is unique in that it was based on repeated prospective assessments of physical activity every 2 years over 14 years of follow-up. It found significantly lower risks of advanced and fatal disease for high levels of vigorous activity, but not for more moderate activity [201]. It is possible that repeated assessments of physical activity over time and study populations with a wide range of activity, including very active participants, is required for an inverse association between physical activity and advanced prostate cancer risk to emerge.

Survival. Physical activity may improve prostate cancer survival and may also ameliorate some of the adverse effects of therapy [207].

The few observational studies of activity after diagnosis and prostate cancer progression have reported beneficial associations. A meta-analysis [199] of four cohort studies of physical activity after diagnosis and prostate cancer mortality found a significant inverse association, with a relative risk of 0.69 (95% CI 0.55–0.85) comparing the highest to lowest activity categories. In the HPFS cohort, both moderate activity (≥2.5 h/week) and vigorous activity (≥1.25 h/week) were both associated with significantly improved overall and prostate cancer-specific survival [208, 209]. The authors estimated that 13–16% of deaths among men diagnosed with non-metastatic prostate cancer in the study population would have been prevented over 10 years if all men had engaged in 1.25 h/week or more of vigorous activity, and 5–10% of deaths could have been avoided with engagement in moderative activity.

A study of PSA recurrence in prostate cancer patients found similar decreases in risk with higher activity levels [210]. This lends support to the results for mortality because PSA recurrence is less susceptible to bias due to reverse causation (i.e., decreasing activity levels in response to disease progression) than prostate cancer mortality is.

Overall, while evidence on physical activity and prostate cancer incidence is mixed, it appears that activity is beneficial among men with prostate cancer.

Summary and Future Directions

Although an inherited genetic component may be larger for prostate cancer than for most other malignancies, evidence that lifestyle factors are important is also overwhelming; the substantial geographic variation and changing incidence among migrants demonstrate this as well. A summary of the evidence for diet and other lifestyle factors and prostate cancer risk is provided in Table 2. Substantial data supports that smoking and obesity/higher BMI are associated with increased risk of advanced prostate cancer, while obesity it inversely associated with risk of localized disease. In addition, an inverse association between vigorous activity and risk of advanced disease seems likely. Dietary factors associated with prostate cancer risk and survival are less well established. Of those studied, it seems probable that dairy intake is associated with increased risk, while fish intake and lycopene/tomato intake are associated with lower risk. However, even these dietary factors remain somewhat controversial within the research community.

Aside from these three dietary factors, most of the evidence on diet and prostate cancer is inconclusive. The role of calcium, vitamin D, and soy/phytoestrogen intake remains to be clarified. And the SELECT trial has complicated the interpretation of the data on Vitamin E and selenium.

SELECT and PHS II established that use of Vitamin E supplements in middle age and later are at best not protective, and possibly harmful, with respect to prostate cancer risk. However, circulating levels of vitamin E are very consistently associated with lower risk in observational studies, with no clear sources of confounding or other biases that might explain these results. The role of dietary and supplemental Vitamin E thus remains uncertain.

SELECT also found that use of selenium supplements in middle age and beyond are not protective for prostate cancer. However, observational studies are quite consistent in finding a substantially lower risk of prostate cancer among men with higher toenail or blood levels of selenium, and again, there are no clear sources of confounding or other bias that seem to explain these

results. Thus the role of selenium in prostate cancer remains unclear and controversial.

Finally, the clear positive associations between height and circulating IGF-1 and prostate cancer risk, along with the long natural history of prostate cancer, suggest that dietary factors in childhood and adolescence likely impact prostate cancer risk; however, specific relationships have yet to be established, as studying early life exposures presents methodological challenges.

In practical terms, men concerned with prostate cancer risk should be encouraged to stop smoking, be as physically active as possible, and achieve or maintain a healthy weight. These recommendations also have the advantage of having a positive impact on risk of type 2 diabetes, cardiovascular disease, and other chronic diseases. Reducing dairy intake while increasing consumption of fish and tomato products is also reasonable advice. Finally, men should be counseled against taking Vitamin E or selenium supplements at levels higher than those found in multivitamins. (This is particularly true for Vitamin E given that meta-analysis of randomized trials find that high-dose Vitamin E supplements increase total mortality [211, 212].) Further research is needed to support more specific dietary recommendations for prostate cancer prevention and for preventing recurrence and progression in prostate cancer patients.

