Effect of Plant- and Animal-Based Foods on Prostate Cancer Risk

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Context: Many studies have explored whether plant and animal-based food consumption is associated with prostate cancer (PCa) risk, but there is much discordance.

Objective: To perform an updated review of the literature that further investigates the association of plant- and animal-based food consumption with PCa risk.

Methods: This review was conducted by using 3 databases and produced a total of 550 references. The search was limited to a publication date range of 2006 to February 2017, English language, and humans. After case reports, comments, letters, editorials, and duplicate references were removed, 297 citations remained for review. Articles that did not investigate the association of dietary patterns or a major component of diet with PCa were excluded.

Results: Of the 297 references found, 47 were eligible for inclusion in this review. The authors identified 2 very large cohort studies (≥100,000 participants), 6 large cohort studies (≥40,000 participants), 11 medium cohort studies (≥10,000 participants), 10 small cohort studies (<10,000 participants), 13 case-control studies, 4 meta-analyses, and 1 population study investigating diet and PCa risk. Most studies showed that plant-based foods are associated with either decreased or unchanged risk of PCa, whereas animal-based foods, particularly dairy products, are associated with either increased or unchanged risk of PCa.

Conclusion: This review of the literature suggests that consumption of higher amounts of plant-based foods may be associated with decreased PCa risk, and consumption of higher amounts of dairy products may be associated with increased PCa risk.

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In the United States, the lifetime risk of prostate cancer (PCa) is 11.6%,[1] which has the highest incidence and second highest mortality rate of all cancers in men.[2] Previous studies[3-6] have shown that increased consumption of animal products is associated with increased PCa risk. One 2001 review[3] found that 16 of 22 studies showed a positive correlation between meat intake and PCa risk. Eight studies in this review assessed red meat intake separately, and all but 1 showed a correlation with increased risk of PCa. Other studies[4-6] have shown a correlation between dairy consumption and increased PCa risk.

These associations are likely related to a multitude of factors. With regard to meat, the formation of heterocyclic amines during high-temperature cooking, hormonal effects,[7] other nutrient components,[3,8] and the relatively lower levels of anticarcinogenic compounds found in meats compared with plants are all likely implicated. Many of these factors may also be implicated in dairy products. For instance, animal protein and dairy intake is associated with elevated insulinlike growth factor 1, which is associated with elevated PCa risk.[9-16] Additionally, dairy has implications distinct from other animal products. Prostate cancer cellular proliferation and invasiveness is inhibited by calcitriol,[17] but increased calcium intake suppresses the formation of calcitriol. Increased calcium intake and low levels of vitamin D are associated with increased PCa risk.[18] Dairy products are the primary source of calcium in Western countries.[19] In countries in which the intake of dairy products is high, PCa rates are high.[20] In Asian countries, in which intake of dairy products is low, PCa rates are low.[21]

A growing body of evidence suggests there may be an association between plant-based diets and decreased PCa risk. The decreasing mortality rates in the United States for several common cancers, including PCa, coincides with decreased meat and dairy intake and increased plant-based food consumption.[22] The widespread implementation of cancer-screening initiatives such as prostate-specific antigen testing possibly contributes to this decrease in mortality but is unlikely to be the sole explanation for the trend. A large epidemiologic study[23] in 1981 estimated that 35% of all cancer could be attributed to dietary causes, and a 2015 review[24] of this landmark report found its estimates to be generally true in the 21st century. One randomized clinical trial[25] studied men with known low-grade PCa who declined standard therapy. The trial found that after being exposed to a year of lifestyle interventions consisting of a vegan diet, exercise, and stress management techniques, the prostate-specific antigen of men in the experimental group decreased, whereas it increased in the control group. Studies reviewed by Kristal and Lampe[26] showed an association between increased consumption of certain vegetables and decreased PCa risk. It is because of these correlations that we sought to review the current literature for the association of dietary patterns and PCa risk.

