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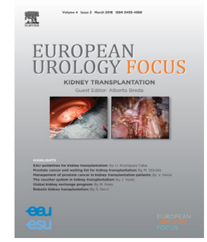

Review – Prostate Cancer

Latest Evidence on the Impact of Smoking, Sports, and Sexual Activity as Modifiable Lifestyle Risk Factors for Prostate Cancer Incidence, Recurrence, and Progression: A Systematic Review of the Literature by the European Association of Urology Section of Oncological Urology (ESOU)

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Abstract

Context: Smoking, sexual activity, and physical activity (PA) are discussed as modifiable lifestyle factors associated with prostate cancer (PCa) development and progression.
Objective: To evaluate the available evidence concerning the association of smoking, sexual activity, and sports and exercise on PCa risk, treatment outcome, progression, and cancer-specific mortality.
Evidence acquisition: A systematic review of studies published between 2007 and 2017 using MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials, and Web of Science databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement criteria was conducted.
Evidence synthesis: While data concerning the impact of smoking on PCa development remain conflicting, there is robust evidence that smoking is associated with aggressive tumor features and worse cancer-related outcome, which seems to be maintained for 10 yr after smoking cessation. Less convincing and limited evidence exists for the association of sexual activity with PCa risk. The findings related to PA and PCa support the inference that exercise might be a useful factor in the prevention of PCa and tumor progression, while it is not finally proved under which specific conditions PA might be protective against disease development.
Conclusions: Smoking is associated with aggressive tumor features and worse cancer-related prognosis; as this negative impact seems to be maintained for 10 yr after smoking cessation, urologists should advise men to quit smoking latest at PCa diagnosis

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to improve their prognosis. As several studies indicate a positive impact of exercise on tumor development, progression, and treatment outcome, it is certainly reasonable to advocate an active lifestyle. Least convincing evidence is available for the interaction of sexual activity and PCa, and well-conducted and longitudinal studies are clearly necessary to evaluate whether the suggested associations between PCa risk and sexual behavior are real or spurious.

Patient summary: In this systematic review, we looked at the impact of smoking, sexual activity, and sports and exercise on prostate cancer risk and outcome after treatment. While the evidence for sexual activity is not overall clear, we found that smoking might lead to more aggressive cancers and result in worse treatment outcome. Physical activity might prevent prostate cancer and improve cancer-related outcomes as well. Hence, it is certainly reasonable to advocate an active lifestyle and advise men to quit smoking.

1. Introduction

Prostate cancer (PCa) is the most prevalent cancer among men worldwide and, after lung, the second most common cause of death from cancer in men in the USA and Europe [1]. Established risk factors for PCa development are age, race, and family history; however, considerable geographic variations suggest that lifestyle and environmental factors contribute to its etiology [2]. Besides diet and metabolism, smoking, physical inactivity, and specific aspects of sexual activity are being discussed [3–7]. In this systematic review, we aim to summarize the impact of the modifiable risk factors smoking, sexual activity, and sports on PCa risk, treatment outcome, progression, and cancer-specific mortality (CSM).

2. Evidence acquisition

A systematic literature search using MEDLINE, Cochrane Central Register of Controlled Trials, and Web of Science databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was conducted to identify relevant studies published between 2007 and 2017. Results were updated on January 15, 2018. Details are displayed in Figure 1. Selected studies were conducted in the USA, Latin America, Europe, Middle East/Africa, and Asia/Pacific region.

3. Evidence synthesis

3.1. Smoking and PCa

Tobacco smoking is considered a major public health concern worldwide due to its responsibility for high levels of mortality and morbidity. Smoking causes increased incidence and mortality from lung and other cancers; furthermore, it considerably impacts the risk for cardiovascular disease, stroke, chronic respiratory disease, and other medical conditions [8,65]. Despite all prevention campaigns and smoking-cessation counseling programs conducted over the past decades and reduction of smoking prevalence in some countries, the worldwide number of smokers is still increasing—from 721 million people smoking daily in 1980 to 967 million in 2012, with considerable geographical variations [9,65].

Studies have reported contradictory results on the relationship of smoking with PCa. While no association was found in some studies, others suggested an elevated risk in smokers with dose-response relationships; on the contrary, there are data indicating that smoking may be associated inversely with PCa diagnosis. Cigarette smoking has also been demonstrated to have correlations with aggressive and advanced PCa in non–African American (non-AA) men, and there is increasing evidence that smokers have worse treatment response or other confounding factors contributing to inferior outcomes.