References

1. H. Shimizu, R.K. Ross, L. Bernstein, R. Yatani, B.E. Henderson, T.M. Mack, Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br. J. Cancer **63**(6), 963–966 (1991)
2. G. Maskarinec, J.J. Noh, The effect of migration on cancer incidence among Japanese in Hawaii. Ethn. Dis. **14**(3), 431–439 (2004)
3. J. Lee, K. Demissie, S.E. Lu, G.G. Rhoads, Cancer incidence among Korean-American immigrants in the United States and native Koreans in South Korea. Cancer Control **14**(1), 78–85 (2007)
4. A.J. Hanley, B.C. Choi, E.J. Holowaty, Cancer mortality among Chinese migrants: a review. Int. J. Epidemiol. **24**(2), 255–265 (1995)
5. M. McCredie, S. Williams, M. Coates, Cancer mortality in migrants from the British Isles and continental Europe to New South Wales, Australia, 1975-1995. Int. J. Cancer **83**(2), 179–185 (1999)
6. L.A. Mucci, J.B. Hjelmborg, J.R. Harris, et al., Familial risk and heritability of cancer among twins in nordic countries. JAMA **315**(1), 68–76 (2016)
7. J.L. Jahn, E.L. Giovannucci, M.J. Stampfer, The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the Prostate-specific Antigen-era. Int. J. Cancer **137**(12), 2795–2802 (2015)
8. J.R. Stark, S. Perner, M.J. Stampfer, et al., Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J. Clin. Oncol. **27**(21), 3459–3464 (2009)
9. D.P. Rose, A.P. Boyar, E.L. Wynder, International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. Cancer **58**(11), 2363–2371 (1986)
10. D. Aune, D.A. Navarro Rosenblatt, D.S. Chan, et al., Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am. J. Clin. Nutr. **101**(1), 87–117 (2015)
11. G.D. Batty, F. Barzi, M. Woodward, et al., Adult height and cancer mortality in Asia: the Asia Pacific Cohort Studies Collaboration. Ann. Oncol. **21**(3), 646–654 (2010)
12. Emerging Risk Factors C, Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int. J. Epidemiol. **41**(5), 1419–1433 (2012)
13. L.A. Proos, Anthropometry in adolescence—secular trends, adoption, ethnic and environmental differences. Horm. Res. **39**(Suppl 3), 18–24 (1993)
14. T.J. Cole, Secular trends in growth. Proc. Nutr. Soc. **59**(2), 317–324 (2000)
15. J. Fudvoye, A.S. Parent, Secular trends in growth. Ann. Endocrinol. (Paris) **78**(2), 88–91 (2017)
16. A. Juul, P. Bang, N.T. Hertel, et al., Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J. Clin. Endocrinol. Metab. **78**(3), 744–752 (1994)
17. G. Beunen, M. Thomis, H.H. Maes, et al., Genetic variance of adolescent growth in stature. Ann. Hum. Biol. **27**(2), 173–186 (2000)
18. A.S. Wiley, Does milk make children grow? Relationships between milk consumption and height in NHANES 1999-2002. Am. J. Hum. Biol. **17**(4), 425–441 (2005)
19. S.J. Whiting, H. Vatanparast, A. Baxter-Jones, R.A. Faulkner, R. Mirwald, D.A. Bailey, Factors that affect bone mineral accrual in the adolescent growth spurt. J. Nutr. **134**(3), 696S–700S (2004)
20. A. Alimujiang, G.A. Colditz, J.D. Gardner, Y. Park, C.S. Berkey, S. Sutcliffe, Childhood diet and growth in boys in relation to timing of puberty and adult height: the Longitudinal Studies of Child Health and Development. Cancer Causes Control **29**(10), 915–926 (2018)

21. L.E. Underwood, Nutritional regulation of IGF-I and IGFBPs. J. Pediatr. Endocrinol. Metab. **9**(Suppl 3), 303–312 (1996)
22. E. Giovannucci, M. Pollak, Y. Liu, et al., Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. Cancer Epidemiol. Biomark. Prev. **12**(2), 84–89 (2003)
23. W.J. Smith, L.E. Underwood, D.R. Clemmons, Effects of caloric or protein restriction on insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children and adults. J. Clin. Endocrinol. Metab. **80**(2), 443–449 (1995)
24. L.B. Signorello, H. Kuper, P. Lagiou, et al., Lifestyle factors and insulin-like growth factor 1 levels among elderly men. Eur. J. Cancer Prev. **9**(3), 173–178 (2000)
25. A.W. Roddam, N.E. Allen, P. Appleby, et al., Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. Ann. Intern. Med. **149**(7), 461–471 (2008)., W483-468
26. M.A. Rowlands, D. Gunnell, R. Harris, L.J. Vatten, J.M. Holly, R.M. Martin, Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. Int. J. Cancer **124**(10), 2416–2429 (2009)
27. C. Xu, F.F. Han, X.T. Zeng, T.Z. Liu, S. Li, Z.Y. Gao, I. Fat Intake, Not linked to prostate cancer: a systematic review and dose-response meta-analysis. PLoS One **10**(7), e0131747 (2015)
28. J.A. Simon, Y.H. Chen, S. Bent, The relation of alpha-linolenic acid to the risk of prostate cancer: a systematic review and meta-analysis. Am. J. Clin. Nutr. **89**(5), 1558S–1564S (2009)
29. M. Carayol, P. Grosclaude, C. Delpierre, Prospective studies of dietary alpha-linolenic acid intake and prostate cancer risk: a meta-analysis. Cancer Causes Control **21**(3), 347–355 (2010)
30. A.J. Carleton, J.L. Sievenpiper, R. de Souza, G. McKeown-Eyssen, D.J. Jenkins, Case-control and prospective studies of dietary alpha-linolenic acid intake and prostate cancer risk: a meta-analysis. BMJ Open **3**(5) (2013)
31. E. Giovannucci, Y. Liu, E.A. Platz, M.J. Stampfer, W.C. Willett, Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int. J. Cancer **121**(7), 1571–1578 (2007)
32. J. Wu, K.M. Wilson, M.J. Stampfer, W.C. Willett, E.L. Giovannucci, A 24-year prospective study of dietary alpha-linolenic acid and lethal prostate cancer. Int. J. Cancer **142**(11), 2207–2214 (2018)
33. D.O. Koralek, U. Peters, G. Andriole, et al., A prospective study of dietary alpha-linolenic acid and the risk of prostate cancer (United States). Cancer Causes Control **17**(6), 783–791 (2006)
34. A.G. Schuurman, P.A. van den Brandt, E. Dorant, H.A. Brants, R.A. Goldbohm, Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study. Cancer **86**(6), 1019–1027 (1999)
35. S.Y. Park, S.P. Murphy, L.R. Wilkens, B.E. Henderson, L.N. Kolonel, Fat and meat intake and prostate cancer risk: the multiethnic cohort study. Int. J. Cancer **121**(6), 1339–1345 (2007)
36. F.L. Crowe, P.N. Appleby, R.C. Travis, et al., Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies. J. Natl. Cancer Inst. **106**(9) (2014)
37. E.L. Van Blarigan, S.A. Kenfield, M. Yang, et al., Fat intake after prostate cancer diagnosis and mortality in the Physicians' Health Study. Cancer Causes Control **26**(8), 1117–1126 (2015)
38. E.L. Richman, S.A. Kenfield, J.E. Chavarro, et al., Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. JAMA Intern. Med. **173**(14), 1318–1326 (2013)
39. M.M. Epstein, J.L. Kasperzyk, L.A. Mucci, et al., Dietary fatty acid intake and prostate cancer survival in Orebro County, Sweden. Am. J. Epidemiol. **176**(3), 240–252 (2012)
40. D.D. Alexander, P.J. Mink, C.A. Cushing, B. Sceurman, A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer. Nutr. J. **9**, 50 (2010)
41. K. Wu, D. Spiegelman, T. Hou, et al., Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: a pooled analysis of 15 prospective cohort studies. Int. J. Cancer **138**(10), 2368–2382 (2016)
42. J.M. Major, A.J. Cross, J.L. Watters, A.R. Hollenbeck, B.I. Graubard, R. Sinha, Patterns of meat intake and risk of prostate cancer among African-Americans in a large prospective study. Cancer Causes Control **22**(12), 1691–1698 (2011)
43. E.L. Richman, S.A. Kenfield, M.J. Stampfer, E.L. Giovannucci, J.M. Chan, 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.) **4**(12), 2110–2121 (2011)
44. A.M. Gilsing, M.P. Weijenberg, R.A. Goldbohm, P.C. Dagnelie, P.A. van den Brandt, L.J. Schouten, Vegetarianism, low meat consumption and the risk of lung, postmenopausal breast and prostate cancer in a population-based cohort study. Eur. J. Clin. Nutr. **70**(6), 723–729 (2016)
45. R. Sinha, Y. Park, B.I. Graubard, 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. **170**(9), 1165–1177 (2009)
46. S. Koutros, A.J. Cross, D.P. Sandler, et al., Meat and meat mutagens and risk of prostate cancer in the Agricultural Health Study. Cancer Epidemiol. Biomark. Prev. **17**(1), 80–87 (2008)
47. S. Sharma, X. Cao, L.R. Wilkens, et al., Well-done meat consumption, NAT1 and NAT2 acetylator genotypes and prostate cancer risk: the multiethnic

