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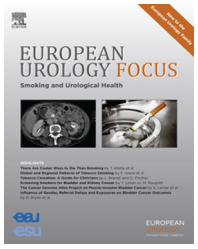

Review – Prostate Cancer

Impact of Metabolic Diseases, Drugs, and Dietary Factors on Prostate Cancer Risk, Recurrence, and Survival: A Systematic Review by the European Association of Urology Section of Oncological Urology

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Abstract

Context: To date, established risk factors for prostate cancer (PCa) are limited to age, race, family history, and certain genetic polymorphisms. Despite great research efforts, available evidence on potentially modifiable risk factors is conflicting. Moreover, most studies on PCa risk factors did not consider the impact of prostate-specific antigen (PSA) testing on PCa diagnosis.

Objective: To provide a detailed overview of the latest evidence on the role of metabolic diseases, drugs, and dietary factors for risk of PCa incidence, recurrence, and survival in men exposed to PSA testing.

Evidence acquisition: A systematic review of the English-language literature was performed using the MEDLINE, Cochrane Central Register of Controlled Trials, and Web of Science databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses recommendations. Randomized, case-control, or cohort studies published during the periods 2008–2017 (on drugs and metabolic diseases) and

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Diabetes
Diet
Food
Metabolic syndrome
Metformin
Metformin
Nonsteroidal anti-inflammatory drugs
Obesity
Prostate cancer
Prostate-specific antigen test
Statin

2003–2017 (on dietary factors), with extensive follow-up (≥8–10 yr for studies on PCa risk; ≥2–5 yr for studies on PCa recurrence, progression, and survival, depending on the review subtopic) and adjusting of the analyses, beyond established risk factors, for either rate of PSA testing (for risk analyses) or PCa stage and primary treatment (for survival analyses), were eligible for inclusion.

Evidence synthesis: Overall, 39 reports from 22 observational studies were included. Studies were heterogeneous regarding definitions of exposure or outcomes, length of follow-up, risk of bias, and confounding. For some risk factors, evidence was insufficient to assess potential effects, while for others there was no evidence of an effect. For selected risk factors, namely metformin, aspirin and statin use, diabetes, obesity, and specific dietary intakes, there was low-quality evidence of modest effects on PCa risk.

Conclusions: Current evidence from long-term observational studies evaluating the effect of drugs, metabolic diseases, and dietary factors for PCa risk considering the impact of PSA testing is still not conclusive. Future research is needed to confirm the associations suggested by our review, exploring their potential biological explanations and selecting those risk factors most likely to trigger effective public health interventions.

Patient summary: We reviewed the available studies published in the recent literature on the potential role of drugs, metabolic diseases, and food and dietary factors for the risk of prostate cancer, considering the impact of prostate-specific antigen testing on prostate cancer diagnosis. We found that for some factors data are currently insufficient to make definitive conclusions, while for others available studies seem to indicate an effect on the risk of prostate cancer.

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1. Introduction

Prostate cancer (PCa) is a major public health problem worldwide [1,2]. To date, established risk factors are limited to age, race, family history, and certain genetic polymorphisms [3–7]. Despite great research efforts, available evidence on potentially modifiable risk factors remains conflicting [6]. This is partly explained by the limitations of available studies in terms of heterogeneous design, short follow-up, risk of bias (RoB), and confounding. Consequently, no definitive recommendations can be provided for specific preventive or dietary measures to reduce PCa risk [8,9].

Of note, patterns and temporal trends in PCa incidence have largely been influenced by prostate-specific antigen (PSA) testing and diagnostic ascertainment [4,5]. Genetic and environmental factors may play a role in the persistent geographical incidence differences despite different levels of PSA testing [5]; however, such risk factors still remain elusive and none of them could have caused an extremely rapid rise in PCa incidence, as observed in most countries using PSA testing [4,5].

In this scenario, despite controversies over whether it is beneficial in reducing disease-specific mortality [6,7,9], PSA testing has been and is currently widely used in many populations [2,4,5], making it difficult to disentangle the potential impact of specific PCa risk factors without considering the bias given by the differential rate of PSA testing.

In this scenario, testing the role of potentially modifiable factors for PCa risk in men exposed to PSA testing is a distinct unmet need.

Herein, we provide a detailed overview of the latest evidence from long-term studies evaluating the differential impact of metabolic diseases, drugs, and dietary factors on PCa risk considering the effect of PSA testing.

2. Evidence acquisition

The review process was performed in accordance with the European Association of Urology (EAU) methodology on the key steps in conducting systematic reviews [10] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement recommendations [11].

2.1. Search strategy

Sensitive computerized bibliographic searches were performed using MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials, and Web of Science databases in December 2017. The detailed review strategy, including full search strategy and keywords, is presented in the Supplementary material. The search strategy was designed using both free text and mesh terms applying a time period (2008–2017 and 2003–2017 for the subchapters “drugs/metabolic diseases” and “food and dietary factors,” respectively) and “English” language filters. Hand search of bibliographies of included studies and previous systematic reviews was also performed to include additional potentially relevant studies.

2.2. Inclusion criteria

As recommended by PRISMA and EAU methodology, a specific population (P), intervention (I), comparator (C), outcome (O), and study design (S; PICOS) framework defined study eligibility (Supplementary material) [10,11]. In brief, studies were considered eligible for this systematic review if they fulfilled the following criteria: (1) population exposed to PSA testing and composed by adult (>18 yr) men without proven PCa (for PCa risk analysis [O]), or adult men with previous confirmed PCa (P) (for PCa

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recurrence/survival analyses [O]) "exposed" or "unexposed" (C) to the putative risk factor for PCa (I); (2) randomized controlled or prospective cohort study design with long-term follow-up (≥8/10 yr, for studies on PCa risk for the subtopics "dietary factors" and drugs/metabolic diseases, respectively, and ≥2/5 yr for studies on PCa recurrence/survival for the subtopics "dietary factors" and drugs/metabolic diseases, respectively) or case-control study design (S); and (3) adjustment of statistical analyses at least for age, race, family history of PCa, rate of PSA testing, PSA (for risk analysis) or PCa stage, and primary treatment (for recurrence/survival analyses; S).

The rational for including only studies with analyses adjusted for rate of PSA testing is grounded in the current evidence on the impact of PSA testing on PCa diagnosis [1,2,4,5,7].

Observational studies with insufficient reporting of the PICOS criteria according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement recommendations [12] were excluded.

2.3. Systematic review process

Mendeley reference software was used to identify and remove duplicates among records identified. After further exclusion of records not related to this review, two independent authors (R.C. and A.M.) screened titles and abstracts of 2543 records related to metabolic diseases and drugs, while two other independent authors (J.D.S.H. and O.R.F.) screened titles and abstracts of 592 records related to food and dietary factors. Disagreement was solved by a third party (S.B.M.) supervising the systematic review process. The same authors carried out the study selection. Separate screening forms were created for each selection phase and adapted to each review subchapter, as appropriate.

The flowchart depicting the overall review process according to PRISMA is shown in Fig. 1.

2.4. Data extraction

Data were extracted independently by two authors (R.C. and O.R.F.) in an a priori developed, standardized data extraction form adapted for each subtopic of the review. This included information on all elements of the PICOS framework, as well as confounders adjusted for in statistical analysis. RoB assessment in observational studies was performed independently by two authors (R.C. and A.M.) according to both Quality in Prognosis Studies tool [13] and Newcastle-Ottawa Scale [14] (Supplementary Tables 1 and 2). Disagreement was solved by a third party (S.B.M.). Overall quality of evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations [15]. A narrative form was used for qualitative data synthesis.

3. Evidence synthesis

Overall, 39 reports from 22 observational studies were included in final qualitative analysis (Fig. 1). Key study findings are shown in Tables 1–3, while additional information regarding design and participant characteristics in studies on drugs and metabolic diseases are given in Supplementary Tables 3 and 4.

Overall, most studies included predominantly Caucasian populations with an average age at baseline of 55–65 yr and an average age at diagnosis of 65–70 yr.

Quantification of intensity of PSA testing was variable across the included studies (Supplementary Table 3), ranging from "the number of PSA tests in the last 2 [16–18], 3 [19], or 5 yr" [20–22] to "a positive history of PSA screening" [23].

In three studies (Finnish Randomized Study of Screening for Prostate Cancer [FinRSP]; Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial; and Prostate testing for cancer and Treatment [ProtecT] study), a systematic PCa screening protocol including systematic prostate biopsies at prespecified PSA levels was used (Supplementary Table 3).

According to GRADE [15], overall quality of evidence of studies on all subtopics was low. RoB was generally higher for studies on the topic "food and dietary factors" (compared with the other subtopics) and for studies with a case-control study design (Supplementary Tables 1 and 2).

3.1. Drugs and PCa

Overall, 16 reports from eight studies were included, of which 11 were on PCa incidence and five on PCa survival (Table 1).

3.1.1. Drugs and PCa incidence

3.1.1.1. Antidiabetic drugs. In a prospective cohort study (PCS) from the FinRSP cohort [24], use of metformin (compared with the use of other oral antidiabetic drugs) was associated with a lower risk of PCa, with a significant inverse trend with increasing amount, duration, and intensity of use. However, the decrease in risk was significant only in the screening arm, raising concerns on the risk of potential detection bias due to the lower baseline PSA value in metformin users before randomization. Use of insulin and other antidiabetic drugs was not associated with overall PCa risk. On the contrary, the risk of metastatic PCa was higher in sulfonylurea users (hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.11–3.77), suggesting hyperinsulinemia as a risk factor for PCa progression.

A population-based case-control study (PBCC) from Denmark [20] found that metformin use was associated with a decreased risk of PCa (adjusted odds ratio [aOR] 0.84, 95% CI 0.74–0.96) and, in particular, localized disease (aOR 0.70, 95% CI 0.57–0.87), while no association with locally advanced or distant metastatic disease was found. Both increasing duration and intensity of metformin use were associated with a decreasing incidence of PCa. However, the decreased risk of PCa was found only in diabetics with a ≥6-yr history (aOR 0.81, 95% CI 0.69–0.96). No significant associations were found between the use of other antidiabetic drugs (including insulin) and PCa risk.

3.1.1.2. Statins. In a PBCC study from the USA [25], statin use was not associated with the risk of overall or grade-/stage-specific PCa.

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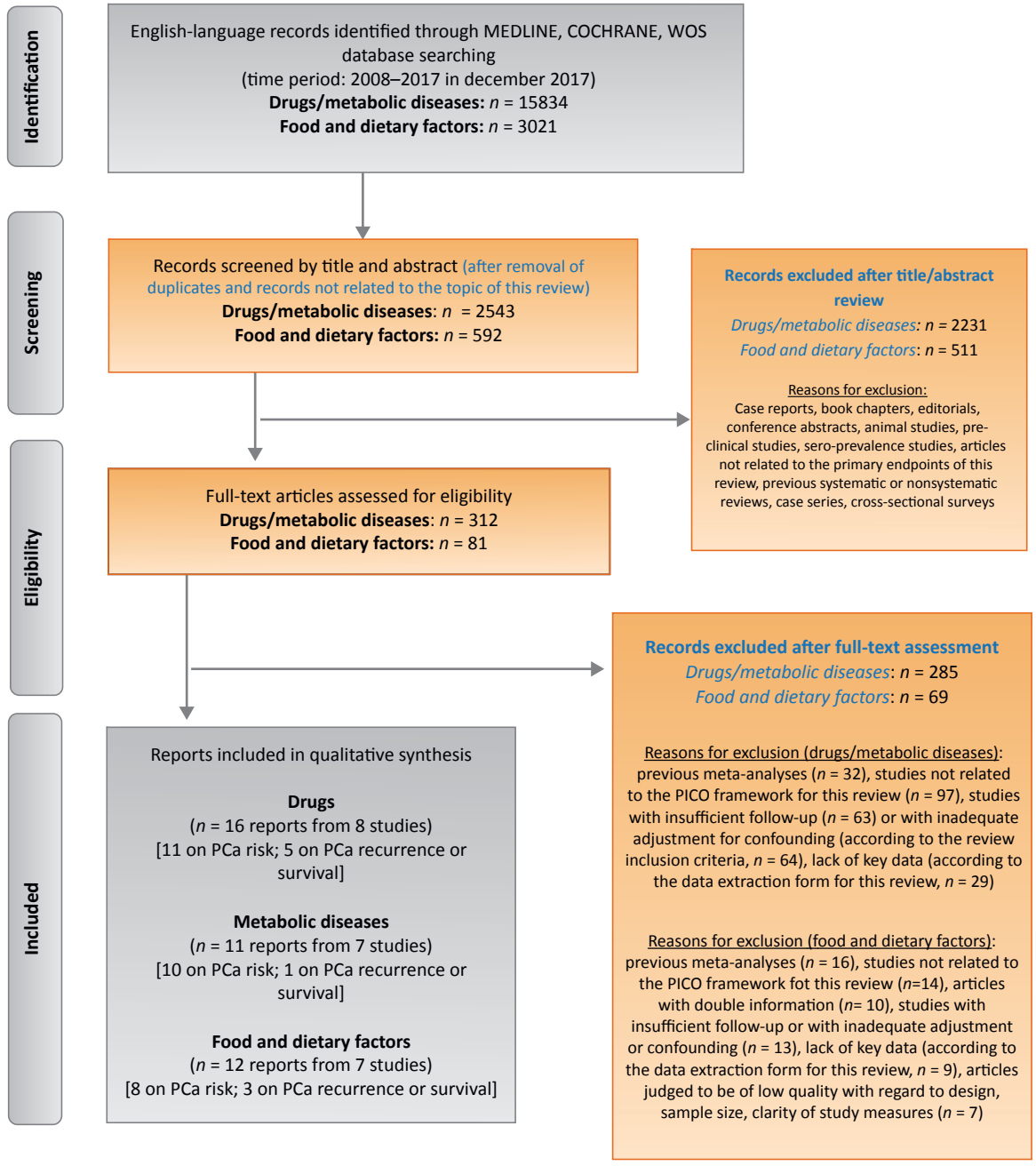