3.1.1. Smoking and risk for PCa

Despite an association of smoking with several solid tumors and a multitude of hypotheses how biological pathways involved in carcinogenesis might be affected, the association of smoking and PCa remains a matter of debate (Table 1) [10–64,70,72].

Considering results of cohort studies published between 2007 and 2017, eight studies did not identify a significant impact of smoking status or habits on PCa risk [10–17], while another 10 studies showed an inverse association of smoking with reduced PCa risk [18–27]. On the contrary, when reviewing case-control studies (CCSs), only two studies did not find an impact on PCa incidence [28,29]: a study from Argentina found the same proportion of smokers in patients with PCa and controls [28]; also, May et al [20] did not find significant differences in the rate of advanced tumor stages between smokers and nonsmokers, while overall PCa risk was not evaluated. However, most CCSs found either an increased risk for PCa or more frequent high-grade PCa (HGPCA) and advanced stages in smokers [31–37].

The different results retrieved from cohort studies and CCSs may at least partially be explained by selection bias (men free of cancer at inclusion in cohorts vs PCa patients in CCSs), various smoking habits, and different smoking prevalence rates (eg, based on geographical regions) [31–37]. Only one CCS found a significantly reduced incidence in smokers [30]. In this study, ever smokers displayed a risk ratio (RR) of 0.70 (95% confidence interval [CI]: 0.58–0.84) compared with nonsmokers, while current smokers had a 50% reduced relative risk (95% CI: 0.36–0.69) [30].

Murphy et al [31] analyzed the impact of smoking in different ethnicities in the USA. While there was no impact of smoking on overall PCa incidence and on low-grade PCa