cohort study. Cancer Epidemiol. Biomark. Prev. **19**(7), 1866–1870 (2010)
48. A. Sander, J. Linseisen, S. Rohrmann, Intake of heterocyclic aromatic amines and the risk of prostate cancer in the EPIC-Heidelberg cohort. Cancer Causes Control **22**(1), 109–114 (2011)
49. S. Rohrmann, K. Nimptsch, R. Sinha, et al., Intake of meat mutagens and risk of prostate cancer in a cohort of U.S. health professionals. Cancer Epidemiol. Biomark. Prev. **24**(10), 1557–1563 (2015)
50. A.J. Cross, U. Peters, V.A. Kirsh, et al., A prospective study of meat and meat mutagens and prostate cancer risk. Cancer Res. **65**(24), 11779–11784 (2005)
51. M. Yang, S.A. Kenfield, E.L. Van Blarigan, et al., Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. Cancer Prev. Res. (Phila.) **8**(6), 545–551 (2015)
52. K.M. Wilson, L.A. Mucci, B.F. Drake, et al., Meat, fish, poultry, and egg intake at diagnosis and risk of prostate cancer progression. Cancer Prev. Res. (Phila.) **9**(12), 933–941 (2016)
53. P.A. Nutting, W.L. Freeman, D.R. Risser, et al., Cancer incidence among American Indians and Alaska Natives, 1980 through 1987. Am. J. Public Health **83**(11), 1589–1598 (1993)
54. J. Zhang, S. Sasaki, K. Amano, H. Kesteloot, Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study. Prev. Med. **28**(5), 520–529 (1999)
55. E. Dewailly, G. Mulvad, H. Sloth Pedersen, J.C. Hansen, N. Behrendt, J.P. Hart Hansen, Inuit are protected against prostate cancer. Cancer Epidemiol. Biomark. Prev. **12**(9), 926–927 (2003)
56. J.M. Chan, P.H. Gann, E.L. Giovannucci, Role of diet in prostate cancer development and progression. J. Clin. Oncol. **23**(32), 8152–8160 (2005)
57. S.H. Nash, J.M. Schenk, A.R. Kristal, et al., Association between serum phospholipid fatty acids and intraprostatic inflammation in the placebo arm of the prostate cancer prevention trial. Cancer Prev. Res. (Phila.) **8**(7), 590–596 (2015)
58. T.M. Brasky, C. Till, E. White, et al., Serum phospholipid fatty acids and prostate cancer risk: results from the prostate cancer prevention trial. Am. J. Epidemiol. **173**(12), 1429–1439 (2011)
59. F.L. Crowe, N.E. Allen, P.N. Appleby, et al., Fatty acid composition of plasma phospholipids and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition. Am. J. Clin. Nutr. **88**(5), 1353–1363 (2008)
60. J.E. Chavarro, M.J. Stampfer, H. Li, H. Campos, T. Kurth, J. Ma, A prospective study of polyunsaturated fatty acid levels in blood and prostate cancer risk. Cancer Epidemiol. Biomark. Prev. **16**(7), 1364–1370 (2007)
61. K.M. Szymanski, D.C. Wheeler, L.A. Mucci, Fish consumption and prostate cancer risk: a review and meta-analysis. Am. J. Clin. Nutr. **92**(5), 1223–1233 (2010)
62. M. Aucoin, K. Cooley, C. Knee, et al., Fish-derived omega-3 fatty acids and prostate cancer: a systematic review. Integr. Cancer Ther. **16**(1), 32–62 (2017)
63. J.E. Torfadottir, U.A. Valdimarsdottir, L.A. Mucci, et al., Consumption of fish products across the lifespan and prostate cancer risk. PLoS One **8**(4), e59799 (2013)
64. J.E. Manson, N.R. Cook, I.M. Lee, et al., Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N. Engl. J. Med. **380**(1), 23–32 (2019)
65. K.M. Wilson, I.M. Shui, L.A. Mucci, E. Giovannucci, Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study. Am. J. Clin. Nutr. **101**(1), 173–183 (2015)
66. E. Giovannucci, Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control **9**(6), 567–582 (1998)
67. J. Ma, E. Giovannucci, M. Pollak, et al., Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. J. Natl. Cancer Inst. **93**(17), 1330–1336 (2001)
68. A. Berruti, L. Dogliotti, G. Gorzegno, et al., Differential patterns of bone turnover in relation to bone pain and disease extent in bone in cancer patients with skeletal metastases. Clin. Chem. **45**(8 Pt 1), 1240–1247 (1999)
69. A. Schneider, L.M. Kalikin, A.C. Mattos, et al., Bone turnover mediates preferential localization of prostate cancer in the skeleton. Endocrinology **146**(4), 1727–1736 (2005)
70. J. Sturge, M.P. Caley, J. Waxman, Bone metastasis in prostate cancer: emerging therapeutic strategies. Nat. Rev. Clin. Oncol. **8**(6), 357–368 (2011)
71. A. Pettersson, J.L. Kasperzyk, S.A. Kenfield, et al., Milk and dairy consumption among men with prostate cancer and risk of metastases and prostate cancer death. Cancer Epidemiol. Biomark. Prev. **21**(3), 428–436 (2012)
72. M.K. Downer, J.L. Batista, L.A. Mucci, et al., Dairy intake in relation to prostate cancer survival. Int. J. Cancer **140**(9), 2060–2069 (2017)
73. M. Yang, S.A. Kenfield, E.L. Van Blarigan, et al., Dairy intake after prostate cancer diagnosis in relation to disease-specific and total mortality. Int. J. Cancer **137**(10), 2462–2469 (2015)
74. R. Gilbert, C. Metcalfe, W.D. Fraser, et al., Associations of circulating 25-hydroxyvitamin D with prostate cancer diagnosis, stage and grade. Int. J. Cancer **131**(5), 1187–1196 (2012)
75. S. Gandini, M. Boniol, J. Haukka, et al., Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int. J. Cancer **128**(6), 1414–1424 (2011)
76. I.M. Shui, A.M. Mondul, S. Lindstrom, et al., Circulating vitamin D, vitamin D-related genetic variation, and risk of fatal prostate cancer in the