Fig. 1 – Flow-diagram showing the step-by-step review process according to the PRISMA statement criteria. The detailed strategy for records identification and selection is provided in the Supplementary material. PCa = prostate cancer; PICO = population, intervention, comparator, and outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; WOS = Web of Science.

3.1.1.3. Aspirin. In a PCS from the Health Professionals Follow-up Study (HPFS) cohort [26], consumption of at least two adult-strength aspirin tablets a week was associated with a 10% lower risk of overall PCa, with no material difference in the risk for higher levels of frequency, duration, or frequency of use. Only men older than 65 yr experienced reduced risks. Most measurements of aspirin use were also associated with modest decreases in the risk of high-grade PCa, with a significant dose relationship for tablets per week. PSA testing did not change the overall set of results.

In a subsequent study from the same cohort with 32 yr of follow-up, regular use of aspirin was not associated with the risk of advanced (≥T3b, N1, or M1 at diagnosis) PCa, even considering the potential effect of PSA testing [16].

In a PCS from the PLCO Cancer Screening Trial cohort [27], daily use of aspirin was significantly associated with a lower risk of PCa (HR [95% CI] 0.91 [0.84–0.99]). The risk was similar considering men taking one or more pill of aspirin per day (vs never use); however, this inverse association appeared to be more pronounced among men aged >65 yr and in those who reported a history of cardiovascular-

Table 1 – Key findings from studies included in the review on the role of drugs for prostate cancer risk, recurrence, and survival.

Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Antidiabetic drugs					
Haring et al (2017) [24] (I)	FinRSP[a] (studies using a systematic PCa screening protocol) Finland PCS 1996–2009	78 615	Antidiabetic drug use Incidence of total, high-grade (GS 7–10), low-grade, metastatic PCa[a]	AC: use of other medications	1. Antidiabetic drug users (vs nonusers) had lowered risk of total (HR 0.85, 95% CI 0.79–0.92) PCa but increased risk of metastatic disease (HR 1.44, 95% CI 1.09–1.91). In analysis excluding PCa cases diagnosed within 3 yr after the baseline, there was a significant inverse association (HR 0.86, 95% CI 0.79–0.94) for overall PCa, but no association with high-grade disease or metastatic disease. After exclusion of sulfonylurea users, the risk increase for metastatic PCa was no longer observed. 2. Overall PCa risk decreased with increasing cumulative use, but no consistent trends were observed for high-grade or metastatic PCa. 3. PCa risk was lowered among metformin users compared with users of other oral antidiabetic drugs, with a significant inverse trend with increasing amount, duration, and intensity of metformin use. No consistent differences in overall PCa risk were observed with the use of sulfonylureas, thiazolidinediones, or insulins. The risk of metastatic PCa was higher in sulfonylurea users compared with other oral antidiabetic drug users (HR 2.04, 95% CI 1.11–3.77). 4. PCa screening did not modify the association between PCa risk and antidiabetic drugs in general, but affected the association for metformin: the decrease in risk was significant only in the screening arm (p for interaction < 0.001).
Preston et al (2014) [20] (I)	Denmark PBCC 1989–2011	12 226 cases 122 260 controls	Antidiabetic drugs (including metformin, insulin) Incidence of PCa	AC: comorbidities (Charlson comorbidity index), diabetic complications (a proxy for diabetic severity), marital status (married, never married, divorced, or widowed), and ever use of PPIs, statins, and 5-ARIs No formal adjustment for PSA testing	1. Metformin use (vs never use) was associated with a decreased risk of PCa. In sensitivity analysis limited to patients with a PSA test, metformin use was associated with a decreased risk of PCa compared with nonuse (aOR 0.66; 95% CI 0.51–0.86). In the stage-stratified analysis, metformin use was associated with a reduced risk of localized cancer (aOR 0.70; 95% CI 0.57–0.87), but not regional or distant metastatic PCa. Increasing duration or intensity of metformin use was associated with decreasing incidence of PCa (durations of 3–5 yr: aOR 0.76; 95% CI 0.58–1.01; >5 yr: aOR 0.75; 95% CI 0.57–0.98). 2. Metformin use was not associated with decreased risk of PCa only in diabetics with a >6-yr history (aOR 0.81; 95% CI 0.69–0.96). 3. A reduced risk of PCa was associated with insulin use but not with the use of other antidiabetic medications. In the sensitivity analysis limited to patients with a PSA test, no significant reduction in PCa risk among users of insulin and other diabetic medications use were found.
Statins					

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Table 1 (*Continued*)

Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Agalliu et al (2008) [25] (I)	KC USA PBCC 2002–2005	1001 cases 942 controls	Statin use (ever vs never use/use for >1/wk for >3 mo) Incidence of total, high-grade, localized PCa	AC: none	1. Statin use was not associated with risk of PCa. No associations were observed with other measures of statin use (current use, duration of use, age at first use, time since first use). 2. No associations were found between statin use and Gleason score, tumor stage (local vs regional/distant), or PCa aggressiveness status (less vs more). 3. In analyses stratified by age, race, first-degree family history of PCa, BMI, use of NSAIDs, and *CYP3A4*/*CYP3A5* gene variants, no differences in risk estimates were observed, except for BMI: no association was found in nonobese men (BMI <30), while a weak association between current use (vs no use) of statin and PCa (OR 1.50 [95% CI 1.00–2.24]) in obese men (BMI ≥30), with OR being higher among long-term (≥5 yr) users (1.8 [1.1–3.0]).
Chan et al (2015) [31] (II)	HPFS USA PCS 1986–2010 (FU: 33 302 person-years)	3949	Statin use (current, overall duration) Lethal PCa (M+ or PCa-specific death)	AC: time period, time from diagnosis to questionnaire, BMI, hours engaged in vigorous physical activity per week, smoking status, aspirin use, clinical stage, PSA at diagnosis, Gleason score, primary treatment, comorbidities (stroke, myocardial infarction, hypertension, diabetes)	1. No statistically significant association was found between postdiagnostic current statin use and lethal PCa, as well as for duration of use (≥6 yr vs none). Results were unchanged when either limiting to men with prior history of PSA screening or after adjusting for prediagnostic statin use. 2. There was no evidence of effect modification by investigated a priori factors, with the exception of stage. Among men diagnosed with T2+ PCa, current use of statins was associated with a reduced risk (HR 0.65, 95% CI 0.43–0.97), whereas among those diagnosed with T1 disease, the HR was 1.26 (95% CI 0.84–1.87; *p* value interaction 0.02).
Murtola et al (2017) [32] (II)	FinRSP Finland PCS 1996–2013 (median FU after diagnosis: 7.5 yr)	6537	Statin use PCa-specific mortality [a]	AC: Gleason score, tumor stage, PSA level at diagnosis, usage of other drugs No formal adjustment for primary treatment	1. Statin use before diagnosis was not significantly associated with risk of PCa death. No risk trends by amount, duration, or intensity of statin use were observed. 2. Statin use after diagnosis was associated with a decreased risk of PCa death even after multivariable adjustment (HR 0.80, 95% CI 0.65–0.98). The risk decrease was significant among men diagnosed with low/medium risk cancer at baseline. The risk estimates decreased in an inverse association with the intensity of statin use. Worse PCa-specific survival was observed in men who discontinued statin use after diagnosis, while active use was associated with improved survival compared with nonuse. 3. No risk reduction was observed for users of nonstatin cholesterol-lowering drugs. 4. Primary treatment modified the survival association: survival was significantly improved by postdiagnostic statin use only in men with ADT as the primary treatment (*p* for interaction 0.059). 5. PSA screening did not show a significant effect modification on the survival associations. 6. Postdiagnostic statin use was associated with a lowered risk of PCa death among men who were not using antihypertensive drugs (HR 0.36, 95% CI 0.15–0.90, *p* for interaction 0.039). 7. A decreased risk among postdiagnostic statin users persisted when deaths due to cardiovascular causes were analyzed as competing causes of death (HR 0.39, 95% CI 0.32–0.49).
Aspirin and NSAIDs					

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Table 1 (*Continued*)

Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Dhillon et al (2011) [26] (I)	HPFS USA PCS 1988–2006 (FU: 727 061 person-years)	47 271	Aspirin use Incidence of total, high-grade (GS 8–10), regionally advanced (T3b–T4 or N1 and M0) PCa	AC: time period; height; BMI; smoking;, intakes of tomato sauce, vitamin D, total kilocalories, fish, red meat; vigorous physical activity; use of statins	1. There was a 10% lower risk of overall PCa for men who consumed at least two adult-strength aspirin tablets a week (HR 0.90 for 2–5 tablets/wk; 95% CI 0.80, 1.02, and HR 0.90 for ≥6 tablets/wk; 95% CI 0.83, 0.99). There was no material difference in risk for higher levels of frequency, duration, or frequency of use. 2. The association of aspirin use with total disease significantly differed by age such that older men (>65 yr) experienced reduced risks (2–5 tablets/wk: HR 0.85 [95% CI 0.73, 0.98], and ≥6 tablets/wk: HR 0.85 [95% CI 0.76, 0.94], *p* for trend = 0.001), whereas men 65 yr and younger did not. A similar pattern emerged after excluding T1c cases. No effect modification by BMI was found. 2. For high-grade PCa, modest decreases in risk were observed for most measurements of aspirin use and a significant dose relationship emerged for tablets per week with the heaviest users (≥6/wk) experiencing a 28% decreased risk compared with nonusers (95% CI 0.54, 0.96). 3. For regionally advanced disease, there was no overall dose-response association for frequency, quantity, or duration of aspirin use. 4. In sensitivity analyses restricted to men who had ever received a PSA test, adjusted for PSA screening in the prior 2-yr cycle, and restricted to men who were screened by PSA in the same 2-yr cycle, overall set of results did not change.
Cao et al (2016) [16] (I)	HPFS USA PCS 1986–2010 (FU: 32 yr)	47 881	Regular aspirin use (≥2 times per week, including standard and low-dose aspirin) Incidence of advanced PCa (≥T3b, N1, or M1 at diagnosis)	AC: height, BMI, physical exam in past 2 yr, pack years of smoking, leisure-time physical activity, alcohol intake, current multivitamin use, regular use of NSAIDs, total energy intake, folate, calcium, red and processed meat intake, and adherence to Alternate Health Eating Index 2010	1. Regular use of aspirin was not associated with the risk of advanced PCa. 2. The association did not appear to vary according to a history of PSA screening.