Methods

We searched Ovid MEDLINE, PubMed, and Embase databases with the following keywords: prostate cancer, dairy products, milk, yogurt, vegetarian diet, vegan diet, lacto-ovo-vegetarian, semi-vegetarian, pesco-vegetarian, and plant-based diet. We used the following search criteria: date range from 2006 to February 2017, English language, and human participants. We found 550 relevant articles and then removed case reports, comments, letters, editorials, and duplicate citations. A total of 297 references remained for review. References and abstracts were divided among authors for review, and articles that did not investigate the association of dietary patterns or a major component of diet with PCa were excluded. The initial decision to exclude an article was made by the reviewing author, and this decision was upheld if all authors agreed. Examples of excluded articles included those studying silibinin, milk thistle, prostate stromal protein 20, soy protein isolate, phytanic acid, meroterpenoids, acai juice, vitamin K, choline, and dietary flavonoids such as cranberry proanthocyanidins. Finally, data were grouped according to study design (prospective cohort vs case-control) and study size (very large, ≥100,000; large, 40,000-99,999; medium, 10,000-39,999; and small, <10,000 participants) for analysis.

Results

We selected 47 articles for inclusion in this review based on the criteria described in the Methods section. These articles included 2 very large cohort studies (XL), 6 large cohort studies (L), 11 medium cohort studies (M), 10 small cohort studies (S), 13 case-control studies, 4 meta-analyses, and 1 population study. All

Table.
Breakdown of the 28 Included Prostate Cancer and Food Consumption Cohort Studies Listed According to Size

Studies	Cohort Size	PCa Cases (n)	Mean Follow-up, y
Very Large Cohort Studies (≥100,000)			
Park et al[59] (2007)	293,888	10,180	6
Gonzalez et al[29] (2010)	153,457	2727	8.7
Large Cohort Studies (≥40,000)			
Stram et al[34] (2006)	82,486	3922	7
Park et al[58] (2007)	82,483	4404	8
Giovannucci et al[75] (2006)	47,750	3544	16
Wu et al[69] (2006)	47,725	3002	14
Takachi et al[35] (2010)	43,475	339	7.4
Kurahashi[52] (2008)	43,435	329	7.5
Medium Cohort Studies (≥10,000)			
Kirsh et al[32] (2007)	29,361	1338	4.2
Mitrou et al[57] (2007)	29,133	1267	17
Butler et al[74] (2010)	27,293	298	11
Egeberg et al[38] (2011)	26,691	1081	12
Tantamango-Bartley et al[30] (2016)	26,346	1079	7.8
Song et al[53] (2013)	21,660	2806	28
Key et al[28] (2014)	15,594	457	14.9
Umesawa et al[37] (2014)	15,471	143	16
Key et al[27] (2009)	12,230	235	10
Neuhouser et al[47] (2007)	12,025	890	11
Koh et al[56] (2006)	10,011	815	10
Small Cohort Studies (<10,000)			
Gilsing et al[31] (2016)	4465	399	20.3
Pettersson et al[60] (2012)	3918	229 (PCa deaths)	7.6
Rohrmann et al[48] (2007)	3892	199	13
Diallo et al[36] (2016)	3313	139	12.6
Kesse et al[54] (2006)	2776	69	7.7
van der Pols et al[61] (2007)	2159	41	65
Chan et al[33] (2006)	1202	392 (PCa progression)	6
Wilson et al[67] (2016)	971	94	3
Yang et al[55,70] (2015)	926	56 (PCa deaths)	9.9

Abbreviation: PCa, prostate cancer.