National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer **121**(12), 1949–1956 (2015)
77. J.M. Schenk, C.A. Till, C.M. Tangen, et al., Serum 25-hydroxyvitamin D concentrations and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. Cancer Epidemiol. Biomark. Prev. **23**(8), 1484–1493 (2014)
78. J. Brandstedt, M. Almquist, J. Manjer, J. Malm, D. Vitamin, PTH, and calcium and the risk of prostate cancer: a prospective nested case-control study. Cancer Causes Control **23**(8), 1377–1385 (2012)
79. D. Albanes, A.M. Mondul, K. Yu, et al., Serum 25-hydroxy vitamin D and prostate cancer risk in a large nested case-control study. Cancer Epidemiol. Biomark. Prev. **20**(9), 1850–1860 (2011)
80. A.R. Kristal, C. Till, X. Song, et al., Plasma vitamin D and prostate cancer risk: results from the Selenium and Vitamin E Cancer Prevention Trial. Cancer Epidemiol. Biomark. Prev. **23**(8), 1494–1504 (2014)
81. J.E. Manson, N.R. Cook, I.M. Lee, et al., Vitamin D supplements and prevention of cancer and cardiovascular disease. N. Engl. J. Med. **380**(1), 33–44 (2019)
82. R. Gilbert, R.M. Martin, R. Beynon, et al., Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. Cancer Causes Control **22**(3), 319–340 (2011)
83. S. Tretli, E. Hernes, J.P. Berg, U.E. Hestvik, T.E. Robsahm, Association between serum 25(OH) D and death from prostate cancer. Br. J. Cancer **100**(3), 450–454 (2009)
84. F. Fang, J.L. Kasperzyk, I. Shui, et al., Prediagnostic plasma vitamin D metabolites and mortality among patients with prostate cancer. PLoS One **6**(4), e18625 (2011)
85. I.M. Shui, L.A. Mucci, P. Kraft, et al., Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: a prospective nested case-control study. J. Natl. Cancer Inst. **104**(9), 690–699 (2012)
86. J. Brandstedt, M. Almquist, J. Manjer, J. Malm, D. Vitamin, PTH, and calcium in relation to survival following prostate cancer. Cancer Causes Control **27**(5), 669–677 (2016)
87. S.K. Holt, S. Kolb, R. Fu, R. Horst, Z. Feng, J.L. Stanford, Circulating levels of 25-hydroxyvitamin D and prostate cancer prognosis. Cancer Epidemiol. **37**(5), 666–670 (2013)
88. S.K. Holt, E.M. Kwon, J.S. Koopmeiners, et al., Vitamin D pathway gene variants and prostate cancer prognosis. Prostate **70**(13), 1448–1460 (2010)
89. L. Chen, G. Davey Smith, D.M. Evans, et al., Genetic variants in the vitamin D receptor are associated with advanced prostate cancer at diagnosis: findings from the prostate testing for cancer and treatment study and a systematic review. Cancer Epidemiol. Biomark. Prev. **18**(11), 2874–2881 (2009)
90. S. Gandini, P. Gnagnarella, D. Serrano, E. Pasquali, S. Raimondi, Vitamin D receptor polymorphisms and cancer. Adv. Exp. Med. Biol. **810**, 69–105 (2014)
91. W.K. Hendrickson, R. Flavin, J.L. Kasperzyk, et al., Vitamin D receptor protein expression in tumor tissue and prostate cancer progression. J. Clin. Oncol. **29**(17), 2378–2385 (2011)
92. E. Giovannucci, A. Ascherio, E.B. Rimm, M.J. Stampfer, G.A. Colditz, W.C. Willett, Intake of carotenoids and retinol in relation to risk of prostate cancer. J. Natl. Cancer Inst. **87**(23), 1767–1776 (1995)
93. J.L. Rowles 3rd, K.M. Ranard, J.W. Smith, R. An, J.W. Erdman Jr., Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. **20**(4), 361–377 (2017)
94. K. Zu, L. Mucci, B.A. Rosner, et al., Dietary lycopene, angiogenesis, and prostate cancer: a prospective study in the prostate-specific antigen era. J. Natl. Cancer Inst. **106**(2), djt430 (2014)
95. C. Gartner, W. Stahl, H. Sies, Lycopene is more bioavailable from tomato paste than from fresh tomatoes. Am. J. Clin. Nutr. **66**(1), 116–122 (1997)
96. E. Giovannucci, E.B. Rimm, Y. Liu, M.J. Stampfer, W.C. Willett, A prospective study of tomato products, lycopene, and prostate cancer risk. J. Natl. Cancer Inst. **94**(5), 391–398 (2002)
97. E.M. Grainger, C.W. Hadley, N.E. Moran, et al., A comparison of plasma and prostate lycopene in response to typical servings of tomato soup, sauce or juice in men before prostatectomy. Br. J. Nutr. **114**(4), 596–607 (2015)
98. C.M. Yang, Y.T. Yen, C.S. Huang, M.L. Hu, Growth inhibitory efficacy of lycopene and beta-carotene against androgen-independent prostate tumor cells xenografted in nude mice. Mol. Nutr. Food Res. **55**(4), 606–612 (2011)
99. S. Elgass, A. Cooper, M. Chopra, Lycopene inhibits angiogenesis in human umbilical vein endothelial cells and rat aortic rings. Br. J. Nutr. **108**(3), 431–439 (2012)
100. M.L. Chen, Y.H. Lin, C.M. Yang, M.L. Hu, Lycopene inhibits angiogenesis both in vitro and in vivo by inhibiting MMP-2/uPA system through VEGFR2-mediated PI3K-Akt and ERK/p38 signaling pathways. Mol. Nutr. Food Res. **56**(6), 889–899 (2012)
101. C.S. Huang, C.H. Chuang, T.F. Lo, M.L. Hu, Anti-angiogenic effects of lycopene through immunomodualtion of cytokine secretion in human peripheral blood mononuclear cells. J. Nutr. Biochem. **24**(2), 428–434 (2013)
102. L.A. Mucci, A. Powolny, E. Giovannucci, et al., Prospective study of prostate tumor angiogenesis and cancer-specific mortality in the health professionals follow-up study. J. Clin. Oncol. **27**(33), 5627–5633 (2009)
103. Y. Wang, E.J. Jacobs, C.C. Newton, M.L. McCullough, Lycopene, tomato products and prostate cancer-specific mortality among men