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Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Veitonmäki et al (2014) [29] (I)	FinRSP Finland PCS 1996–2009	78 615 (screening arm 30 194; control arm 48 421)	NSAID use Incidence of total, metastatic PCa[a]	AC: simultaneous use of other medications, usage of other NSAIDs	1. When compared with NSAID nonusers, the overall PCa risk was elevated among current NSAID prescription users (HR 1.45, 95% CI 1.33–1.59 and HR 1.32, 95% CI 1.10–1.59 in the screening and the control arm, respectively). Previous use or over-the-counter use was not associated with PCa risk. A similar risk association was also observed for acetaminophen, but not for aspirin. Both current and previous coxib uses were associated with an elevated PCa risk. The increased PCa risk associated with overall NSAID, coxib, and acetaminophen use was not modified by tumor grade. The association between NSAID use and PCa risk was not modified by cumulative COX-2 inhibition. Stratification by the use of other drug groups or NSAIDs before randomization, Charlson comorbidity index, or propensity for NSAID use did not modify the risk association with PCa. 2. Current, but not previous, use of prescription NSAIDs, coxibs, and acetaminophen was associated with an elevated risk of metastatic PCa in both trial arms. Aspirin use was not significantly associated with metastatic PCa risk, with the exception of elevated risk among prescription users in the control arm. Intensity of NSAID and coxib use was directly correlated with the risk of metastatic PCa after adjustment for the use of other drugs.
Jacobs et al (2011) [30] (I)	CPS-II Nutrition Cohort USA PCS 1992–2007	78 485	Regular use of acetaminophen (≥30 pills/ mo; for >/<5 yr) Incidence of total, aggressive (stages III–IV or GS ≥7 or PCa-specific death) PCa	AC: education, BMI, diabetes, use of NSAIDs, rheumatoid arthritis, or osteoarthritis	1. Current regular acetaminophen use regardless of duration was not associated with PCa risk. Current regular use for ≥5 yr (long-term regular use) was associated with lower risk of both total (HR 0.62, 95% CI 0.44–0.87) and aggressive (RR 0.49, 95% CI 0.27–0.88) PCa, while current regular use for <5 yr was not associated with PCa risk. 2. In a subanalysis using follow-up from 1999 forward (when duration of use could be more precisely measured), intermediate-duration regular acetaminophen use (2–5 yr) was not associated with the risk of PCa.
Shebl et al (2012) [27] (I)	PLCO USA PCS From 1993–2001 (enrollment) to 2009 (median FU: 11.7 yr)	3575 cases 25 875 controls	Regular aspirin and ibuprofen use (at study entry) Incidence of total, aggressive (GS ≥7 or stage III–IV) PCa [a]	AC: study center, aspirin (for ibuprofen) and ibuprofen (for aspirin) use, physical activity, dietary fat consumption, other dietary factors	1. Daily use of aspirin only was significantly associated with a lower risk of PCa with an HR (95% CI) of 0.91 (0.84–0.99). There was no evidence of an association between ibuprofen use and PCa risk. 2. Risks associated with daily aspirin use were similar, but slightly lower for aggressive than for nonaggressive cancers. History of various medical conditions (including diabetes, hypertension, stroke, heart attack, arthritis) did not appreciably modify the association between the use of either drugs and PCa risk. 3. The risk for PCa associated with taking ≥1 pill of aspirin per day (vs never use) was 0.92 (95% CI 0.85–0.99). A significant negative trend with the frequency of aspirin use (p for trend 0.04) was observed. 4. In stratified analysis, the inverse associations appeared more pronounced among men taking ≥1 pill of aspirin daily who were older than 65 yr (HR [95% CI] of 0.87 [0.78–0.97]) and who reported having a history of cardiovascular-related diseases (HR [95% CI] 0.89 [0.80–0.99]) or arthritis (HR [95% CI] 0.88 [0.78–1.00]) despite the lack of significant interaction.

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Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Salinas et al (2010) [28] (I)	KC USA PBCC 2002–2005	1001 cases 942 controls	Aspirin/NSAIDs use (ever, daily, daily low dose, long term) Incidence of PCa	AC: none	1. Ever use of aspirin was associated with an 18% reduction in the relative risk of PCa (OR 0.82, 95% CI 0.68, 0.99). 2. Daily use of aspirin (OR 0.78, 95% CI 0.64, 0.95) and daily low-dose use (OR 0.71, 95% CI 0.56, 0.90) were associated with further risk reductions. Daily low-dose aspirin use was associated with decreased ORs for both less (OR 0.73, 95% CI 0.56–0.95) and more (OR 0.71, 95% CI 0.50–1.01) aggressive PCa. 3. Current use of aspirin was associated with a 21% decrease in the risk of PCa relative to nonusers (OR 0.79, 95% CI 0.65, 0.96), although former users had no reduction in risk. 4. Long-term use of aspirin was also associated with a significant reduction in risk, with men who used aspirin for >5 yr having an OR of 0.76 (95% CI 0.61, 0.96). There were no significant patterns of risk in relation to time since first or last use of aspirin. The strongest reduction in risk was in current users with >5 yr of use (OR 0.74, 95% CI 0.58, 0.94). 6. There were no associations between the use of nonaspirin NSAIDs and PCa risk. As the majority of nonaspirin NSAID use was for ibuprofen (controls, 50.5%; cases, 45.8%), this drug was examined separately; however, no association was found. 7. There was no evidence of any relation to PCa risk of using acetaminophen.
Downer et al (2017) [33] (II)	Physicians' Health Study USA PCS 1982–2015 (for PCa patients)	For survival analysis in PCa patients diagnosed with nonmetastatic disease: 3462 (for survival analysis, the pre-PSA era included cases diagnosed before 1992)	Postdiagnostic regular aspirin use (taking >3 tablets/wk for at least 1 yr) Incidence of lethal (M+ or PCa-specific death) PCa and PCa-specific survival	AC for risk analysis: BMI, height, smoking, hypertension, type 2 diabetes (yes vs no) No formal adjustment for PSA screening AC for survival analysis: Charlson comorbidity index, BMI, smoking, hypertension, type 2 diabetes, stage PSA, Gleason score, primary treatment	1. Risk analysis: (A) Current use was associated with a lower risk of lethality regardless of duration. Compared with never use, past regular aspirin use among men initially free of diagnosed cancer was associated with a lower risk of lethal PC regardless of time since quitting. (B) Associations between aspirin and reduced lethal PCa did not hold among cases diagnosed in the PSA era. 2. Survival analysis: (A) Compared with never users, current postdiagnostic use among men diagnosed with nonlethal PC was associated with a lower risk of lethality (HR 0.68, 95% CI 0.52–0.90) regardless of duration. Past postdiagnostic use was associated with a higher risk of lethality (HR 1.50, 95% CI 1.10–2.05). (B) Associations between current postdiagnostic aspirin and improved survival did not hold for cases diagnosed in the PSA era.
5-Alpha reductase inhibitors					

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Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Preston et al (2014) [17] (I)	HPFS USA PCS 1996–2010 (FU:14 yr, 448 803 person-years)	38 058	5-ARI use Incidence of total, high-grade (GS 8–10), advanced (stage T3b–T4, N1, M1, and PCa death) PCa	AC: time period, smoking history, vigorous physical activity, BMI, height, diabetes mellitus, physical examinations, prostate biopsy or rectal ultrasonography, vasectomy, use of other medications	1. There was a 23% lower risk of overall PCa for men who had ever used 5-ARIs (vs never use; HR 0.77; 95% CI 0.65–0.91), and a significantly decreased risk of intermediate- (GS 7; HR 0.67; 95% CI 0.49–0.91) and low-grade (GS 2–6; HR 0.74; 95% CI 0.57–0.95) PCa, but no significant association with high-grade (even considering GS 4 + 3 = 7) or lethal PCa (even including stage T3b–T4). 2. When analyzed as a continuous variable, increased duration of use was associated with significantly lower risk of overall PCa (HR for 1 yr of additional use 0.95; 95% CI 0.92–0.99), localized disease (HR 0.95; 95% CI 0.90–1.00), and low-grade disease (HR 0.92; 95% CI 0.85–0.99). 3. In the analysis among only those men who underwent PSA testing in 1996, very similar results to the primary analysis were found (no association with high-grade/lethal disease and significant association with a reduced risk of overall, localized, and low/intermediate-grade disease)
Murtola et al (2016) [34] (II)	FinRSP Finland PCS 1996–2013 (median FU after diagnosis: 7.5 yr)	6537 PCa cases from both study arms	5-ARI/alpha-blockers use PCa-specific mortality [a]	AC: medication use, Gleason score, clinical tumor stage, PSA level at diagnosis, use of other drug groups, simultaneous usage of alpha-blockers or 5-ARIs No formal adjustment for primary treatment	1. Prediagnostic 5-ARI use (vs nonuse) was not associated with the risk of PCa death. Stratification by amount, duration, or intensity of 5-ARI use showed no survival trends. Postdiagnostic 5-ARI usage was not significantly associated with PCa survival. No risk associations by amount, duration, or intensity of use were observed. In cases with >10 yr of follow-up, no association was observed between pre/postdiagnostic use and PCa-specific survival. 2. In prediagnostic alpha-blocker users, PCa-specific survival was worse (HR 1.29; 95% CI 1.08–1.54), with no difference in overall survival. Postdiagnostic alpha-blocker usage was associated with increased risk of PCa death (HR 1.56, 95% CI 1.30–1.86; ongoing use: HR 1.46, 95% CI 1.15–1.84; discontinued use: HR 1.67, 95% CI 1.32–2.11). Worse PCa-specific survival was observed only during the first 5 yr of usage, with the risk difference disappearing in longer use. The increased risk of PCa death was especially high in cases diagnosed in the screening arm and in those using antidiabetic drugs also. When the analysis was limited to include only cases with >10 yr of follow-up after diagnosis, both pre- and postdiagnostic alpha-blocker usage were not significantly associated with increased mortality.
Other drugs					
Blanc-Lapierre et al (2014) [21] (I)	PROtEuS Canada PBCC 2005–2009	1588 cases (response rate 86% of eligible) 1618 controls (response rates 63% of eligible)	Oral anticoagulants use Incidence of total, low-grade, high-grade (GS ≥7) PCa	AC: education, diabetes, BMI, statin use	1. Ever use of oral anticoagulants was not significantly associated with the risk of PCa (a weak, inverse, non–statistically significant association was found). The association did not vary substantially according to time since first use, duration of use, current use, age at first use, or indication. 2. Similar results were observed among patients screened within the last 2 yr and with regard to cancer aggressiveness.

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Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for at statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Kaapu et al (2016) [35] (II)	FinRSP Finland PCS 1996–2013 (median FU after diagnosis: 7.5 yr)	6537 PCa cases from both study arms	Antiarrhythmic drugs (digoxin and sotalol) pre/ postdiagnostic use Risk of PCa death and PCa-specific survival [a]	AC: tumor risk group, use of other drugs (for BPH, diabetes, hypercholesterolemia or hypertension, aspirin, other NSAIDs) No formal adjustment for primary treatment	1. Prediagnostic digoxin use was not significantly associated with the risk of PCa death. Further adjustment for tumor risk group and use of other medications did not change the result. Postdiagnostic digoxin usage was not significantly associated with PCa survival. Further model adjustment did not change the result. No consistent survival differences were observed by cumulative amount and duration of postdiagnostic digoxin use. 2. Prediagnostic sotalol usage did not affect the risk of PCa death, and no clear risk trends were observed by cumulative usage. Postdiagnostic usage of sotalol was generally not significantly associated with the risk of PCa death. 3. Use of ADT as primary treatment of PCa did not modify the effect of digoxin, although a significant risk decrease was observed among men not receiving ADT and using digoxin before diagnosis (HR 0.20, 95% CI 0.048–0.86).

I = study on PCa incidence; II = study on PCa recurrence/progression or survival; ADT = androgen deprivation therapy; aOR = adjusted odds ratio; BMI = body mass index; BPH = Benign prostatic hyperplasia; CI = confidence interval; CPS = Cancer Prevention Study; FinRSP = Finnish Randomized Study of Screening for Prostate Cancer; FU = follow-up; GS = Gleason score; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; KC = King County; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PBCC = population-based case-control study; PCa = prostate cancer; PCS = prospective cohort study; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial; PPI = proton pump inhibitor; PSA = prostate-specific antigen; PROtEuS = Prostate Cancer & Environment Study; 5-ARI = 5-alpha reductase inhibitor.
Sentences and data are reported in the table as provided by study authors in the original manuscripts.
[a] Studies using a systematic PCa screening protocol.