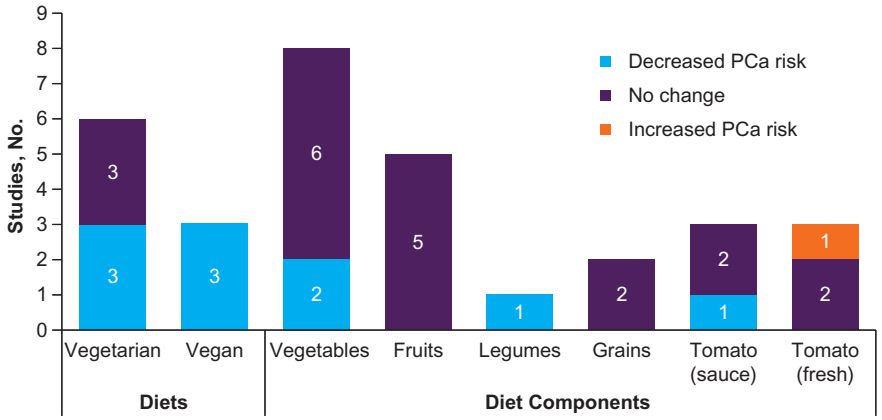

Figure 1.
Associations between various plant-based foods and prostate cancer risk based on 28 cohort study findings.
Abbreviation: PCa, prostate cancer.

CIs displayed are at the 95% level. The breakdown of the included cohort studies is listed according to size in the **Table**.

Plant-Based Foods

Ten prospective cohort studies, 5 case-control studies, and 1 meta-analysis were reviewed for the effect of plant-based foods on PCa risk. These results are summarized in **Figure 1** and **Figure 2**. Of the 5 prospective cohort studies that investigated the effects of a vegetarian diet, 2 showed an association with decreased incidence of all cancers, which included PCa (relative risk [RR], 0.89; 95% CI, 0.83-0.96, M study)[27,28] while 3 showed no change in risk.[29-31] Three studies[27,28,30] also examined vegan diets, and all 3 found an association with decreased PCa risk (RR, 0.81; 95% CI, 0.66-0.98, M study)[27,28] (hazard ratio [HR], 0.64; 95% CI, 0.48-0.83, M study).[30]

Many cohort studies investigated the effects of specific plant-based food elements. For example, 8 studies[28,29,32-37] examined the effects of overall vegetable consumption, and 2 studies[28,32] found an

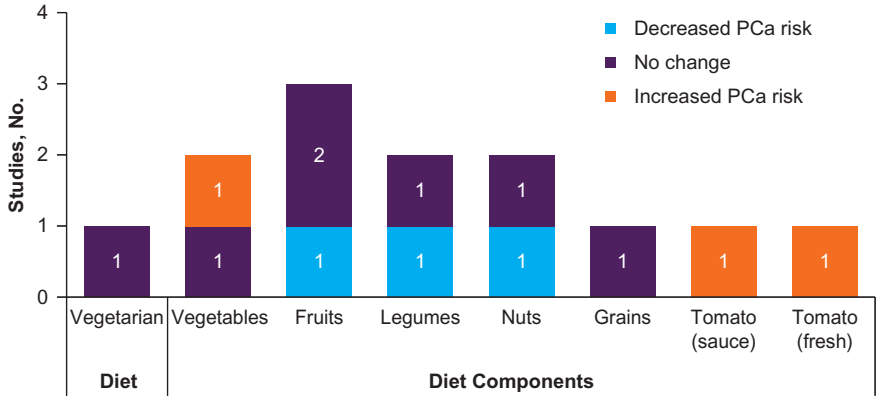

Figure 2.
Associations between various plant-based foods and prostate cancer risk based on case-control studies.
Abbreviation: PCa, prostate cancer.

association between increased vegetable intake and decreased PCa risk (RR, 0.81; 95% CI, 0.66-0.98, M study),[28] (RR, 0.41; 95% CI, 0.22-0.74, M study)[32] whereas 6 studies[29,33-37] found no difference in risk. Five studies[32-36] looked at the effects of fruit intake and found no significant difference in PCa risk. One cohort study[36] examined legumes and found an association with increased intake and decreased PCa risk (HR, 0.53; 95% CI, 0.34-0.85, S study). Two studies[33,38] looked at grains specifically and found no change in PCa risk. Three studies[33,34,36] looked at the effects of tomato sauce. One of these studies[33] found an association with increased intake of tomato sauce and decreased risk of PCa (HR, 0.56; 95% CI, 0.38-0.82, S study), and 2 studies[34,36] found no change in risk. These same studies[33,34,36] also looked at the effects of fresh tomatoes: 2 studies[34,36] found no difference in PCa risk, and 1 study[33] found an association of fresh tomato consumption with increased PCa risk (HR, 1.58; 95% CI, 1.10-2.25, S study). One meta-analysis[39] found that increased intake of soy was associated with reduced PCa risk (RR, 0.74; 95% CI, 0.63-0.89).