diagnosed with nonmetastatic prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Int. J. Cancer **138**(12), 2846–2855 (2016)
104. M.J. Messina, V. Persky, K.D. Setchell, S. Barnes, Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr. Cancer **21**(2), 113–131 (1994)
105. D.M. Tham, C.D. Gardner, W.L. Haskell, Clinical review 97: potential health benefits of dietary phytoestrogens: a review of the clinical, epidemiological, and mechanistic evidence. J. Clin. Endocrinol. Metab. **83**(7), 2223–2235 (1998)
106. H. Adlercreutz, W. Mazur, Phyto-oestrogens and Western diseases. Ann. Med. **29**(2), 95–120 (1997)
107. A. Bylund, J.X. Zhang, A. Bergh, et al., Rye bran and soy protein delay growth and increase apoptosis of human LNCaP prostate adenocarcinoma in nude mice. Prostate **42**(4), 304–314 (2000)
108. E. Kyle, L. Neckers, C. Takimoto, G. Curt, R. Bergan, Genistein-induced apoptosis of prostate cancer cells is preceded by a specific decrease in focal adhesion kinase activity. Mol. Pharmacol. **51**(2), 193–200 (1997)
109. C.C. Applegate, J.L. Rowles, K.M. Ranard, S. Jeon, J.W. Erdman, Soy consumption and the risk of prostate cancer: an updated systematic review and meta-analysis. Nutrients **10**(1) (2018)
110. M. Zhang, K. Wang, L. Chen, B. Yin, Y. Song, Is phytoestrogen intake associated with decreased risk of prostate cancer? A systematic review of epidemiological studies based on 17,546 cases. Andrology **4**(4), 745–756 (2016)
111. S.Y. Park, S.P. Murphy, L.R. Wilkens, B.E. Henderson, L.N. Kolonel, S. Multiethnic Cohort, Legume and isoflavone intake and prostate cancer risk: the Multiethnic Cohort Study. Int. J. Cancer **123**(4), 927–932 (2008)
112. N.E. Allen, C. Sauvaget, A.W. Roddam, et al., A prospective study of diet and prostate cancer in Japanese men. Cancer Causes Control **15**(9), 911–920 (2004)
113. N. Kurahashi, M. Iwasaki, S. Sasazuki, et al., Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol. Biomark. Prev. **16**(3), 538–545 (2007)
114. M.C. Bosland, I. Kato, A. Zeleniuch-Jacquotte, et al., Effect of soy protein isolate supplementation on biochemical recurrence of prostate cancer after radical prostatectomy: a randomized trial. JAMA **310**(2), 170–178 (2013)
115. Q. Jiang, Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radic. Biol. Med. **72**, 76–90 (2014)
116. M. Meydani, Vitamin E. Lancet **345**(8943), 170–175 (1995)
117. S.N. Meydani, M.G. Hayek, Vitamin E and aging immune response. Clin. Geriatr. Med. **11**(4), 567–576 (1995)
118. E.A. Ripoll, B.N. Rama, M.M. Webber, Vitamin E enhances the chemotherapeutic effects of adriamycin on human prostatic carcinoma cells in vitro. J. Urol. **136**(2), 529–531 (1986)
119. K. Gunawardena, D.K. Murray, A.W. Meikle, Vitamin E and other antioxidants inhibit human prostate cancer cells through apoptosis. Prostate **44**(4), 287–295 (2000)
120. Alpha-Tocopherol BCCPSG, The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N. Engl. J. Med. **330**(15), 1029–1035 (1994)
121. O.P. Heinonen, D. Albanes, J. Virtamo, et al., Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J. Natl. Cancer Inst. **90**(6), 440–446 (1998)
122. W.J. Blot, J.Y. Li, P.R. Taylor, et al., Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J. Natl. Cancer Inst. **85**(18), 1483–1492 (1993)
123. S.M. Lippman, E.A. Klein, P.J. Goodman, et al., Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA **301**(1), 39–51 (2009)
124. E.A. Klein, I.M. Thompson Jr., C.M. Tangen, et al., Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA **306**(14), 1549–1556 (2011)
125. S.M. Lippman, P.J. Goodman, E.A. Klein, et al., Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). J. Natl. Cancer Inst. **97**(2), 94–102 (2005)
126. J.M. Gaziano, R.J. Glynn, W.G. Christen, et al., Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA **301**(1), 52–62 (2009)
127. U. Peters, A.J. Littman, A.R. Kristal, R.E. Patterson, J.D. Potter, E. White, E. Vitamin, selenium supplementation and risk of prostate cancer in the Vitamins and lifestyle (VITAL) study cohort. Cancer Causes Control **19**(1), 75–87 (2008)
128. V.A. Kirsh, R.B. Hayes, S.T. Mayne, et al., Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. J. Natl. Cancer Inst. **98**(4), 245–254 (2006)
129. J.M. Chan, M.J. Stampfer, J. Ma, E.B. Rimm, W.C. Willett, E.L. Giovannucci, Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. Cancer Epidemiol. Biomark. Prev. **8**(10), 893–899 (1999)
130. T.J. Key, P.N. Appleby, R.C. Travis, et al., Carotenoids, retinol, tocopherols, and prostate cancer risk: pooled analysis of 15 studies. Am. J. Clin. Nutr. **102**(5), 1142–1157 (2015)
131. G.F. Combs Jr., S.B. Combs, The nutritional biochemistry of selenium. Annu. Rev. Nutr. **4**, 257–280 (1984)