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Table 2 – Key findings from studies included in the review on the role of metabolic diseases for prostate cancer risk, recurrence, and survival.

Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk], or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Metabolic syndrome					
Blanc-Lapierre et al (2015) [18] (I)	PROtEuS Canada PBCC 2005–2009	1937 cases (79.4% of eligible) 1995 controls (55.5% of eligible)	Metabolic syndrome (defined by NCEP-ATP III, WHO, IDF) Incidence of total, low-grade (GS <7 or 3 + 4), and high-grade (GS >7 or 4 + 3) PCa	AC: family income	1. Patients with a history of MetS (≥3 components according to the NCEP-ATP III definition) were at a significantly lower risk of PCa (OR 0.70 [0.60–0.82]) compared with those with <3 MetS components. This association was also observed when using other definitions for MetS or abdominal obesity. The ORs did not vary significantly according to PCa aggressiveness (low grade: OR 0.69 [0.58–0.82], high grade: OR 0.75 [0.60–0.94]). 2. The risk decreased with the number of MetS components present (p trend <0.01) in a nonlinear manner, suggesting a synergistic interaction of MetS components. 3. The negative association tended to be more pronounced among men <40 yr at MetS onset and among men diagnosed with PCa before age 65. 4. In a model including all MetS components and the same controlling factors, history of dyslipidemia (adjusted for statin use, OR 0.58 [0.47–0.71]) was associated with PCa risk, while history of type 2 diabetes (adjusted for metformin use) or abdominal obesity or hypertension was not.
Obesity					
Möller et al (2015) [37] (I)	HPFS USA PCS 1986–2010 (FU: 24 yr, 938 614 person-years)	47 491 Analysis on BMI at age 21: 45 695; on WC: 31 069; on childhood body shape: 34 983	- BMI at age 21 - Cumulative average BMI since baseline - Adult WC Incidence of total (stage > T1a), low-grade, GS 7, high-grade (GS 8–10), advanced (stage T3b/T4, N1, or M1) PCa	AC: vigorous activity, energy intake, smoking, diabetes, anthropometric measures	1. Higher BMI at age 21 was associated with: (a) significantly lower risk of advanced, and Gleason 7 PCa (adjusted RRs in the range 0.69–0.77 comparing BMI 26 to BMI 20–21.9; a significant trend was seen across BMI categories only for advanced and Gleason 7); (b) weak inverse associations for total, nonadvanced, and low-grade PCa. 2. Cumulative average BMI since baseline was: (a) inversely associated with total, nonadvanced, Gleason 7, and low-grade PCa among men ≤65 yr; (b) not significantly associated with PCa in men >65 yr. 3. Associations of BMI at age 21 and adult BMI and PCa were somewhat attenuated when additionally adjusting for childhood body shape, or mutual adjustment for BMI in early or late adulthood, respectively. 4. Higher WC was associated with a lower risk of nonadvanced, Gleason 7, and low-grade PCa, but not with the risk of total PCa. The observed associations were weakened when adjusting for either childhood body shape or adult BMI.

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Table 2 (*Continued*)

Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk], or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Stevens et al (2017) [23] (I)	CPS-II Nutrition Cohort USA PCS 1997–2013	46 094	WC Incidence of total, high-grade (GS >7), low-grade PCa	AC: history of diabetes, physical activity, energy intake, education, alcohol intake, BMI	There was no significant association between WC (categorical/ continuous analyses) and total, high-grade, or low-grade PCa after adjustment for BMI.
Kelly et al (2017) [19] (I)	PLCO[a] (studies using a systematic PCa screening protocol) USA PCS 1993–2001 (enrollment) to 2009 (median FU: 11.5 yr, 695 205 person-years)	69 873	- BMI at age 21 - BMI at age 50 - BMI at study entry - BMI trajectories Incidence of total, aggressive (GS ≥7 or stage III–IV) PCa[a]	AC: study center, education, marital status, cigarette smoking status, diabetes, myocardial infarction	1. BMI was modestly associated with the risk of total PCa (BMI at age 20: HR 0.82 [95% CI 0.68–0.99] comparing BMI ≥30 with the reference BMI [18.5–25]; BMI at age 50: HR 0.95 [95% CI 0.91–1.00] comparing BMI 25–30 with the reference and HR 0.87 [95% CI 0.81–0.94] comparing BMI ≥30 with the reference; BMI at baseline: HR 0.93 [95% CI 0.87–1.00] comparing BMI ≥30 with the reference). 2. BMI (at any age/mean/maximum) was not associated with either aggressive or nonaggressive PCa. 3. Weight change was not associated with PCa risk. 4. In trajectory analyses, there was a slight inverse association between BMI trajectory of men who were overweight at age 20 and remained overweight or became obese, and total PCa.
Dimitropoulou et al (2011) [38] (I)	ProtecT UK NCC 2000–2008	For BMI analysis: 919 cases/3931 controls For WC analysis: 960 cases/ 4156 controls For WHR analysis: 948 cases/4069 controls	- BMI - WC - WHR Screen-detected total, localized (T1–2 N0M0), high-grade (GS 8–9), intermediate-grade (GS 7), low-grade PCa[a]	AC: none	1. There was no evidence of any important relationship between any of the measures of adiposity and (PSA-detected) total PCa. 2. There was a weak association between BMI and low-grade PCa (p trend 0.045; BMI ≥30 vs <25: OR 0.76, 95% CI 0.59, 0.97). 3. There was no association with either WC or WHR for disease stage or grade.
Boehm et al (2015) [22] (I)	PROtEuS Canada PBCC 2005–2012	1921 cases/1982 controls	- WC - WHR - BMI Incidence of total, low-grade (GS ≤6), high-grade (GS >7) PCa	AC: physician visits per year	1. Increased abdominal obesity (WC >102 cm), adjusted for BMI, was associated with an increased risk of overall (OR 1.23 [95% CI 1.05–1.46]) and high-grade (OR 1.47 [95% CI 1.22–1.78]) PCa. In analyses stratified according to BMI categories, a positive association between WC >102 cm and high-grade PCa was observed among overweight as well as obese men. 2. Compared with men with BMI <25, overweight men (BMI 25–30) were at a lower risk of total (OR 0.87 [95% CI 0.74–1.01]), low-grade (OR 0.83 [95% CI 0.68–1.00]), and high-grade (OR 0.89 [95% CI 0.75–1.06]) PCa; obese men (BMI ≥30) were at a lower risk of total (OR 0.72, 95% CI [0.60–0.87]), low-grade (OR 0.71 [95% CI 0.55–0.90]), and high-grade (OR 0.73 [95% CI 0.59–0.91] PCa. 3. Adjusting for PSA testing or diabetes or physical activity had minimal effect on results. 4. In analyses adjusted for BMI, a weak association was found between WHR and high-grade PCa (OR 1.20 [95% CI 1.01–1.43]); in subgroup analyses according to BMI categories, no significant associations were observed.

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Dickerman et al (2017) [39] (II)	HPFS USA PCS 1986–2012 (FU: 48 804 person-years)	5158 For analysis of PSA recurrence: 4482	- Long-term weight change (age 21 to diagnosis) - Short-term weight change (over 4/8 yr before diagnosis) - BMI at age 21 - BMI at diagnosis Incidence of lethal PCa (M+ or death due to PCa)	AC: weight; height; smoking status at diagnosis; diabetes at diagnosis; heart/lung disease by the time of diagnosis; intakes of tomato sauce, coffee, alpha-linolenic acid, calcium, and energy; physical activity at diagnosis; clinical stage; Gleason grade; PSA at diagnosis; primary treatment	1. Long-term weight gain was not associated with an increased risk of lethal PCa. Among never smokers, higher long-term weight gain was associated with an increased risk of lethal disease. In sensitivity analyses (restricting to those surviving ≥4 yr after diagnosis), those who gained >30 pounds from age 21 to diagnosis had a 1.45-fold higher risk of lethal cancer compared with those with stable weight (±10 pounds; 95% CI 1.02–2.06, *p* trend = 0.06). This association was stronger among never smokers (HR 2.31, 95% CI 1.35–3.98, *p* trend = 0.001). 2. Short-term (over 4 and 8 yr preceding diagnosis) weight gain was not associated with the risk of lethal PCa. 3. Among those with a BMI of ≥25 at age 21: (a) long-term weight gain of >30 pounds was associated with a 1.85-fold higher risk of lethal cancer (95% CI 0.87–3.92) compared with those with stable weight; (b) those who gained >5 pounds in the 8 yr prior to diagnosis had a 2.64-fold increased risk of lethal disease (95% CI 1.12–6.23) compared with those with stable weight. 4. BMI at age 21 and BMI at diagnosis were not significantly associated with the risk of lethal PCa. Weight change and obesity (BMI) were not associated with an increased risk of biochemical recurrence.
Diabetes					
Kasper et al (2009) [40] (I)	HPFS USA PCS 1986–2004	47 781	Diabetes mellitus Incidence of total (stage >T1a), high-grade, low-grade, advanced PCa	AC: level of physical activity, current BMI, BMI at 21 yr, height, smoking habits, and intakes of calories, bacon, tomato sauce, alpha-linolenic acid, calcium, fish, and vitamin E supplementation	1. History of DM diagnosis was: (a) associated with a 17% reduced risk of total PCa (HR [95% CI] 0.83 [0.74–0.94]), a 28% reduced risk for localized PCa (0.72 [0.62, 0.84]), a 31% reduced risk for high-grade PCa (0.69 [0.55, 0.87]), and a 24% reduced risk for low-grade PCa (0.76 [0.62, 0.92]); b) not significantly associated with advanced PCa. 2. In the pre-PSA era (vs PSA era): (a) the inverse relationship between DM and PCA seems to be stronger in high-grade (vs low-grade) PCa; (b) total PCa risk appears to be lower; (c) in both eras, there were a similar association for nonadvanced PCa. 3. As time since DM diagnosis increased, there was a significant trend of a decrease in the risk for total PCa (for diagnoses >6 yr). There was no significant trend over time for any of the subgroups of PCa (possibly due to small sample sizes). 4. In additional analyses, the inverse relationship between DM and PCa was stronger in men with BMI ≥25 and ≥30 (at diagnosis) and with BMI ≥30 at age 21.