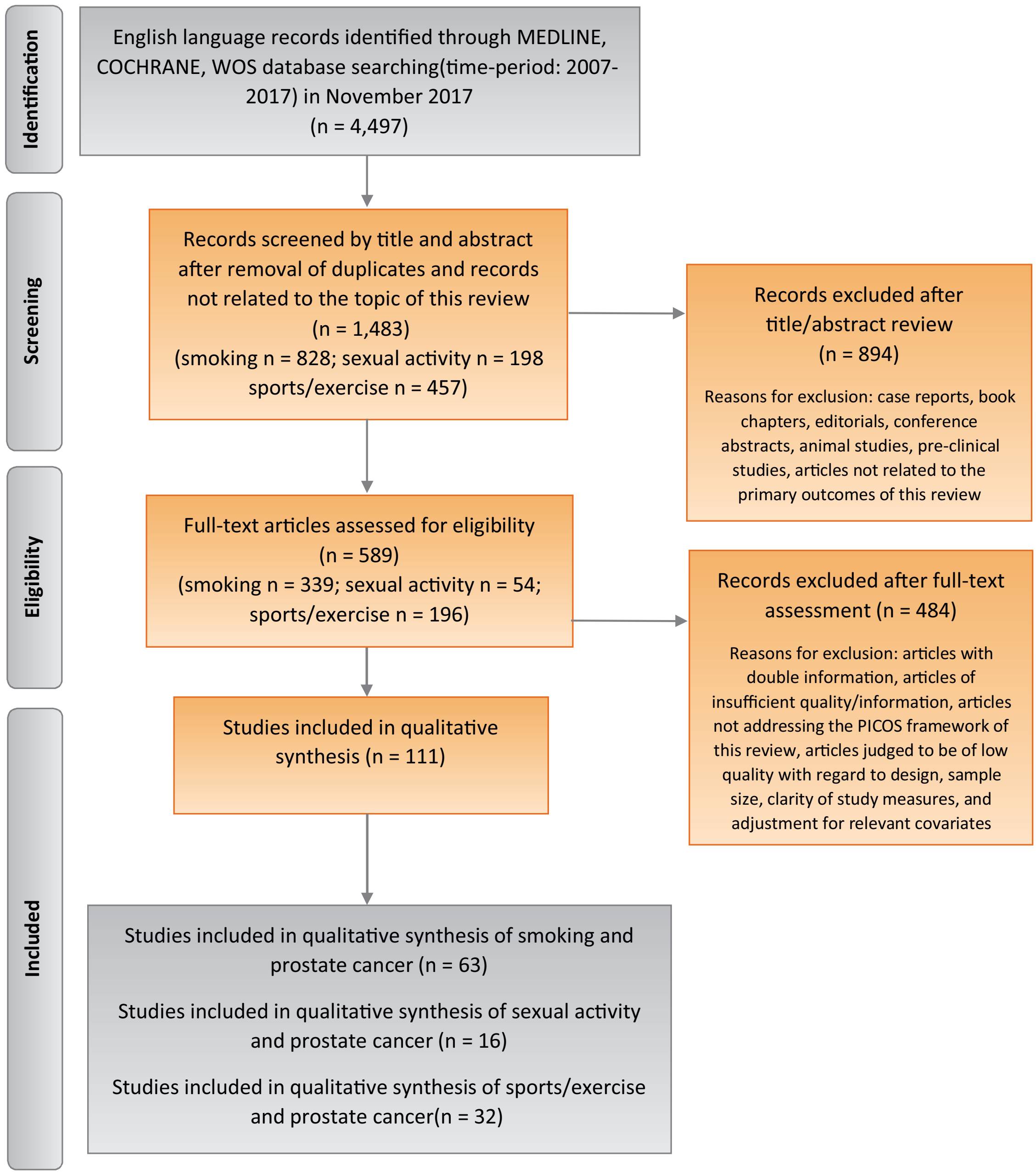

Fig. 1 – Flow diagram showing the step-by-step review process according to the PRISMA statement criteria. The detailed strategy for records identification and selection is outlined in the Supplementary material. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; WOS = Web of Science.

and HGPCA in white men, heavy smokers among AA men had a considerably enhanced PCa risk in comparison with never smokers and light smokers (odds ratio [OR] 2.57; 95% CI: 1.09, 6.10). Furthermore, in AA men, the incidence of HGPCA was significantly enhanced in light (OR 1.21; 95% CI 0.69, 2.13) and heavy smokers (OR 1.89; 95% CI 1.03, 3.48) [31].

Three relevant meta-analyses (MAs) including also studies published prior to 2007 were additionally reviewed to pick up possible differences based on the time period of study conduction [38,39,64]. Ordóñez-Mena et al [38] reported lower risks for incident PCa in current (hazard ratio [HR] 0.81; 95% CI: 0.72–0.91) and former smokers (HR 0.88; 95% CI: 0.82–0.95) based on the results of 19 prospective US and European cohorts. An MA of 24 prospective studies conducted until 2007 found no increased risk of incident PCa in smokers (RR 1.04; 95% CI: 0.87–1.24), but stratified by the amount of smoking, smokers had a significantly elevated risk (cigarettes/d or yr: RR 1.22; 95% CI: 1.01–1.46; pack years [PY]: RR 1.11; 95% CI 1.01–1.22) [39]. In former and current smokers, the risk of fatal PCa increased by 24–30% in comparison with that in nonsmokers [39]. Islami et al [64] showed that current cigarette smoking was inversely associated with incidental physical activity

Table 1 – Characteristics of studies evaluating the association between smoking and risk of prostate cancer, and between smoking and treatment outcome/mortality/progression.