Of the case-control studies[40-44] reviewed, 1 study[40] found an association with decreased PCa risk and increased fruit consumption (odds ratio, [OR], 0.65; 95% CI, 0.45-0.92), and the other study[41] showed an association with decreased PCa risk and increased legume (OR, 0.4; 95% CI, 0.22-0.74) and nut (OR, 0.43; 95% CI, 0.22-0.85) consumption. One study[42] showed an association with increased risk of PCa and the consumption of vegetables (OR, 1.25; 95% CI, 1.05-1.50), tomato sauce, and fresh tomatoes (OR, 1.25; 95% CI, 0.99-1.59). Three studies[42-44] showed no significant change in PCa risk with the consumption of a vegetarian diet,[43] vegetables in particular,[44] fruits,[42,44] legumes,[42] nuts,[42] or grains.[42]

Meat

Six prospective cohorts, 4 case-control studies, 1 meta-analysis, and 1 population study were reviewed regarding the effect of meat and fish on PCa risk. A summary of these data along with the data for eggs and dairy are found in **Figure 3** and **Figure 4**. In a large population study,[45] meat intake was associated

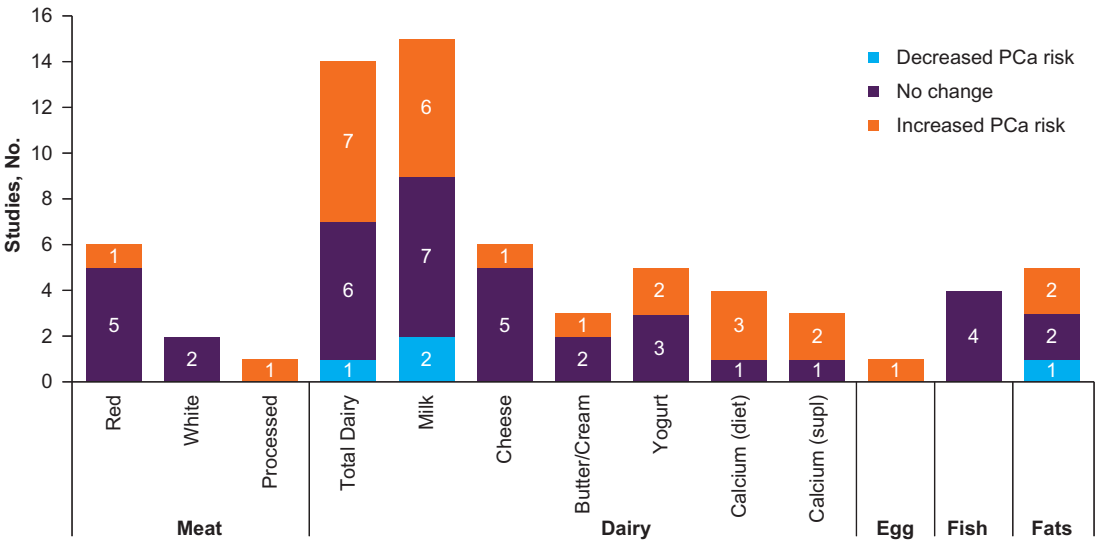

Figure 3.
Associations between various animal-based foods and prostate cancer risk based on cohort studies.
Abbreviation: PCa, prostate cancer