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Dankner et al (2016) [41] (I)	Israel PCS 2002–2012	1. Follow-up 2005–2012: 99 744 2. Follow-up 2002–2012: 1 034 074	Diabetes mellitus Incidence of total, low-grade, high-grade (Middle East Cancer Consortium grading system) PCa	AC: socioeconomic status	1. Men with incident diabetes (vs men without diabetes) were at higher risk of total PCa (HR [95% CI] 1.65 [1.55–1.76]) during the 1 st year following diabetes diagnosis, while the risk decreased by the 3rd and subsequent years following diabetes diagnosis (0.89 [0.84, 0.95]), as it was for the prevalent diabetes group (0.80 [0.76, 0.85]). 2. A decreased risk during the 3rd and subsequent years following diagnosis was observed for low-medium grade PCa (GS 2–6; 0.83 [0.77, 0.89]) but not for high-grade cancer (GS 7–10). 3. Subanalyses controlling for PSA testing during 2002–2003 achieved similar results. 4. Mean PSA values were significantly lower for men with diabetes, even prior to diabetes diagnosis. Although mean values increased with age, they increased more rapidly among men without diabetes. For men diagnosed with diabetes 10 yr previously, mean PSA values were similar to those of men with long-term diabetes (for both, approximately 20% lower than in men who were diabetes free). 5. Among men with incident diabetes (vs men who remained diabetes free), the proportion with positive PSA tests (>4 μg/l) was 8% lower (ratio 0.92) in the year they were diagnosed (2002) and decreased to about 20% lower (ratio ~0.80) at about 6–8 yr after diagnosis, thus reaching the same ratio as for men with prevalent diabetes.
Turner et al (2011) [42] (I)	ProtecT UK NCC 2002–2006	1291 cases 6479 controls	Diabetes mellitus Incidence of screen-detected total, localized (T1–T2, NX-O, MO), advanced (T3–T4), high-grade (GS ≥7) PCa[a]	AC: none	1. In the age-adjusted model, presence of diabetes was associated with a reduced risk of total (OR 0.78 [95% CI 0.61–0.99]), localized (T1–T2; 0.76 [0.59–0.98]), and well-differentiated (GS 2–6; OR 0.69 [0.52–0.93]) PCa. These associations were not altered after controlling for family history of PCa. 2. In additional analyses excluding PCa diagnosed in the 1 st year after the diagnosis of diabetes, or in patients with data on BMI, the association was not statistically significant. 3. There was no evidence that the inverse association was greater with increasing length of time since diabetes diagnosis. 4. Among controls, men with diabetes had marginally lower PSA levels than those without diabetes (geometric means: 0.915 vs 1.03 ng/ml; $p = 0.15$). In a sensitivity analysis investigating whether the reduced odds of PCa resulted from undetected PCa, the association was not significant (OR "adjusted" for possible differential misclassification 0.82 [0.65–1.03], $p = 0.09$).
Hypercholesterolemia					

Table 2 (*Continued*)

Authors (publication year)	Study ID Country Study design Enrollment period	Participants included in analytic cohort	Definition of exposure/ outcome	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa and PSA testing [for PCa risk], or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Mondul et al (2010) [55] (I)	CLUE II USA PCS From 1989 (mean FU: 11.9 yr)	6816	Desirable (<200 mg/dl), borderline (200–240 mg/dl), high (>240 mg/dl) plasma cholesterol concentration Incidence of total, advanced (≥T3), high-grade (GS ≥7) PCa	AC: highest attained education level; cigarette smoking status; BMI; intakes of meat, dairy products, and tomato products; alcohol intake	1. There was no (statistically significant) association between cholesterol concentration and incidence of total, advanced, or organ-confined PCa. The associations did not appreciably differ after exclusion of cholesterol-lowering drug users, diabetes medication users, men who never had a PSA test, or men with a family history of PCa. Excluding the first 2 yr of follow-up also did not change the results. 2. The association between cholesterol and high-grade PCa differed by BMI. Among men with high BMI (BMI >median value of 26.5), men with desirable cholesterol (compared with men with hypercholesterolemia) were less likely to develop high-grade (GS ≥7) PCa (HR 0.46 [95% CI 0.24–0.87]), particularly when restricted to high-grade, organ-confined cases (0.36 [0.16–0.79]).

I = study on PCa incidence; II = study on PCa recurrence/progression or survival; BMI = body mass index; CI = confidence interval; CPS = Cancer Prevention Study; DM = diabetes mellitus; FU = follow-up; GS = Gleason score; HPFS = Health Professionals Follow-up Study; IDF = International Diabetes Federation; HR = hazard ratio; MetS = metabolic syndrome; NCC = nested case-control study; NCEP-ATP III = National Cholesterol Education Program Expert Panel Adult Treatment Panel III; OR = odds ratio; PBCC = population-based case-control study; PCa = prostate cancer; PCS = prospective cohort study; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial; PSA = prostate specific antigen; ProtecT = Prostate Testing for Cancer and Treatment; PROtEuS = Prostate Cancer and Environment Study; RR = risk ratio; WC = waist circumference; WHO = World Health Organization; WHR = waist-to-hip ratio.

Sentences and data are reported in the table as provided by study authors in the original manuscripts.

[a] Studies using a systematic PCa screening protocol.

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Table 3 – Key findings from studies included in the review on the role of food and dietary factors for prostate cancer risk, recurrence, and survival.

Study	Study ID Country Enrollment period (follow-up)	Study design; exposure; outcomes	Participants (total number/ PCa patients)	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa, and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Dietary factors and prostate cancer incidence					
Fat and fatty acid intake					
Leitzmann et al (2004) [43]	HPFS USA 1986–2000	PCS Intakes of fatty acids (a-linolenic (ALA), eicosapentaenoic (EPA), docosahexaenoic (DHA), linoleic (LA), arachidonic (AA) acids) Risk of PCa	47 866; 2965	AC: total energy intake; % of energy derived from polyunsaturated fat, saturated fat, monounsaturated fat, trans-fat, protein, and alcohol; BMI at age 21; height; history of type 2 diabetes mellitus; vasectomy; vigorous physical activity; cigarette smoking in the past 10 yr; intakes of energy-adjusted lycopene, calcium, and supplemental vitamin E No formal adjustment for PSA testing	1. No association was observed for intakes of total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources, and risk of total PCa. Similarly, LA and AA showed no association with the risk of PCa, as well as fish-oil supplement use. 2. Intakes of EPA, DHA, and EPA + DHA showed a significant or borderline significant inverse relation. For risk of organ-confined PCa, the relations were similar to those for total PCa, albeit somewhat weaker; only EPA was statistically significant. 3. ALA from nonanimal sources was associated with an increased risk of advanced PCa (RR 2.02, 95% CI 1.35–3.03). 4. To examine whether increased PSA screening among men with high intake of ALA from nonanimal sources and men with high intake of EPA + DHA may have accounted for the observed associations, additional analyses were performed excluding all noncases who did not have a PSA test by 2000. The relations were essentially unaltered. Similar results were observed when we limited the analysis to men who did not have a PSA test by 1994.
Pelser et al (2013) [44]	NIH-American Association of Retired Persons (AARP) Diet and Health Study USA 1995–1997, (FU: 9 yr)	PCS Total dietary fat, saturated fat, unsaturated fat, fatty acids (ALA, EPA, DHA, LA, DPA; quintile 1–5) Incidence of overall, advanced and fatal PCa	288 268; 23 281	AC: marital status, education, self-reported diabetes, total energy, alcohol intake, intake of tomatoes, BMI, vigorous physical activity, smoking	1. Intakes of total fat, polyunsaturated fat, and total trans-fatty acids were not associated with incidence of total, nonadvanced, advanced, or fatal PCa. 2. Saturated fat intake was related to increased risk of advanced PCa (HR 1.21; 95% CI 1.00–1.46). 3. There were no associations between total n-3 or n-6 polyunsaturated fatty acids and risk of overall or any subset of PCa, nor was there any association with the ratio of n-6/n-3 fatty acids. 4. There were no associations between any of these of individual fatty acids and nonadvanced PCa. 5. ALA intake was related to increased risk of advanced PCa (HR 1.17; 95% CI 1.04–1.31). 6. There were no significant interactions between PSA screening and the results for saturated fat, ALA or EPA.
Isoflavones					

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Table 3 (*Continued*)

Study	Study ID Country Enrollment period (follow-up)	Study design; exposure; outcomes	Participants (total number/ PCa patients)	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa, and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Reger et al (2018) [45]	PLCO (intervention arm)[a] (studies using a systematic PCa screening protocol) USA 1993–2001 (FU: 11.5 yr)	PCS Total isoflavone intake Intakes of genistein, daidzein, glycitein, formononetin, biochanin A, coumestrol (quartiles) Risk of PCa	27 004; 2598[a]	AC: BMI, smoking status, alcohol intake, education, marital status, physical activity, family history of other cancer, aspirin use, ibuprofen use, vasectomy, and intakes of energy, iron, processed meats, red meat, and caffeine	1. After adjustment for confounders, HRs (95% CIs) of advanced PCa for comparing quintile 5 with quintile 1 of dietary intake of total isoflavones, genistein, daidzein, and glycitein were 1.91 (1.25–2.92; p trend 0.007), 1.51 (1.02–2.22; p trend 0.012), 1.80 (1.18–2.75; p trend 0.013), and 1.67 (1.15–2.43; p trend 0.003), respectively. 2. No statistically significant associations were observed between the intake of total or individual isoflavones and nonadvanced and total PCa. 3. A sensitivity analysis that included the 806 cases of PCa diagnosed within the first 2 yr of enrollment showed weaker, less significant, but still positive associations between the intake of individual isoflavones and the risk of advanced PCa.
Meat					
Cross et al (2005) [46]	PLCO USA 1993–2001	PCS Meat intake (red meat, white meat, processed meat, barbecued meat, pan-fried meat, very well done meat [quintile 1–5]) or meat-related mutagens Risk of PCa	1338; 868[a]	AC: study center, BMI, smoking status, physical activity, total energy intake, supplemental vitamin E use, lycopene intake, history of diabetes, aspirin use	1. There was no association between red or white meat consumption, meat-cooking method (rare, medium, or well done), and processed meat consumption, and risk of total, incident, or advanced PCa. 2. However, in another analysis, there was an elevated risk for total (RR 1.42; 95% CI 1.05–1.92; p trend = 0.02) and incident (RR 1.69; 95% CI 1.19–2.40; p trend = 0.003), but not advanced, PCa comparing men who consumed >10 g/d of very well-done meat with nonconsumers. 3. While 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine intake was associated with an increased risk for overall and incident (but not advanced) PCa, intakes of 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline, heterocyclic amines 2-amino-3,8-dimethylimidazo[4,5-b]quinoxaline, and benzo(a)pyrene, as well as overall mutagenic activity from meat, were not associated with PCa risk.

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Table 3 (*Continued*)

Study	Study ID Country Enrollment period (follow-up)	Study design; exposure; outcomes	Participants (total number/ PCa patients)	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa, and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Sinha et al (2009) [47]	NIH-AARP Diet and Health Study USA 1995–2003 (FU: 9 yr)	PCS Meat consumption (type, cooking method, and related mutagens), heme iron, nitrite/ nitrate Risk of PCa	175 343; 10 313	AC: education, marital status, self-reported history of diabetes, BMI, smoking, vigorous physical activity, and intakes of total energy, alcohol, tomatoes, vitamin E, a-linolenic acid, zinc, selenium, and calcium	1. Red meat intake was associated with an increased risk for all PCa (Table 2), especially in the top two deciles, compared with the first decile (ninth decile: HR 1/4 1.14, 95% CI 1.04, 1.26; 10th decile: HR 1/4 1.13, 95% CI 1.02, 1.25; *p* trend 1/4 0.003). The associations were stronger for advanced disease, with approximately 30% higher risk being observed among men in the fifth quintile as compared with those in the first. 2. Processed meat intake was associated with an increased risk of advanced PCa, especially in the top decile, compared with the first (HR 1/4 1.45, 95% CI 1.10, 1.92; *p* trend 1/4 0.006). 3. In the continuous data, there was an increased risk of 10% per 10-g increase in red processed meat intake (95% CI 1.03, 1.17; *p* trend 0.003). 4. There was no association between total iron intake and the risk of total, advanced, or fatal PCa. 5. Heme iron intake was associated with an increased risk of 9% for total PCa and 28% for advanced disease. 6. The only meat-cooking method associated with increased risk was grilled/barbecued meats for total (11% increased risk) and advanced (36% increased risk) PCa.
Fish					
Chavarro et al (2008) [48]	Physician's Health Study USA 1982–1995 (FU: 19 yr)	PCS Fish and seafood n-3 fatty acid intakes Risk of PCa	20 167; 2161	AC: BMI, physical activity, smoking status, use of multivitamins and vitamin E supplements, random assignment to aspirin or carotene, and intakes of dairy foods, meat, alcohol, and tomato products	1. Most PCa cases presented as localized (71.6%) and low-grade (62.3%) disease, and were diagnosed during the era of widespread PSA screening (84.3%). PSA screening was the most common presentation mode (61.9%). 2. Total fish intake was unrelated to PCa risk, even when this association was examined separately according to different tumor characteristics (stage, grade, lethality, date of diagnosis).
Calcium					

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Table 3 (*Continued*)