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Evaluating the association between smoking and risk of prostate cancer						
Cohort studies						
No significant impact of smoking status and/or smoking habits on PCa incidence						
Giovannucci et al (2007) [10]	Health Professionals Follow-up Study; USA, 1986	Cohort, incidence	2002 (NR)	47 750; 3544	Never smoker Current/former (quit ≤10 yr)	Incidence (ref: nonsmoker): Current/former smoker: RR 0.98 (95% CI: 0.89–1.07)
Gonzalez et al (2007) [11]	Vitamins and Lifestyle (VITAL); USA, 2000–2002	Cohort, incidence	2004 (3.3)	35 244; 832	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.92 (95% CI: 0.70–1.20) Current smoker: RR 0.94 (95% CI: 0.82–1.05)
Rohrmann et al (2007) [12]	Private census; Washington County, MD, USA, 1963 and 1975	Cohort, incidence	1978; 1994 (NR)	26 810 and 28 292; 147 and 351	Never smoker Ever smoker Current smoker	1963 cohort: Incidence (ref: nonsmoker): Ever smoker: RR 1.16 (95% CI: 0.84–1.60) Current smoker: RR 1.00 (95% CI: 0.63–1.59) 1975 cohort: Incidence (ref: nonsmoker): Ever smoker: RR 1.01 (95% CI: 0.83–1.24) Current smoker: RR 0.98 (95% CI: 0.73–1.33)
Butler et al (2009) [13]	Singapore Chinese Health Study; Singapore, 1993–1998	Cohort, incidence	2006 (10.4)	27 293; 250	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.95 (95% CI: 0.74–1.16) Current smoker: RR 0.88 (95% CI: 0.65–1.19)
Geybels et al (2012) [14]	Netherlands Cohort Study; The Netherlands, 1986	Cohort, incidence	2003 (17.3)	58 279; 3451	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 1.01 (95% CI: 0.88–1.13) Current smoker: RR 0.98 (95% CI: 0.82–1.18)
Karlsen et al (2012) [15]	Danish Diet, Cancer and Health Study; Denmark, 1993–1997	Cohort, incidence	2000–2002 (NR)	20 914; 129	Nonsmoker Current smoker	Incidence (ref: nonsmoker): Current smoker: RR 1.00 (95% CI: 0.70–1.43)
Shafique et al (2012) [16]	Collaborative study; Scotland, 1970–1972	Cohort, incidence	2007 (28)	6017; 318	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 1.08 (95% CI: 0.84–1.32) Current smoker: RR 0.93 (95% CI: 0.69–1.26)
Onitilo et al (2013) [17]	Marshfield Clinic, USA, 1995–2009	Cohort, incidence	2011 (NR)	33 832; 3432	Before and after DM onset: Never smoker Ever smoker	Incidence (ref: nonsmoker): Before DM onset: ever smoker: RR 0.92 (95% CI: 0.85–1.18) After DM onset: ever smoker: RR 0.83 (95% CI: 0.74–0.94)
Significant impact of smoking status and/or smoking habits on PCa incidence						
Watters et al (2009) [18]	NIH–AARP; USA, 1995–1996	Cohort, incidence	2003 (NR)	283 312; 16 640	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.89 (95% CI: 0.86–0.91) Current smoker: RR 0.85 (95% CI: 0.80–0.90)
Grundmark et al (2011) [19]	Uppsala Longitudinal Study of Adult Men (ULSAM); Sweden, 1970–1974	Cohort, incidence	2003 (26.5)	2045; 208	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.67 (95% CI: 0.50–0.83) Current smoker: RR 0.60 (95% CI: 0.44–0.83)

Table 1 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Karppi et al (2012) [20]	Kuopio Ischaemic Heart Disease Risk Factor; Finland, 1984–1989	Cohort, incidence	2008 (15)	997; 68	Nonsmoker Smoker	Incidence (ref: nonsmoker): Smoker: RR 0.85 (95% CI: 0.76–0.95)
Bae et al (2013) [21]	Seoul Male Cancer Cohort Study; South Korea, 1991–1992	Cohort, incidence	2008 (NR)	14 450; 87	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.65 (95% CI: 0.40–0.90) Current smoker: RR 0.70 (95% CI: 0.43–1.13)
Heikkila et al (2013) [22]	IPD-Work Consortium; Europe, 1985–2002	Cohort, incidence	2008 (12)	116 056; 865	Nonsmoker Current smoker	Incidence (ref: nonsmoker): Current smoker: RR 0.70 (95% CI: 0.59–0.84)
Lemogne et al (2013) [23]	GAZEL study; France, 1989	Cohort, incidence	2009 (15.2)	8877; 412	Never smoker Ever smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.86 (95% CI: 0.73–1.00)
Rohrmann et al (2013) [24]	European Prospective Investigation into Cancer and Nutrition (EPIC); Europe, 1992–2000	Cohort, incidence	2009 (11.9)	145 112; 4623	Never smoker Ever smoker Current smoker	Incidence (ref: nonsmoker): Ever smoker: RR 0.93 (95% CI: 0.89–0.98) Current smoker: RR 0.90 (95% CI: 0.83–0.97)
Sawada et al (2014) [25]	Japan Public Health Center-based prospective study (JPHC study); Japan, 1990–2010	Cohort, self-reported questionnaires, overall incidence, and localized PCa	2010 (16)	48 218; 913	Never smoker Past smoker Current smoker	Incidence (multivariate adjustment; ref: never smoker) Past smoker: OR 0.84 (95% CI: 0.70–0.998) Current smoker 0–20 PY: OR 0.67 (95% CI: 0.49–0.91) Current smoker 20–40 PY: OR 0.84 (95% CI: 0.70–1.02) Current smoker $\geq$40 PY: OR 0.80 (95% CI: 0.65–0.99); overall $p = 0.05$ Incidence of localized PCa (ref: never smokers): Significantly reduced risk in smokers: $p = 0.007$ Incidence of advanced PCa (ref: never smokers): Similar risk in smokers: $p = 0.79$
Everatt et al (2014) [26]	Lithuania, 1997–2008	Cohort, incidence	2008 (NR)	6976; 1780	Never smoker Current smoker	Incidence (adjustment for age, education, alcohol consumption, BMI): Lower PCa risk in current smokers vs never smokers (no details provided)
Perez-Cornago et al (2017) [27]	UK Biobank; UK	Cohort; self-reported questionnaires; incidence	2014 (5.6)	219 335; 4575	Never smoker Former smoker Current smoker	Incidence (multivariate adjustment for several parameters including race, BMI, DM, sexual intercourse, having children): Current smoker (ref: never smoker): HR 0.85 (95% CI: 0.77–0.95) Former smoker (ref: nonsmoker): HR 0.93 (95% CI: 0.88–0.99)
Case-control studies						
No significant impact of smoking status and/or smoking habits on PCa incidence						
Pacheco et al (2016) [28]	Two centers, Argentina, 2011–2013	CCS, self-reported questionnaires; prevalence of smoking; incidence	2013 (no FU)	326 PCa patients; 394 patients with other cancers; 629 controls	Tobacco use: Active use Passive use Past use No use	Prevalence: tobacco use significantly more prevalent in both cancer groups than in controls PCa incidence (multivariate analysis): tobacco use not associated with diagnosis of PCa