132. C. Redman, J.A. Scott, A.T. Baines, et al., Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. Cancer Lett. **125**(1–2), 103–110 (1998)
133. D.G. Menter, A.L. Sabichi, S.M. Lippman, Selenium effects on prostate cell growth. Cancer Epidemiol. Biomark. Prev. **9**(11), 1171–1182 (2000)
134. M.P. Rayman, The importance of selenium to human health. Lancet **356**(9225), 233–241 (2000)
135. J. Neve, Human selenium supplementation as assessed by changes in blood selenium concentration and glutathione peroxidase activity. J. Trace Elem. Med. Biol. **9**(2), 65–73 (1995)
136. A.J. Duffield-Lillico, B.L. Dalkin, M.E. Reid, et al., Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int. **91**(7), 608–612 (2003)
137. L.C. Clark, G.F. Combs Jr., B.W. Turnbull, et al., Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA **276**(24), 1957–1963 (1996)
138. A.R. Kristal, A.K. Darke, J.S. Morris, et al., Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk. J. Natl. Cancer Inst. **106**(3), djt456 (2014)
139. J. Yarmolinsky, C. Bonilla, P.C. Haycock, et al., Circulating selenium and prostate cancer risk: a mendelian randomization analysis. J. Natl. Cancer Inst. **110**(9), 1035–1038 (2018)
140. N.E. Allen, R.C. Travis, P.N. Appleby, et al., Selenium and prostate cancer: analysis of individual participant data from fifteen prospective studies. J. Natl. Cancer Inst. **108**(11) (2016)
141. M. Outzen, A. Tjonneland, E.H. Larsen, et al., Selenium status and risk of prostate cancer in a Danish population. Br. J. Nutr. **115**(9), 1669–1677 (2016)
142. Z. Cui, D. Liu, C. Liu, G. Liu, Serum selenium levels and prostate cancer risk: a MOOSE-compliant meta-analysis. Medicine (Baltimore) **96**(5), e5944 (2017)
143. K. Sayehmiri, M. Azami, Y. Mohammadi, A. Soleymani, Z. Tardeh, The association between Selenium and Prostate Cancer: a systematic review and meta-analysis. Asian Pac. J. Cancer Prev. **19**(6), 1431–1437 (2018)
144. S.A. Kenfield, E.L. Van Blarigan, N. DuPre, M.J. Stampfer, L.G. E, J.M. Chan, Selenium supplementation and prostate cancer mortality. J. Natl. Cancer Inst. **107**(1), 360 (2015)
145. F. Islami, D.M. Moreira, P. Boffetta, S.J. Freedland, A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. Eur. Urol. **66**(6), 1054–1064 (2014)
146. M. Huncharek, K.S. Haddock, R. Reid, B. Kupelnick, Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. Am. J. Public Health **100**(4), 693–701 (2010)
147. Services USDoHaH, *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General* (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, 2014)
148. M.G. Oefelein, M.I. Resnick, Association of tobacco use with hormone refractory disease and survival of patients with prostate cancer. J. Urol. **171**(6 Pt 1), 2281–2284 (2004)
149. T. Pickles, M. Liu, E. Berthelet, et al., The effect of smoking on outcome following external radiation for localized prostate cancer. J. Urol. **171**(4), 1543–1546 (2004)
150. J. Pantarotto, S. Malone, S. Dahrouge, V. Gallant, L. Eapen, Smoking is associated with worse outcomes in patients with prostate cancer treated by radical radiotherapy. BJU Int. **99**(3), 564–569 (2007)
151. D.M. Moreira, J.A. Antonelli, J.C. Presti Jr., et al., Association of cigarette smoking with interval to biochemical recurrence after radical prostatectomy: results from the SEARCH database. Urology **76**(5), 1218–1223 (2010)
152. C.E. Joshu, A.M. Mondul, C.L. Meinhold, et al., Cigarette smoking and prostate cancer recurrence after prostatectomy. J. Natl. Cancer Inst. **103**(10), 835–838 (2011)
153. S.A. Kenfield, M.J. Stampfer, J.M. Chan, E. Giovannucci, Smoking and prostate cancer survival and recurrence. JAMA **305**(24), 2548–2555 (2011)
154. M. Rieken, S.F. Shariat, L.A. Kluth, et al., Association of cigarette smoking and smoking cessation with biochemical recurrence of prostate cancer in patients treated with radical prostatectomy. Eur. Urol. **68**(6), 949–956 (2015)
155. B.D. Carter, N.D. Freedman, E.J. Jacobs, Smoking and mortality—beyond established causes. N. Engl. J. Med. **372**(22), 2170 (2015)
156. B. Foerster, C. Pozo, M. Abufaraj, et al., Association of smoking status with recurrence, metastasis, and mortality among patients with localized prostate cancer undergoing prostatectomy or radiotherapy: a systematic review and meta-analysis. JAMA Oncol. **4**(7), 953–961 (2018)
157. R. Pasquali, F. Casimirri, S. Cantobelli, et al., Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism **40**(1), 101–104 (1991)
158. C.S. Mantzoros, E.I. Georgiadis, Body mass and physical activity are important predictors of serum androgen concentrations in young healthy men. Epidemiology **6**(4), 432–435 (1995)
159. J.C. Seidell, K.M. Flegal, Assessing obesity: classification and epidemiology. Br. Med. Bull. **53**(2), 238–252 (1997)