Study	Study ID Country Enrollment period (follow-up)	Study design; exposure; outcomes	Participants (total number/ PCa patients)	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa, and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Giovannucci et al (2006) [49]	HPFS USA 1986–2002 (FU: 16 yr)	PCS Calcium intake (quintiles): dietary calcium (<585–≥933), supplemental calcium (0–>400), total calcium (<750–≥1500) intake Risk of PCa	47 750; 3544	AC: BMI at age 21, height, cigarette pack-years in the previous 10 yr, vigorous physical activity level, history of diabetes mellitus, and intakes of total calories, red meat, fish, a-linolenic acid, tomato sauce No formal adjustment for PSA testing	1. No significant trend was noted for calcium intake and risk of total PCa, although a statistically significant higher risk was observed for high (>2000 mg/d) versus low (500–749 mg/d) intake for overall, high-grade (GS >7), and advanced PCa. The association with high-grade PCa remained significant after adjustment for phosphorus intake. No significant associations were found for nonadvanced, low-grade, and organ-confined PCa. 2. Additional analyses tested whether calcium was acting as a surrogate of dairy products for the association with advanced PCa. In these analyses, calcium intake, dietary calcium, and calcium from supplementary sources were each independently associated with an elevated risk of advanced disease. When total calcium intake and total dairy products were modeled simultaneously, a positive trend remained for calcium, but not for dairy products. A similar result was obtained when calcium intake was modeled simultaneously with lactose intake. 3. In this study, analyses were not formally adjusted for PSA screening, and therefore less frequent PCa screening could have led to a more advanced stage of diagnosis. However, men with higher calcium intake had actually had PSA tests slightly more frequently than those with lower intakes.
Fruits and vegetables					
Takachi et al (2010) [50]	The Japan Public Health Center-Based Prospective Study Japan 1990–1993 and 1995–1998 (FU: 6–11 yr)	PCS Fruit and vegetable intakes Risk of PCa	43 475; 339	AC: study area, BMI, smoking status, alcohol, vitamin supplement use, green tea consumption, men who live with their wives, consumption of dairy and soy products No formal adjustment for PSA testing (CF: several screening examinations [as a representative index for a history of PCa screening])	1. No significant association was found between the intakes of fruits and total vegetables, and risk of total PCa after adjustment for all potential confounding factors, including history of screening examinations. 2. No specific vegetable group was significantly associated with the risk of total PCa. 3. Neither fruit nor total vegetable intake showed a significant inverse association with localized or advanced PCa. No specific vegetable group showed a significant association with either localized or advanced PCa. 4. To weaken the influence of cancer detected by PSA screening, analyses were performed to test the association between fruit and vegetable intake, and total PCa after excluding screening-detected tumors. Fruit consumption was not associated with total PCa, as well as total vegetable consumption. 5. In stratified analyses by cohort, age, smoking status, and BMI, and in the analysis that excluded vitamin supplement users, no significant inverse association was observed between the consumption of fruits and total vegetables or subtypes, and risk of total PCa.

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Study	Study ID Country Enrollment period (follow-up)	Study design; exposure; outcomes	Participants (total number/ PCa patients)	Additional covariates (ACs) adjusted for in statistical analysis (beyond age, race, family history of PCa, and PSA testing [for PCa risk] or stage, grade, and primary treatment [for PCa recurrence/progression/ survival])	Main results (as provided by study authors)
Umesawa et al (2014) [51]	The Japan Collaborative Cohort Study for Evaluation of Cancer Risks Japan 1988–1990 (FU: 16 yr)	PCS Vegetable and carotene intakes Risk of PCa	15 471; 143	AC: BMI; smoking status; ethanol intake; daily green tea intake; work schedule; frequency of dairy product, bean product, fish product, and beef intakes; saturated fatty acid, isoflavone, and alpha-tocopherol intake No formal adjustment for PSA testing	1. No significant associations were observed between total vegetable intake and overall PCa risk. 2. Green and yellow vegetable intake and other vegetable intake were not associated with the risk of PCa. 3. Beta-carotene intake was not associated with the risk of PCa. 4. As for alpha-carotene intake, compared with the lowest quintile, the highest and the secondary lowest quintile showed a lower risk of PCa, but no significant trend was found. However, there was no significant trend of increased risk of PCa with increasing intake of alpha-carotene.
Dietary factors and PCa progression/mortality					
Richman et al (2010) [52]	CaPSURE Diet and Lifestyle Substudy USA 2004–2005 (FU: 2 yr)	PCS Postdiagnostic intake of processed red meat, unprocessed red meat, fish, poultry, eggs (quartiles 1–4) Risk of PCa recurrence or progression	1294 PCa patients	AC: energy intake, time from diagnosis to questionnaire, BMI, nonvigorous activity, PSA at diagnosis, other food groups, smoking, race, education, income, marital status, vigorous activity, frequency of fried food, tomato products, cruciferous vegetables	1. There was no evidence of an association of processed red meat, unprocessed red meat, or fish with PCa progression. 2. An increased risk of PCa progression was associated with higher poultry intake, which was not statistically significant 3. A significant two-fold increased risk of PCa progression was seen among men in the highest quartile of egg intake compared with men in the lowest quartile (HR 2.02; 95% CI 1.10, 3.72), which appeared to be limited to the highest level of intake. In secondary analyses excluding patients with lack of data on biological evidence of recurrence, the results for egg consumption remained positive but became nonsignificant. 4. There was an interaction between prognostic risk, total poultry, and risk of PCa progression. Greater poultry intake was associated with an increased risk of progression among men with high prognostic risk, but there was no association among men with low/ intermediate prognostic risk (p for interaction 0.003).
Tomaszewski et al (2014) [53]	CaPSURE Diet and Lifestyle Substudy USA 2004–2005 (FU: 2.8 yr)	PCS Postdiagnostic folate intake Risk of PCa recurrence after radical prostatectomy (RP), external beam radiation therapy (EBRT) and, brachytherapy (BT)	1153 PCa patients treated for T1–T2c PCa	AC: total energy intake, months between diagnosis and questionnaire, BMI, total caloric intake, methionine, and vitamin B2, B6, and B12 intake	1. Total or dietary folate intake was not associated with PCa recurrence. 2. On secondary analysis stratified by treatment, patients in the lowest decile of dietary folate intake (range 123–252 μg) were at a 2.6-fold increase risk of progression after RP (HR 2.56, 95% CI 1.23–5.29, $p = 0.01$), although total folate was not associated with risk. In patients treated with EBRT and BT, we observed no evidence of an association between PCa progression and increased intake of total or dietary folate.

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Van Blarigan et al (2015) [54]	The Physicians' Health Study USA 1988–1995 (FU: 10 yr)	PCS Postdiagnostic saturated fatty acids, vegetable fat intake Risk of PCa mortality (secondary outcome in this study)	926 PCa patients (56 PCa deaths)	AC: time from diagnosis to questionnaire, calories, modified D'Amico risk category, BMI, smoking, and intakes of alcohol, protein, and other fats	1. There was an increased risk of PCa-specific death among men who consumed greater amounts of saturated fat after diagnosis. 2. Men who obtained 5% more calories from saturated fat and 5% less calories from carbohydrate had a 2.8-fold higher risk of PCa-specific mortality (HR 2.78; 95% CI 1.01, 7.64; $p = 0.05$). The results were not statistically significant in the categorical model, likely due to the small number of events limiting the power to examine this outcome.

BMI = body mass index; CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; CI = confidence interval; FU = follow-up; GS = Gleason score; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NIH = National Institutes of Health; PCa = prostate cancer; PCS = prospective cohort study; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial; PSA = prostate specific antigen; RR = risk ratio.
Sentences and data are reported in the table as provided by study authors in the original manuscripts.
[a] Studies using a systematic PCa screening protocol.

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related diseases or arthritis, despite a lack of significant interaction.

Finally, in a PBCC study [28], ever use of aspirin (odds ratio [OR] 0.82 [95% CI 0.68–0.99]), daily use (OR 0.78 [95% CI 0.64–0.95]), and daily low-dose use (OR 0.71 [95% CI 0.56–0.90]) were associated with a reduced risk of overall PCa. Daily low-dose use of aspirin was associated with a decreased risk of both less and more aggressive PCa. Current and long-term users had a decreased risk of PCa compared with nonusers, while former users did not.

3.1.1.4. Nonaspirin nonsteroidal anti-inflammatory drugs. In the PLCO cohort [27], there was no evidence of an association between ibuprofen use and PCa risk. Nonetheless, this was in part likely attributed to the low prevalence of ibuprofen use among participants.

In the FinRSP study cohort [29], *current* use of nonsteroidal anti-inflammatory drug (NSAID) prescription (compared with nonuse), but not previous or over-the-counter use, was associated with an increased risk of PCa (HR 1.45, 95% CI 1.33–1.59, and HR 1.32, 95% CI 1.10–1.59 in the screening and control arms, respectively). A similar risk association was also observed for the use of acetaminophen and coxib, but not for aspirin. The increased PCa risk was not modified by tumor grade. Current (but not previous) use of NSAIDs, coxibs, and acetaminophen was also associated with an increased risk of metastatic PCa in both trial arms. The authors concluded that, taken together, these findings do not seem to support causal associations but rather protopathic bias (due to treatment of symptoms of undiagnosed PCa, presumably pain due to metastases), given that risk elevation was observed only for ongoing use, was strongest for metastatic disease, did not differ by amount or duration of use, and was noted for NSAIDs and acetaminophen (that has a different mechanism of action), but not for aspirin (which is mainly used for prevention of cardiovascular and cerebrovascular disorders and less often as analgesic). The modest risk elevation for localized and low-grade PCa, evident in both study arms (thus not likely explained by more active screening), was not dose dependent, suggesting that the indications for NSAID usage were likely behind this association.

A PCS from the Cancer Prevention Study (CPS)-II nutrition cohort [30] showed that, while current regular acetaminophen use (regardless of duration) was not associated with PCa risk, long-term regular use (≥5 yr) was associated with lower risks of both total (HR 0.62, 95% CI 0.44–0.87) and aggressive (risk ratio [RR] 0.49, 95% CI 0.27–0.88) PCa.

Finally, in a PBCC study [28], there were no associations between the use of nonaspirin NSAIDs, including ibuprofen and acetaminophen, and PCa risk.

3.1.1.5. 5-Alpha reductase inhibitors. In a study from the HPFS cohort with 14 yr of follow-up [17], ever (vs never) use of 5-alpha reductase inhibitors (5-ARIs) was associated with a 23% lower risk of overall PCa (HR 0.77,; 95% CI 0.65–0.91) and a decreased risk of intermediate- (Gleason score [GS] 7; HR 0.67, 95% CI 0.49–0.91) and low-grade (GS 2–6; HR 0.74, 95% CI 0.57–0.95) PCa, but not with high-grade (even including GS 4 + 3 = 7) or lethal PCa. However, the number of patients with high-grade or lethal PCa was limited. Analyses among men who underwent PSA testing in 1996 showed very similar results to the primary analyses.

3.1.1.6. Oral anticoagulants. In a PBCC study [21], ever use of oral anticoagulants was not associated with the risk of PCa. The association did not vary according to the duration of use, age at first use, or indication. Similar results were observed with regard to cancer aggressiveness.

3.1.2. Drugs and PCa recurrence, progression, and survival

3.1.2.1. Statins. In one PCS from the HPFS cohort [31], no significant association with lethal PCa (defined as M+ or PCa-specific death) was reported for both postdiagnostic current statin use and duration of use (≥6 yr vs none). There was evidence of effect modification by disease stage: among men diagnosed with T2+ PCa, current use of statins was associated with a reduced risk of lethal PCa (HR 0.65, 95% CI 0.43–0.97), whereas there was no association among those diagnosed with T1 disease.

In the study from the FinRSP cohort [32], postdiagnostic *active* statin use was associated with a decreased risk of PCa death (adjusted HR [aHR] 0.80, 95% CI 0.65–0.98), while prediagnostic statin use was not. The risk decreased in an inverse association with the intensity of statin use. The risk decrease was significant among men with low/medium-risk cancer (according to EAU guidelines) at baseline. Of note, survival was significantly improved only in men with androgen deprivation therapy (ADT) as the primary treatment and among men who were not using antihypertensive drugs. No risk reduction was observed for users of nonstatin cholesterol-lowering drugs. In this study, the associations were not likely explained by more active screening participation among statin users; moreover, risk of healthy-user bias appeared to be low, as statin users were not healthier but instead had a higher prevalence of medication use for comorbid conditions compared with the nonusers. In addition, a decreased risk among postdiagnostic statin users persisted when deaths due to cardiovascular causes were analyzed as competing causes of death (HR 0.39, 95% CI 0.32–0.49; Table 1).