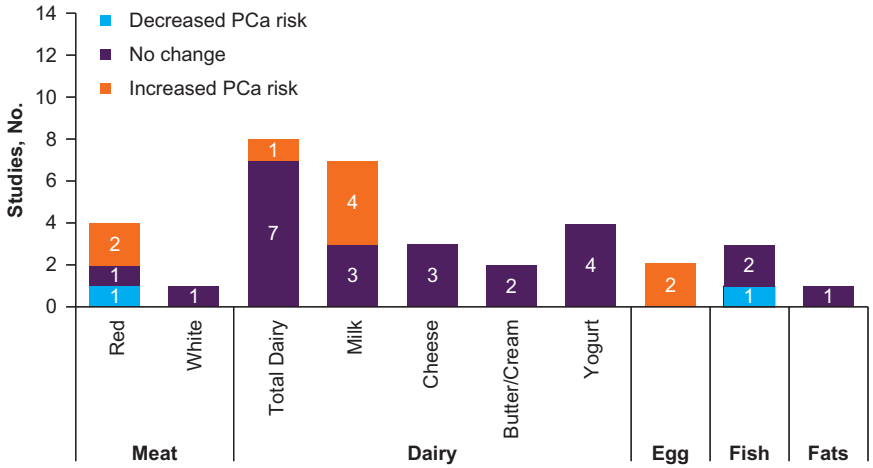

Figure 4.
Associations between various animal-based foods and prostate cancer risk based on case-control studies.
Abbreviation: PCa, prostate cancer.

with increased PCa mortality. Two prospective cohorts[28] showed no significant effect of eating meat on PCa incidence.

Red meat (beef, pork, or lamb) intake has been associated with increased PCa incidence.[46] Five studies[33,41,44,47,48] showed no effect. One prospective cohort[31] showed increased incidence of advanced PCa when eating meat once weekly compared with eating meat 6 to 7 days per week (HR, 1.75; 95% CI, 1.03-2.97, S study) but no association for all PCa. In one case-control study,[42] red meat intake was associated with decreased PCa (OR, 0.83; 95% CI, 0.70-0.99). Two case-control studies[40,49] found an increase in PCa among men in the highest tertile of red meat consumption compared with those in the lowest tertile of daily red meat consumption (OR, 1.68; 95% CI, 1.18-2.38 and RR, 1.43; 95% CI, 1.11-1.84, respectively).

Processed meat (eg, salted or smoked) was not associated with an increase in PCa in a meta-analysis of 4 prospective cohorts.[44] Regular sausage intake was associated with an increase in advanced PCa in a US cohort (HR, 2.83; 95% CI, 1.34-5.99, S study),[48] but no increase in PCa was found in a Canadian population.[41]

White meat, generally poultry, was not associated with increased PCa in 1 meta-analysis of 4 prospective cohorts,[44] 2 prospective cohorts,[31,48] and 1 case-control study.[41] Fish intake was not associated with change in incidence or outcomes in PCa in a meta-analysis of 4 prospective cohorts,[44] 4 prospective studies,[27,28,33,48] and 1 case-control study.[42] Another case-control study[41] showed a decrease in the incidence of PCa with fish intake in Canada (OR, 0.54; 95% CI, 0.30-0.97).

Dairy

Two meta-analyses, 14 prospective cohorts, and 8 case-control studies assessed the association of total dairy intake and PCa risk. Meta-analyses from Aun et al[50] and Qin et al[51] showed increased correlation with PCa (RR, 1.07; 95% CI, 1.02-1.12 and RR, 1.13; 95% CI, 1.02-1.24, respectively). Seven prospective cohorts were associated with increased risk (HR, 1.32; 95% CI, 1.01-1.72, XL study[29]; HR, 1.65; 95% CI, 1.02-2.66, S study[48]; RR, 1.63; 95% CI, 1.14-2.32, L study[52]; HR, 1.12; 95% CI, 0.93-1.35, M study[53]; RR, 1.35; 95% CI, 1.02-1.78, S study[54]; and HR, 1.76; 95% CI, 1.21-2.55, S study).[55] One study[38] reported no point estimate or CI. Six prospective cohorts[47,56-60] showed no correlation, and 1 prospective

cohort[61] showed a decreased risk when dairy was consumed during childhood (OR, 0.34; 95% CI, 0.11-1.04, S study). One case-control study[41] showed increased risk (OR, 2.19; 95% CI, 1.22-3.94), and 7 case-control studies[21,40,42,44,49,62,63] showed no association.