Table 1 (***Continued***)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
May et al (2016) [29]	Two centers, Germany, 2013–2014	CCS, self-reported questionnaires; baseline PCa characteristics; presence of advanced tumor stage	2014 (no FU)	124 PCa patients	Nonsmoker Former smoker Active smoker	Baseline characteristics: no significantly different distribution in local tumor stage and N/M stage between smokers (active and former) and nonsmokers ($p = 0.198$) Presence of advanced tumor stage (N+/M+; multivariate analysis, ref: nonsmoker): Former/active smoker: OR 1.84 (95% CI: 0.85–3.96), $p = 0.120$ Pack years (cont): OR 1.01 (95% CI: 0.99–1.03), $p = 0.223$
Significant impact of smoking status and/or smoking habits on PCa incidence						
Koutros et al (2013) [30]	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO); USA, 1993–2001	Nested CCS, incidence	2009 (3.4)	28 243; 680 (824)	Never smoker Ever smoker Current smoker	Incidence (ref: never smoker): Ever smoker: RR 0.70 (95% CI: 0.58–0.84) Current smoker: RR 0.50 (95% CI: 0.36–0.69)
Murphy et al (2013) [31]	USA, 2001–2012	Cross-sectional study; overall incidence and incidence of HGPCA and LGPCA, PCa recurrence	2012 (NR)	1085 overall; 527 PCa patients; 558 controls; predominantly AA (79.9% and 71.3%, respectively, $p = 0.01$).	Never smoker Light smoker (<20 cigarettes/d) Heavy smoker ($\geq$20 cigarettes/d)	Incidence (multivariate analysis; Caucasian men; ref: never smoker): Smoker: overall PCa risk: OR 1.04 (0.65, 1.19); LGPCA: 0.69 (0.33, 1.46); HGPCA: 1.60 (0.78, 3.31) Incidence (multivariate analysis; AA men; ref: never smoker): Heavy smoker (ref: never smoker and light smoker): OR 2.57 (95% CI: 1.09, 6.10) Incidence of LGPCA: Light smoker: OR 1.36 (95% CI: 0.84, 2.21; ref: never smoker) Heavy smoker: OR 1.15 (95% CI: 0.63, 2.11; ref: never and light smoker) Incidence of HGPCA: Light smoker: OR 1.21 (95% CI 0.69, 2.13; ref: never smoker) Heavy smokers: OR 1.89 (95% CI 1.03, 3.48; ref: never and light smoker) Additional information (not further specified): former smokers in AA men have increased odds (ref: never smoker) for PCa incidence; heavy smokers in AA men have lower risk (odds) for PCa recurrence
Ho et al (2014) [32]	REDUCE study; USA/Canada, Europe	CCS: multicenter, randomized, double-blind, placebo-controlled study (participants randomized to 0.5 mg dutasteride daily or placebo); biopsy after 2 and 4 yr; incidence of PCa detected on biopsy	NR (4)	6240 PCa patients	Never smoker Current smoker Former smoker	Incidence (ref: never smoker): Similar risk for PCa diagnosis on first biopsy for never smokers, smokers ($p = 0.41$), and former smokers ($p = 0.43$) Incidence of LGPCA: Current smoker ($p = 0.66$) Former smoker ($p = 0.96$) Incidence of HGPCA (ref: never smoker): Current smoker: OR 1.44 (95% CI 1.04–2.00, $p = 0.028$) Former smoker: OR 1.21, $p = 0.12$ Multivariate analysis: Results largely unchanged after adjusting for various clinical and demographic characteristics PY: PCa (OR 0.83, 95% CI: 0.73–0.95, $p = 0.007$), but unrelated to HGPCA ($p = 0.395$) Additional information: Among men with negative first on-study biopsies, smokers were 36% less likely to receive a second on-study biopsy ($p < 0.001$)