3.1.2.2. Aspirin. In one PCS from the Physicians' Health Study cohort [33], current postdiagnostic regular aspirin use (>3 tablets/wk for at least 1 yr) was associated with lower risk of lethality (M+ or PCa-specific death; HR 0.68, 95% CI 0.52–0.89), regardless of duration. Accordingly, current postdiagnostic use (vs never use) among men diagnosed with nonlethal PCa was associated with lower risk of lethality (HR 0.68, 95% CI 0.52–0.90), regardless of duration. However, both associations did not hold among cases diagnosed in the PSA era.

3.1.2.3. 5-ARIs and alpha-blockers. In one PCS from the FinRSP cohort [34], prediagnostic 5-ARI use (vs nonuse) was not associated with the risk of PCa death. As such, previously reported increased proportion of high-grade cases does not seem to affect PCa-specific survival, at least in the short

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term, and at the same time, previously reported decrease in overall PCa risk does not seem to translate into improved survival. Taken together, these findings may suggest that 5-ARIs impact predominantly the occurrence of low-risk disease unlikely to progress into fatal stage, rather than development of aggressive disease. Postdiagnostic 5-ARI use was not significantly associated with PCa survival.

Both pre- and postdiagnostic alpha-blocker use was associated with worse PCa-specific survival (HR 1.29, 95% CI 1.08–1.54, and HR 1.56, 95% CI 1.30–1.86, respectively). However, worse survival was observed only during the first 5 yr of usage. When the analysis was limited to cases with >10 yr of follow-up after diagnosis, associations were no longer significant. Taken together, these associations are likely noncausal and caused by the underlying indications for drug usage rather than by the drug itself. For postdiagnostic use, this suggests that lower urinary tract symptoms after PCa diagnosis might be indicative of PCa progression.

3.1.2.4. Antiarrhythmic drugs. In one PCS from the FinRSP cohort [35], prediagnostic digoxin use was not significantly associated with the risk of PCa death and postdiagnostic use was not significantly associated with PCa survival, with no consistent differences by cumulative amount and duration of use. These findings suggest that the potentially lower risk of Gleason 7–10 PCa in men under systematic PCa screening [36] does not translate into improved disease-specific survival.

A significant risk decrease was observed only among men not receiving ADT and using digoxin before diagnosis (HR 0.20, 95% CI 0.048–0.86). Neither pre- nor postdiagnostic sotalol use was associated with a risk of PCa death.

3.2. Metabolic diseases and PCa

Overall, 11 reports from seven studies were included, with 10 on PCa incidence and one on PCa survival (Table 2).

3.2.1. Metabolic diseases and PCa incidence

3.2.1.1. Metabolic syndrome. In one PBCC [18], patients with a history of metabolic syndrome (MetS; three or more vs less than three components) were at a significantly lower risk of overall (OR 0.70 [0.60–0.82]), low-grade (OR 0.69 [0.58–0.82]), and high-grade (OR 0.75 [0.60–0.94]) PCa. The risk decreased with the number of MetS components present (p trend < 0.01) in a nonlinear manner, suggesting a synergistic interaction of MetS components. However, a potential selection bias may have occurred. In a model including all MetS components, the history of dyslipidemia (adjusted for statin use, OR 0.58 [0.47–0.71]) was associated with PCa risk, while the history of type 2 diabetes (adjusted for metformin use), abdominal obesity, or hypertension was not.

3.2.1.2. Obesity (body mass index)

3.2.1.2.1. Body mass index. Overall, four studies evaluated the role of body mass index (BMI) for PCa risk, of which two were PCS [19,37], one nested case-control (NCC) study [38], and one PBCC study [22].

In the study from the HPFS cohort [37], a higher BMI at age 21 was associated with a significantly lower risk of lethal, advanced, and Gleason 7 PCa (adjusted RRs in the range of 0.69–0.77 comparing BMI 26 with BMI 20–22), although a significant trend was seen only for advanced and Gleason 7 PCa. There was a weak inverse association with total, nonadvanced, and low-grade PCa. However, for this association, detection bias (reduced PCa detection in obese men as a consequence of PSA hemodilution and/or reduced diagnostic performance due to larger prostate volumes) cannot be ruled out entirely. Associations of BMI at age 21 and adult BMI and PCa were attenuated when additionally adjusting for childhood body shape, or for mutual adjustment for BMI in early or late adulthood, respectively; this may suggest that body size in early adulthood might be more strongly related to PCa development than body size later in life.

In the study from the PLCO cohort [19], BMI >30 (compared with BMI 18.5–25) at age 20 and 50, and at baseline was associated with a decreased risk of total PCa (HR [95% CI] 0.82 [0.68–0.99], 0.87 [0.81–0.94], and 0.93 [0.87–1.00], respectively). BMI (at any age, mean, maximum) was not associated with PCa aggressiveness. Risk of detection bias could not be ruled out.

In the NCC study from the ProtecT study cohort [38], there was no evidence of any important relationship between BMI and PSA-detected total PCa. However, a weak association between BMI and low-grade PCa (p trend 0.045; BMI ≥30 vs <25: OR 0.76, 95% CI 0.59, 0.97) was reported. In this study, the risk of detection bias appeared to be low.

Finally, in a PBCC [22], higher BMI (BMI 25–30 and ≥30, both compared with BMI <25) was associated with a lower risk of total (OR [95% CI] 0.87 [0.74–1.01] and 0.72 [0.60–0.87], respectively), low-grade (0.83 [0.68–1.00] and 0.71 [0.55–0.90], respectively), and high-grade (only for BMI >30, OR 0.73 [0.59–0.91]) PCa.

3.2.1.2.2. Waist circumference. Overall, four studies evaluated the role of waist circumference (WC) for PCa risk [22,23,37,38].

In a PBCC study [22], increased WC (>102 cm), after adjustment for BMI, was associated with an increased risk of overall (OR 1.23 [95% CI 1.05–1.46]) and high-grade (OR 1.47 [95% CI 1.22–1.78]) PCa.

In the HPFS cohort [37], higher WC was associated with a lower risk of nonadvanced (aRR for top vs bottom quintile: 0.93, 95% CI 0.82–1.04, p trend 0.03), Gleason 7 (aRR 0.84, 95% CI 0.70–1.00, p trend 0.02), and low-grade PCa (aRR 0.88, 95% CI 0.75–1.02, p trend 0.01), but not with the risk of total PCa. However, the observed associations were weakened when adjusting for either childhood body shape or adult BMI. Moreover, these findings might have potentially been influenced by the detection bias.

In the NCC study from the ProtecT study cohort [38], there was no evidence of any important relationship between WC and PSA-detected total or stage-/grade-specific PCa. Similarly, in a PCS from the CPS-II nutrition cohort [23], there was no significant association between WC and PCa risk after adjustment for BMI.

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3.2.1.2.3. Waist-to-hip ratio. In a PBCC [22], a weak association was found between waist-to-hip ratio (WHR) and high-grade PCa (OR 1.20 [95% CI 1.01–1.43]) in analyses adjusted for BMI; however, in subgroup analyses according to BMI categories, no significant associations were observed.

In the NCC study from the ProtecT study cohort [38], there was no evidence of any important relationship between WHR and PSA-detected PCa.

3.2.1.2.4. Weight change. In the PCS from the PLCO cohort [19], weight change was not associated with PCa risk. In trajectory analyses, there was a slight inverse association between a specific BMI trajectory (men who were overweight at age 20 and remained overweight or became obese) and risk of total PCa.

3.2.1.3. Diabetes. In the PCS from the HPFS cohort [39], history of diabetes mellitus (DM) diagnosis was associated with a reduced risk of total (HR [95%CI] 0.83 [0.74–0.94]), localized (0.72 [0.62, 0.84]), high-grade (0.69 [0.55, 0.87]), and low-grade (0.76 [0.62, 0.92]) PCa, but not with advanced PCa.

Associations for nonadvanced PCa were similar in the pre-PSA and PSA eras. However, in the pre-PSA era, total PCa risk appeared to be lower and the decreased risk associated with DM seemed to be stronger for high-grade (vs low-grade) disease. There was a significant trend of a decreased risk of total PCa with increasing time since DM diagnosis.

In a PCS involving 1 million men in Israel [40], men with incident DM were at a higher risk of total PCa during the 1 st year following diabetes diagnosis, while the risk decreased by the 3rd and subsequent years (HR [95% CI] 0.89 [0.84, 0.95]), as it was for the prevalent diabetes group (0.80 [0.76, 0.85]). This was observed for low-medium–grade (0.83 [0.77, 0.89]) but not for high-grade (GS 7–10) PCa. Of note, mean PSA values were significantly lower for men with diabetes. As such, the reduced risk of low-moderate–grade but not of high-grade PCa among men with DM may suggest a potential detection bias.

In the NCC study from the ProtecT study cohort [41], presence of DM was associated with a reduced risk of total (OR 0.78 [95% CI 0.61–0.99]), localized (T1–T2; 0.76 [0.59–0.98]), and well-differentiated (ie, low-grade; GS $\leq$6; OR 0.69 [0.52–0.93]) PCa. There was no evidence that the inverse association was greater with increasing length of time since diabetes diagnosis. In additional analyses excluding PCa cases diagnosed in the 1st year after DM diagnosis, or in patients with data on BMI, the association was no longer significant. Of note, among controls, men with DM had marginally lower PSA levels; in a sensitivity analysis, the OR "adjusted" for possible differential misclassification was 0.82 (95% CI 0.65–1.03; $p = 0.09$). In this study, both selection bias and surveillance bias were unlikely.

3.2.1.4. Dyslipidemia. In a PCS from the CLUE II cohort [42], there was no significant association between hypercholesterolemia and risk of PCa. However, among men with BMI >26.5, men with desirable cholesterol (compared with men with hypercholesterolemia) were less likely to develop high-grade (GS $\geq$7) PCa (HR 0.46 [95% CI 0.24–0.87]), particularly if organ confined (0.36 [0.16–0.79]).

3.2.2. Metabolic diseases and PCa recurrence, progression, and survival

3.2.2.1. Obesity. In one PCS from the HPFS cohort [39], long-term weight gain was not associated with an increased risk of lethal PCa in overall population. However, risk was increased in selected subgroups (never smokers, men with BMI $\geq$25 at age 21, and men surviving $\geq$4 yr after diagnosis, especially if never smokers). Short-term weight gain (over 4 or 8 yr before diagnosis) was not associated with the risk of lethal PCa in the overall study population, but the risk was increased in men with a BMI of $\geq$25 at age 21 and in men who gained >5 pounds in the 8 yr prior to diagnosis. BMI at age 21 and BMI at diagnosis were not significantly associated with the risk of lethal PCa. Finally, weight change and obesity (BMI) were not associated with an increased risk of biochemical recurrence. The authors concluded that, according to these findings, weight gain might have an early influence on prostatic carcinogenesis and might play a role in the development of tumors more likely to progress. However, the risk of detection bias cannot be entirely ruled out, and it may be difficult to disentangle the reciprocal influence of obesity and weight gain.

3.3. *Dietary factors and PCa*

Overall, 12 reports from seven studies were included, of which eight were on PCa incidence and three on PCa recurrence, progression, or survival (Table 3).

3.3.1. Dietary factors and PCa incidence

3.3.1.1. Intake of fats/fatty acids. One PCS from the HPFS cohort [43] evaluated the association between intakes of fatty acids (a-linolenic [ALA], eicosapentaenoic [EPA], docosahexaenoic [DHA], linoleic [LA], and arachidonic [AA] acids) and risk of PCa. No association with the risk of total PCa was observed for intakes of total ALA, ALA from meat and dairy sources, ALA from nonanimal sources, LA, AA, and fish-oil supplement use. On the contrary, intakes of EPA, DHA, and EPA + DHA showed a significant or borderline significant inverse relation with total PCa risk. For the risk of organ-confined PCa, the relations were similar to those for total PCa, albeit somewhat weaker (only EPA was statistically significant). Of note, ALA from nonanimal sources was associated with an increased risk of advanced PCa (RR 2.02, 95% CI 1.35–3.03).