Increased risk of PCa with total milk consumption was found in 3 of 4 meta-analyses (RR, 1.03; 95% CI, 1.00-1.07,[50] RR, 1.13; 95% CI, 1.02-1.24,[51] and RR, 1.50; 95% CI, 1.03-2.17[64]); 6 of 15 prospective cohorts (RR, 1.34; 95% CI, 1.04-1.71, M study[5]; HR, 2.03; 95% CI, 1.12-3.70, S study[48]; RR, 1.53; 95% CI, 1.07-2.19, L study[52]; HR, 1.19; 95% CI, 1.06-1.33, M study[53]; HR, 1.76; 95% CI, 1.21-2.55, S study[55]; and RR, 1.23; 95% CI, 0.99-1.54, XL study[59]); and 4 of the 7 case-control studies (OR, 1.73; 95% CI, 1.16-2.39,[21]; OR, 2.01; 95% CI, 1.42-2.82[40]; OR, 2.27; 95% CI, 1.25-4.09[41]; and OR, 1.43; 95% CI, 1.09-1.88[62]). Two prospective cohorts[47,61] found a decreased risk of PCa (HR, 0.59; 95% CI, 0.40-0.85, M study[47] and OR, 0.34; 95% CI, 0.11-1.04, S study[61]), and the remaining studies that analyzed dairy consumption and PCa risk[44,49,54,57,58,60,63] found no association.

One of 2 meta-analyses (RR, 1.23; 95% CI, 0.94-1.61),[64] and 1 of 6 prospective cohort studies (HR, 1.43; 95% CI, 1.01-2.03, S study)[48] found increased risk of PCa with increased cheese intake. Five cohorts[52,54,57,58,60] and 3 case-control studies[41,44,62] showed no association. The case-control studies[41,44,62] that evaluated cheese and PCa risk found no association. One meta-analysis[64] showed no association between butter, cream, or yogurt and PCa risk. One cohort study[57] found increased risk for PCa with butter and cream consumption (RR, 1.11; 95% CI, 0.93-1.33, M study), and 2 cohort studies[58,60] found no association. Two cohort studies found an increased risk for PCa with yogurt consumption (RR, 1.52; 95% CI, 1.10-2.12, L study[52]; RR, 1.61; 95% CI, 1.07, 2.43, S study[54]), and 3 cohort studies[57,58,60] showed no association. No effect on PCa risk was found in the case-control studies that evaluated consumption of butter and cream[21,41] and yogurt.[21,41,44,62]

Eggs

Although 2 case-control studies (OR, 2.43; 95% CI, 1.70-3.48[40]; OR, 1.89; 95% CI, 1.15-3.10[65]) showed an association between egg consumption and PCa incidence and mortality, a review[66] of 9 cohort studies and 11 case-control studies performed prior to July 2012 did not find evidence to support an association. However, later studies (OR, 2.43; 95% CI, 1.70-3.48[40]; OR, 1.98; 95% CI, 1.08-3.63, S,[67]; and RR, 1.14; 95% CI, 1.01-1.28[68]) suggested an association between a higher intake of eggs and a higher risk of advanced PCa.

Mixed Diets

Studies examining whole dietary patterns have been limited and inconsistent. In one study,[69] Western dietary patterns (eg, processed and red meats, high-fat dairy, and refined grains) were not associated with increased PCa incidence, whereas another study[43] found an increased risk (OR, 1.82; 95% CI, 1.15-2.87). One cohort study[70] found an association of Western dietary patterns with a higher risk of PCa mortality (HR, 2.53; 95% CI, 1.00-6.42, S study). Prudent dietary patterns (vegetables, fruits, fish, legumes, whole grains) have not been associated with changes in incidence of PCa[69,43] nor PCa mortality.[70] Mediterranean diet patterns (whole grains, fruits, vegetables, low fat dairy, nuts, poultry, legumes, fish, olive oil) were not associated with PCa incidence in one study[42] but were associated with a lower incidence in another study[71] (OR, 0.22; 95% CI, 0.08-0.58).