Table 1 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Pouresmaeili et al (2014) [33]	Shahid Beheshti University of Sciences; Iran, NR	CCS, single center; incidence	Single assessment, no FU	74 PCa patients; 116 controls	Smoking status: Smoking yes/no Smoking and opiate use yes/no No smoking and no opiate use	Incidence of PCa in patients with positive smoking status 44% vs 27% (control group – all others)
Shahabi et al (2014) [34]	California Collaborative Case–Control Study of Prostate Cancer; USA, 1997–2003	CCS, questionnaire, 2 study sites (LA county and SF bay area); incidence of localized and advanced PCa	Single assessment, no FU	761 localized PCa patients; 1199 advanced PCa patients; 1139 controls	The following variables were evaluated: History of tobacco smoking (ever/ never) Smoking status (never, former, current) Age at smoking start Duration of smoking Type of tobacco (cigarettes, cigars, pipes) Cigarettes smoked per day (lifetime average) Pack years of cigarette smoking Years since quitting	Incidence of localized PCa in non-Hispanic white men (ref: never smoker): Former smoker (regardless of time since smoking cessation): OR 1.3; 95% CI: 1.0–1.6 Current smoker: OR 1.1 (95% CI: 0.8–1.5) Ever smoker: OR 1.5 (95% CI: 1.1–2.1) Incidence of advanced PCa in non-Hispanic white men (ref: never smoker): Current smoker: OR 1.4 (95% CI: 1.0–1.9) No association between smoking intensity, duration, PY, and advanced PCa; no statistically significant trends in Hispanics or AAs
Bashir et al (2014) [35]	Faisalabad, Pakistan, 2011–2013	CCS, questionnaire study, 3 centers; incidence	Single assessment, no FU	140 PCa patients; 280 controls	Nonsmoker Current smoker	Incidence (ref: nonsmoker): Current smoker: OR 2.47 (95% CI: 1.17–5.18)
Lassed et al (2016) [36] See comment in PubMed Commons	Clinic of Urology-Nephrology and Kidney Transplant Daksi, Constantine, Algeria, 2011–2013	CCS, single center questionnaire; incidence	Single assessment, no FU	90 PCa patients; 190 controls	Nonsmoker Former smoker Current smoker	Incidence (ref: nonsmoker): Former smoker: OR 3.17; 95% CI: 1.76–5.69; RR 2.27; 95% CI: 1.47–3.50; $p = 0.0001$ Current smoker: OR 4.05; 95% CI 1.84–8.89; RR 2.60; 95% CI 1.57–4.31; $p = 0.0006$