160. R.W. Taylor, D. Keil, E.J. Gold, S.M. Williams, A. Goulding, Body mass index, waist girth, and waist-to-hip ratio as indexes of total and regional adiposity in women: evaluation using receiver operating characteristic curves. Am. J. Clin. Nutr. **67**(1), 44–49 (1998)
161. Global BMIMC, E. Di Angelantonio, N. Bhupathiraju Sh, et al., Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet **388**(10046), 776–786 (2016)
162. J.C. Seidell, T.L. Visscher, Body weight and weight change and their health implications for the elderly. Eur. J. Clin. Nutr. **54**(Suppl 3), S33–S39 (2000)
163. A.G. Renehan, M. Tyson, M. Egger, R.F. Heller, M. Zwahlen, Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet **371**(9612), 569–578 (2008)
164. A. Discacciati, N. Orsini, A. Wolk, Body mass index and incidence of localized and advanced prostate cancer—a dose-response meta-analysis of prospective studies. Ann. Oncol. **23**(7), 1665–1671 (2012)
165. A. Perez-Cornago, P.N. Appleby, T. Pischon, et al., Tall height and obesity are associated with an increased risk of aggressive prostate cancer: results from the EPIC cohort study. BMC Med. **15**(1), 115 (2017)
166. X. Zhang, G. Zhou, B. Sun, et al., Impact of obesity upon prostate cancer-associated mortality: a meta-analysis of 17 cohort studies. Oncol. Lett. **9**(3), 1307–1312 (2015)
167. Prospective Studies C, G. Whitlock, S. Lewington, et al., Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet **373**(9669), 1083–1096 (2009)
168. S.P. Kelly, H. Lennon, M. Sperrin, et al., Body mass index trajectories across adulthood and smoking in relation to prostate cancer risks: the NIH-AARP diet and health study. Int. J. Epidemiol. **48**(2), 464–473 (2019)
169. S.E. Bonn, F. Wiklund, A. Sjolander, et al., Body mass index and weight change in men with prostate cancer: progression and mortality. Cancer Causes Control **25**(8), 933–943 (2014)
170. A. Cantarutti, S.E. Bonn, H.O. Adami, H. Gronberg, R. Bellocco, K. Balter, Body mass index and mortality in men with prostate cancer. Prostate **75**(11), 1129–1136 (2015)
171. A.W. Hsing, J. Deng, I.A. Sesterhenn, et al., Body size and prostate cancer: a population-based case-control study in China. Cancer Epidemiol. Biomark. Prev. **9**(12), 1335–1341 (2000)
172. W.R. Robinson, J. Stevens, M.D. Gammon, E.M. John, Obesity before age 30 years and risk of advanced prostate cancer. Am. J. Epidemiol. **161**(12), 1107–1114 (2005)
173. M. Barba, I. Terrenato, H.J. Schunemann, et al., Indicators of sexual and somatic development and adolescent body size in relation to prostate cancer risk: results from a case-control study. Urology **72**(1), 183–187 (2008)
174. E. Moller, K.M. Wilson, J.L. Batista, L.A. Mucci, K. Balter, E. Giovannucci, Body size across the life course and prostate cancer in the health professionals follow-up study. Int. J. Cancer **138**(4), 853–865 (2016)
175. E. Giovannucci, E.B. Rimm, M.J. Stampfer, G.A. Colditz, W.C. Willett, Height, body weight, and risk of prostate cancer. Cancer Epidemiol. Biomark. Prev. **6**(8), 557–563 (1997)
176. S.O. Andersson, J. Baron, R. Bergstrom, C. Lindgren, A. Wolk, H.O. Adami, Lifestyle factors and prostate cancer risk: a case-control study in Sweden. Cancer Epidemiol. Biomark. Prev. **5**(7), 509–513 (1996)
177. A. Discacciati, N. Orsini, S.O. Andersson, O. Andren, J.E. Johansson, A. Wolk, Body mass index in early and middle-late adulthood and risk of localised, advanced and fatal prostate cancer: a population-based prospective study. Br. J. Cancer **105**(7), 1061–1068 (2011)
178. A.G. Schuurman, R.A. Goldbohm, E. Dorant, P.A. van den Brandt, Anthropometry in relation to prostate cancer risk in the Netherlands cohort study. Am. J. Epidemiol. **151**(6), 541–549 (2000)
179. G.G. Giles, G. Severi, D.R. English, et al., Early growth, adult body size and prostate cancer risk. Int. J. Cancer **103**(2), 241–245 (2003)
180. A.J. Littman, E. White, A.R. Kristal, Anthropometrics and prostate cancer risk. Am. J. Epidemiol. **165**(11), 1271–1279 (2007)
181. M.E. Wright, S.C. Chang, A. Schatzkin, et al., Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer **109**(4), 675–684 (2007)
182. W.R. Robinson, C. Poole, P.A. Godley, Systematic review of prostate cancer's association with body size in childhood and young adulthood. Cancer Causes Control **19**(8), 793–803 (2008)
183. N. Keum, D.C. Greenwood, D.H. Lee, et al., Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J. Natl. Cancer Inst. **107**(2) (2015)
184. C. Rodriguez, S.J. Freedland, A. Deka, et al., Body mass index, weight change, and risk of prostate cancer in the cancer prevention study II nutrition cohort. Cancer Epidemiol. Biomark. Prev. **16**(1), 63–69 (2007)
185. J.K. Bassett, G. Severi, L. Baglietto, et al., Weight change and prostate cancer incidence and mortality. Int. J. Cancer **131**(7), 1711–1719 (2012)
186. B.A. Dickerman, T.U. Ahearn, E. Giovannucci, et al., Weight change, obesity and risk of prostate cancer progression among men with clinically localized prostate cancer. Int. J. Cancer **141**(5), 933–944 (2017)
187. B.M. Whitley, D.M. Moreira, J.A. Thomas, et al., Preoperative weight change and risk of adverse outcome following radical prostatectomy: results from