Discussion

Our review of the literature found that the majority of prospective cohort studies investigating plant-based food consumption showed either no significant association or an association with decreased risk of PCa (**Figure 1**). This finding held true when a subset that included only the larger cohort studies (>10,000 participants) was considered. Only 1 study[33] showed a small elevation of PCa risk with the consumption of plant-

based food, specifically fresh tomatoes. However, this was an isolated finding, and other studies[72,73] indicated that tomato products, particularly when cooked, are associated with decreased PCa risk.

With regard to animal-based foods, the majority of prospective cohort studies demonstrated an association with either no change in risk or an increased risk of PCa (**Figure 3**). This finding was true for dairy products, and the pattern held when a subset of only the larger cohort studies were considered. In addition, 3 meta-analyses showed an association between dairy products and increased PCa risk.[50,51,64] Furthermore, increased intake of calcium also appeared to be associated with increased PCa risk.[18,57,74,75] Since dairy products are rich in calcium, this raises the possibility of calcium playing an important role in the link between dairy and PCa.

Strengths

This large review evaluated 47 studies comprising more than 1,000,000 participants. It was a comprehensive review of all available data since 2006 to get a broad perspective of the effects of current dietary patterns on PCa. We also looked at the effects of subsets of food categories, such as fruits, vegetables, nuts, legumes, whole grains, red meats, processed meats, white meats, milk, cheese, butter/cream, yogurt, and eggs. Many of the studies attempted to control for confounding nondietary lifestyle factors, such as smoking, exercise, and sun exposure by using multivariate Cox regression.[27,28,30,34] The systematic reviews attempted to control for publication bias and small study effects using funnel plot analysis via the Begg rank correlation test and the Egger regression test.[39,50,51,64]

Limitations

Our study had a number of limitations. First, despite the broad search and detailed method of data extraction, we did not include a meta-analysis with our systematic review because the significant heterogeneity found among the studies preclude meaningful quantitative analysis. Not only were several types of studies included (eg, systematic reviews, prospective cohorts, and case-control studies), but there was also significant heterogeneity within each subset. Second, epidemiologic data cannot prove causation, so any change in risk for PCa is by association and subject to confounding factors. For instance, people who follow more prudent diets are also less likely to smoke or drink alcohol and more likely to exercise. As with most observational nutrition studies, the presented data were primarily collected by dietary recall, which has inherent flaws. The effect of diet on PCa is also difficult to study because of the inherent indolence of the disease and variability in staging. Some of the studies looked at PCa incidence, whereas others looked at PCa mortality. Very few studies[47] tried to determine associations of diet with more aggressive forms of PCa. Even if more studies had looked at this factor, we would likely find the definition of aggressive cancer to be variable as well.

Future Research

One of the biggest obstacles in the field of dietary research is the lack of standardized methods for capturing and reporting diet and lifestyle data. However, despite the heterogeneity in methods and discordant conclusions found in the literature, our review shows that, in general, plant-based foods may be associated with a decreased risk of PCa, whereas dairy products may be associated with an increased risk of PCa. It would be helpful to test the validity of these findings through more randomized controlled trials such as the one conducted by Ornish et al.[25] There is also a need to better understand the possible effect of nondietary lifestyle factors, such as smoking and exercise, on PCa risk so that future dietary studies can better control for these factors.

Conclusion

Our review of the literature suggests that consumption of higher amounts of plant-based foods may be associated with decreased PCa risk, and the consumption of higher amounts of dairy products may be associated with

increased PCa risk. There does not appear to be a clear association between increased PCa risk and increased consumption of other types of animal-based foods, including red, white, or processed meat, fish, and eggs.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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