In a PCS from the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort [44], intakes of total fat, polyunsaturated fat, total trans-fatty acids, total n-3 or n-6 polyunsaturated fatty acids, and n-6/n-3 fatty acid ratio were not associated with PCa risk. On the contrary, intake of saturated fat and ALA was associated with an increased risk of advanced PCa (HR 1.21, 95% CI 1.00–1.46, and HR 1.17, 95%CI 1.04–1.31, respectively).

3.3.1.2. Isoflavone and phytoestrogen intakes. In a PCS from the PLCO cohort [45], no statistically significant association was observed between intake of total isoflavones and risk of total or nonadvanced PCa. On the contrary, dietary intake of

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total isoflavones was associated with an increased risk of advanced PCa (HR [95% CI] 1.91 [1.25–2.92]; *p* trend 0.007).

3.3.1.3. Meat intake. In a PCS from the PLCO cohort [46], there was no association of red or white meat consumption, processed meat consumption, and meat-cooking method with the risk of total or advanced PCa. However, in another analysis, consumption of >10 g/d of very well-done meat was associated with an increased risk for total (RR 1.42, 95% CI 1.05–1.92; *p* trend = 0.02) and incident (RR 1.69, 95% CI 1.19–2.40; *p* trend = 0.003), but not advanced, PCa. While 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine intake was associated with an increased risk for overall and incident (but not advanced) PCa, intakes of 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline, heterocyclic amines 2-amino-3,8-dimethylimidazo[4,5-b]quinoxaline and benzo(a)pyrene, as well as overall mutagenic activity from meat were not associated with PCa risk.

In a PCS from the NIH-AARP Diet and Health Study cohort [47], red meat intake was associated with an increased risk of all PCa, the associations being stronger for advanced disease. Grilled/barbecued meat was associated with the risk of both total and advanced PCa. Processed meat intake was also associated with an increased risk of advanced PCa. Moreover, there was an increased risk of 10% per 10-g increase in red processed meat intake (95% CI 1.03, 1.17; *p* trend 0.003).

3.3.1.4. Fish intake. In a PCS from the Physician's Health Study cohort with 19 yr of follow-up [48], total fish intake was unrelated to PCa risk, even in stratified analyses according to PCa stage, grade, lethality, and date of diagnosis.

3.3.1.5. Calcium intake. In a PCS from the HPFS cohort [49], no significant trend was noted for calcium intake and risk of total PCa, although a statistically significant higher risk was observed for high (>2 g/d) vs low (0.5–0.75 g/d) intake for overall, high-grade (GS >7), and advanced PCa. The association with high-grade PCa remained significant after adjustment for phosphorus intake. Of note, in this study, analyses were not adjusted for PSA testing, and therefore less frequent PSA testing could have led to a more advanced PCa stage at diagnosis. However, men with higher calcium intake actually had PSA tests slightly more frequently than those with lower intake.

3.3.1.6. Fruit and vegetable intakes. In the Japan Public Health Center-Based Prospective Study [50], no significant association was found between fruit and total (or specific group) vegetable intakes and the risk of total or stage-specific PCa. These findings were confirmed by the Japan Collaborative Cohort Study for Evaluation of Cancer Risks [51], where vegetable intake, as well as beta-carotene intake, was not associated with PCa risk. In this study, there was also no significant trend of increased risk of PCa with increasing intake of alpha-carotene.

3.3.2. Dietary factors and PCa recurrence, progression, and survival

In a PCS from the Diet and Lifestyle substudy cohort of Cancer of the Prostate Strategic Urologic Research Endeavor [52], there was no evidence of an association between intake of red meat or fish and PCa progression. No significant association was found for higher poultry intake, as well as for egg intake (after excluding patients with lack of biological evidence of recurrence). However, greater poultry intake was associated with an increased risk of progression among men with high (but not low-intermediate) prognostic risk PCa (*p* for interaction = 0.003).

In another study from the same cohort in men with M0 disease at presentation [53], total folate and dietary folate intake was not associated with PCa recurrence. However, patients with severely deficient dietary folate intake (lowest decile, range 123–252 μg) were at a 2.6-fold increase risk of PCa progression after radical prostatectomy (HR 2.56, 95% CI 1.23–5.29, *p* = 0.01).

Finally, in a PCS from the Physicians' Health Study cohort [54], there was an increased risk of PCa death among men who consumed greater amounts of saturated fat after diagnosis. However, PCa death was a secondary outcome in this study due to the small number of events.

3.4. Limitations at study and review levels

The evidence provided in our review must be critically interpreted considering the potential limitations at both review and study levels (described in detail in the Supplementary material).

In brief, the review strategy might not have been able to identify all relevant studies on the topics of interest. Moreover, our review included only the latest evidence available and only studies focusing on PSA-screened populations.

Definitions of exposure to the specific risk factors considered in this review were variable across the studies. In particular, among studies evaluating the potential impact of drugs on PCa risk, information on exact dose, frequency, and length of treatment was rarely reported (Table 1 and Supplementary Table 3).

Selection of studies was driven by a specific PICOS framework, leading to potential exclusion of relevant studies due to insufficient reporting of the information required for assessing study eligibility. In addition, our PICOS framework might have led to exclusion of studies evaluating specific risk factors considered in the review plan (ie, antihypertensive drugs or testosterone replacement therapy; Supplementary material).

This systematic review was not designed to evaluate associations between drugs, metabolic diseases, and dietary factors in men undergoing regular screening for PCa, but rather in men exposed to PSA testing.

Although all studies included in the review adjusted statistical analyses for the rate of PSA testing, the heterogeneous definitions and measurements of this covariate across studies, as well as the variable rates of PSA testing among populations (Supplementary Table 3), might have led to heterogeneous extent of "adjustment," increasing the RoB. Moreover, specific information on indications, methods, and frequency of diagnostic ascertainment of PCa was rarely reported in most reports included in the review, increasing the risk of detection bias. As such, we could

not evaluate the extent to which the patient's comorbidity burden or life expectancy might have influenced decision to perform PSA testing and/or undergo further diagnostic evaluation.

However, these limitations at a study level are grounded in the highly heterogeneous prevalence of PSA testing among different populations [4,5], the diversity in recommendations on the use of PSA testing and type of diagnostic ascertainment provided over time by different organizations worldwide [5,9], and the lack of information on the purpose of PSA testing in most studies on PCa risk factors.

For these reasons, it is not possible to make inferences on the impact of the risk factors evaluated in our review on PCa risk in the context of standardized screening protocols.

It is important to note that competing risks of mortality may have resulted in reduced PCa detection (and thus PCa risk) in observational studies focused on associations between risk factors and PCa incidence. As not all studies included in our review performed formal competing-risk regression analyses (Tables 1–3), the possibility of a detection bias cannot be entirely ruled out.

Although we included only studies with extensive follow-up, it might have still been limited to evaluate some PCa outcomes, considering its long natural history.

The findings of this review may not be generalizable to all men exposed to PSA testing, as results of several studies were themselves of limited generalizability (Supplementary Table 4).

Finally, due to the overall low quality of evidence and the several limitations of included studies (Supplementary material), causality of associations between risk factors and PCa risk is uncertain; as such, the evidence provided cannot be directly translated in a public health perspective.

4. Conclusions

Elucidation of potentially modifiable risk factors for PCa has been hindered by differences in PSA testing among populations worldwide.

Our systematic review provided a detailed overview of the latest evidence from long-term observational studies on

Table 4 – Overview of collective evidence from our systematic review on the effect on PCa risk of those factors for which evidence was available.

Topic (outcome)	Summary of findings
Antidiabetic drugs(PCa risk)	1. Use of metformin may be associated with a modest decreased risk of PCa, particularly of localized disease and in men with a long history of diabetes. Yet, it is difficult to disentangle the specific effect of antidiabetic drugs from that of underlying diabetes; moreover, there is a risk of detection bias. 2. Use of sulfonylureas might be associated with an increased risk of metastatic PCa. 3. There is no evidence of an effect of insulin (and other antidiabetic drugs) use on PCa risk.
Statins (PCa death)	Postdiagnostic statin use may be associated with a reduced risk of PCa death in selected patient populations, such as patients with low-medium risk PCa, those treated with ADT, and those not using antihypertensive drugs.
Aspirin and NSAIDs (PCa risk)	1. Despite findings of included studies not always being consistent and information on dose and duration being elusive, there is no evidence of an effect of regular aspirin use for the risk of advanced (high stage and/or N+ M+ disease) PCa, while regular aspirin use may be associated with a slightly decreased risk of overall PCa, especially among older men (>65 yr). 2. There was no evidence of an effect of nonaspirin NSAIDs (and in particular ibuprofen and acetaminophen) on PCa risk.
5-alpha reductase inhibitors (PCa death)	1. Despite a reduction in the overall PCa risk and a potential increased risk of high-grade disease, there was no evidence of an effect of both pre- and postdiagnostic 5-ARI use on PCa death.
Obesity (PCa risk, recurrence, or survival)	1. Interpretation of available evidence on the role of obesity for PCa risk is challenging due to highly variable definitions of exposure and outcomes, length of follow-up, and lack of data on drug doses in most studies. Moreover, detection bias due to potential PSA hemodilution among obese men cannot be ruled out entirely. 2. BMI at age 20–21 might be associated with a modest decreased risk of overall and (potentially) more advanced PCa, even if this association appeared attenuated when considering childhood body shape. 3. BMI at middle age might be associated with a modest decreased risk of overall PCa. 4. There is no evidence of an effect of both WC and WHR on PCa risk after adjustment on BMI. 5. Long-term (but not short-term) weight gain might be associated with an increased risk of lethal PCa in selected patient populations (ie, never smokers, and overweight or obese men at age 21). 6. There was no evidence of an effect of BMI on either biochemical recurrence or lethal PCa. 7. Evidence was judged too heterogeneous to evaluate the impact of BMI on grade-specific PCa.
Diabetes mellitus (PCa risk)	1. Evidence on the role of diabetes mellitus for PCa risk in populations exposed to PSA testing is not definitive. 2. The potential inverse association reported between diagnosis of diabetes mellitus and PCa among PSA-screened population seems to be restricted to total and (possibly) low-grade/localized disease. 3. The extent to which BMI, surveillance bias, and detection bias may significantly modify these associations remains undetermined.
Food and dietary factors (PCa risk)	1. Evidence on potential associations between meat consumption, and risk of overall and stage-specific PCa is conflicting. 2. Intake of specific fatty acids (ie, EPA, DHA, EPA + DHA) may be associated with a reduced risk of total PCa, while intake of other fatty acids (ALA from nonanimal sources), saturated fats, isoflavones, and high doses of calcium may be associated with an increased risk of advanced PCa. However, evidence is not conclusive. 3. There was no evidence of an effect of fruit, vegetable, and fish intake on PCa risk.

ALA = a-linolenic acid; BMI = body mass index; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; NSAID = nonsteroidal anti-inflammatory drug; PCa = prostate cancer; PSA = prostate specific antigen; WC = waist circumference; WHR = waist-to-hip ratio; 5-ARI = 5-alpha reductase-inhibitor.

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the role of selected, partially modifiable risk factors for PCa considering the impact of PSA testing on PCa diagnosis.

For some risk factors, evidence was insufficient to assess potential effects, while for others there was no evidence of an effect. For selected risk factors, there was low-quality evidence of modest effects on PCa risk (Table 4).

Given the burden of PCa and the increasing prevalence of many of the risk factors evaluated in our review among populations worldwide, even modest effects of such factors on PCa risk might theoretically represent key drivers for public health interventions. However, judgments on potential implications of our collective findings are beyond the scope of this review.

Our review distinctly highlights the need for further high-quality research in this field. Future studies are needed to confirm the associations suggested by our review, taking into account the multifactorial etiological background of PCa, exploring their potential biological explanations and selecting those risk factors most likely to trigger effective public health interventions.

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Study concept and design: Campi, Brookman-May, Minervini, Rodriguez-Faba.
Acquisition of data: Campi, Minervini, Henríquez, Rodriguez-Faba.
Analysis and interpretation of data: Campi, Minervini, Rodriguez-Faba.
Drafting of the manuscript: Campi, Minervini, Rodriguez-Faba.
Critical revision of the manuscript for important intellectual content: Brookman-May, Akdoğan, Brausi, Klatte, Langenhuijsen, Linares-Espinos, Marszalek, Roupret, Stief, Volpe.
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Appendix A. Supplementary data

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