the Shared Equal Access Regional Cancer Hospital database. Prostate Cancer Prostatic Dis. **14**(4), 361–366 (2011)
188. C.E. Joshu, A.M. Mondul, A. Menke, et al., Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev. Res. (Phila.) **4**(4), 544–551 (2011)
189. I.M. Lee, Exercise and physical health: cancer and immune function. Res. Q. Exerc. Sport **66**(4), 286–291 (1995)
190. J.L. Durstine, W.L. Haskell, Effects of exercise training on plasma lipids and lipoproteins. Exerc. Sport Sci. Rev. **22**, 477–521 (1994)
191. P.F. Kokkinos, B. Fernhall, Physical activity and high density lipoprotein cholesterol levels: what is the relationship? Sports Med. **28**(5), 307–314 (1999)
192. P. Kokkinos, J. Myers, Exercise and physical activity: clinical outcomes and applications. Circulation **122**(16), 1637–1648 (2010)
193. S.P. Helmrich, D.R. Ragland, R.W. Leung, R.S. Paffenbarger Jr., Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N. Engl. J. Med. **325**(3), 147–152 (1991)
194. J.E. Manson, D.M. Nathan, A.S. Krolewski, M.J. Stampfer, W.C. Willett, C.H. Hennekens, A prospective study of exercise and incidence of diabetes among US male physicians. JAMA **268**(1), 63–67 (1992)
195. J.L. Abramson, V. Vaccarino, Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch. Intern. Med. **162**(11), 1286–1292 (2002)
196. E.S. Ford, Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology **13**(5), 561–568 (2002)
197. A.P. Simopoulos, Energy imbalance and cancer of the breast, colon and prostate. Med. Oncol. Tumor Pharmacother. **7**(2–3), 109–120 (1990)
198. J. Flanagan, P.K. Gray, N. Hahn, et al., Presence of the metabolic syndrome is associated with shorter time to castration-resistant prostate cancer. Ann. Oncol. **22**(4), 801–807 (2011)
199. I.N. Benke, M.F. Leitzmann, G. Behrens, D. Schmid, Physical activity in relation to risk of prostate cancer: a systematic review and meta-analysis. Ann. Oncol. **29**(5), 1154–1179 (2018)
200. V. Rangul, E.R. Sund, P.J. Mork, O.D. Roe, A. Bauman, The associations of sitting time and physical activity on total and site-specific cancer incidence: results from the HUNT study, Norway. PLoS One **13**(10), e0206015 (2018)
201. E.L. Giovannucci, Y. Liu, M.F. Leitzmann, M.J. Stampfer, W.C. Willett, A prospective study of physical activity and incident and fatal prostate cancer. Arch. Intern. Med. **165**(9), 1005–1010 (2005)
202. A.V. Patel, C. Rodriguez, E.J. Jacobs, L. Solomon, M.J. Thun, E.E. Calle, Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men. Cancer Epidemiol. Biomark. Prev. **14**(1), 275–279 (2005)
203. N.F. Johnsen, A. Tjonneland, B.L. Thomsen, et al., Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Int. J. Cancer **125**(4), 902–908 (2009)
204. S.C. Moore, T.M. Peters, J. Ahn, et al., Physical activity in relation to total, advanced, and fatal prostate cancer. Cancer Epidemiol. Biomark. Prev. **17**(9), 2458–2466 (2008)
205. A. Grotta, M. Bottai, H.O. Adami, et al., Physical activity and body mass index as predictors of prostate cancer risk. World J. Urol. **33**(10), 1495–1502 (2015)
206. S.A. Kenfield, J.L. Batista, J.L. Jahn, et al., Development and application of a lifestyle score for prevention of lethal prostate cancer. J. Natl. Cancer Inst. **108**(3) (2016)
207. L. Bourke, D. Smith, L. Steed, et al., Exercise for men with prostate cancer: a systematic review and meta-analysis. Eur. Urol. **69**(4), 693–703 (2016)
208. S.A. Kenfield, M.J. Stampfer, E. Giovannucci, J.M. Chan, Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J. Clin. Oncol. **29**(6), 726–732 (2011)
209. B.A. Dickerman, E. Giovannucci, C.H. Pernar, L.A. Mucci, M.A. Hernan, Guideline-based physical activity and survival among US men with nonmetastatic prostate cancer. Am. J. Epidemiol. **188**(3), 579–586 (2019)
210. E.L. Richman, S.A. Kenfield, M.J. Stampfer, A. Paciorek, P.R. Carroll, J.M. Chan, Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res. **71**(11), 3889–3895 (2011)
211. E.R. Miller 3rd, R. Pastor-Barriuso, D. Dalal, R.A. Riemersma, L.J. Appel, E. Guallar, Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann. Intern. Med. **142**(1), 37–46 (2005)
212. G. Bjelakovic, D. Nikolova, L.L. Gluud, R.G. Simonetti, C. Gluud, Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA **297**(8), 842–857 (2007)