Table 1 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Tang et al (2017) [37]	Shanghai, China, 3/ 2013–4/2016	Prospective single-center study; overall incidence and incidence of HGPCA	Single biopsy assessment, no FU	1795 men undergoing biopsy; 737 PCa	Never smoker Current smoker Former smoker	Overall PCa incidence (ref: never smoker): Current smoker: 1.46 (1.16–1.84) Former smoker: 1.20 (0.91–1.57) Incidence of LGPCA (ref: never smoker): Current/former smoker: OR 0.84 (95% CI: 0.61–1.16) Incidence of grade group $\geq$4 (ISUP 2014) and intraductal carcinoma (ref: never smoker): Current smoker: OR 1.89; 95% CI:1.44–2.48 Differences among smokers for LGPCA and HGPCA: $\geq$30 vs $<$30 PY: OR 1.50; 95% CI:1.09–2.06 Cigarettes smoked per day (cutoff 20): OR 1.02; 95% CI: 0.73–1.42 Age at smoking start not significant Grade groups not significantly different between never smokers and former smokers No significant difference for former smokers based on 5-yr cut-off for smoking cessation for LGPCA and HGPCA: OR 1.15, 95% CI 0.66–2.01 Intraductal cancer (ref: never smoker): Current smoker: OR 2.29; 95% CI: 1.14–4.59
Data from meta-analysis						
Huncharek et al (2010) [39]	USA, Europe, Asia	MA of 24 cohort studies published between 1966 and 2003; PCa-related death	NR	21 579 PCa patients	Current smoker Former smoker Never smoker	Incidence (ref: never smoker): Current smoker: RR 1.04; 95% CI: 0.87–1.24 Cigarettes per day or year: RR 1.22; 95% CI: 1.01–1.46 PY: RR 1.11; 95% CI: 1.01–1.22
Islami et al (2014) [64]	USA, Europe, Asia Pacific	MA of 51 articles/ studies published between 1958 and January 21, 2014	NR	11 823 PCa deaths, 503 49 PCa cases; 4 082 606 cohort participants	Never smoker Current smoker Former smoker Ever smoker	Incidence (ref: never smoker): Current smoker: RR 0.90; 95% CI: 0.85–0.96 with considerable heterogeneity between studies Studies completed until 1995 (prior to PSA screening era): ever smoking with clear positive association with PCa (RR 1.06; 95% CI: 1.00–1.12) PAR for smoking 6.7% (USA), 9.5% (Europe)
Ordóñez-Mena et al (2016) [38] See comment in PubMed Commons	CHANCES: coordinated multicountry study aiming to facilitate harmonization of data from ongoing prospective cohort studies; Europe, USA	MA of 19 population-based prospective cohort studies; CSM	NR (12 yr)	897 021; 140 205 cancer patients	Never smoker Former smoker Current smoker Years since smoking cessation	Cancer Incidence (ref: never smoker): Former: HR 0.88 (95% CI: 0.82; 0.95); RAP: –1.67 (95% CI: –2.80; –0.54) Current: HR 0.81 (95% CI: 0.72; 0.91); RAP: –2.89 (95%CI: –4.81; –0.97) Years since smoking cessation (ref: current smoker) $\leq$9 yr: HR 1.00 (95% CI: 0.90–1.12); RAP: 0.51 (95% CI: –0.83 to 1.84) 10–19 yr: HR 1.03 (95% CI: 0.89–1.19); RAP: 1.09 (95% CI: –0.17 to 2.35) $\geq$20 yr: HR 1.08 (95% CI: 0.99–1.18); RAP: 0.75 (95% CI: –0.38 to 1.88) Overall p linear = 0.0480
Evaluating the association between smoking and treatment outcome/mortality/progression						
Cohort studies						
Significant impact of smoking status and/or smoking habits on mortality/progression/treatment outcome						
Studies including patients treated by surgery and studies including mixed cohorts						

Table 1 (***Continued***)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Rohrmann et al (2007) [12]	Private census; Washington County, MD, USA, 1963 and 1975	Cohort; fatal PCa	2000 (NR)	226 810 (1963) and 28 292 (1975); 240 and 184	Never smoker Ever smoker Current smoker	1963 cohort: Fatal PCa (ref: never smoker): Ever smoker: HR 0.97 (95% CI: 0.76–1.23) Current smoker: HR 0.93 (95% CI: 0.67–1.29) 1975 cohort: Fatal PCa (ref: never smoker): Ever smoker: HR 1.13 (95% CI: 0.85–1.49) Current smoker: HR 1.25 (95% CI 0.84–1.87) However, current smokers ≥20 cigarettes/d (RR 2.38; 95% CI 0.94–5.99) and former smokers (RR 2.75; 95% CI: 1.13–6.74) had a greater risk of death from prostate cancer during the first 10 yr of follow-up
Watters et al (2009) [18]	NIH–AARP; USA, 1995–1996	Cohort; fatal PCa	2005 (NR)	283 312; 394	Never smoker Ever smoker Current smoker	Risk of fatal PCa (ref: never smoker): Current smoker; HR 1.69 (95% CI: 1.25–2.27)
Moreira et al (2010) [40]	Shared Equal Access Regional Cancer Hospital (SEARCH) cohort; USA, 1999–2008	Cohort study; baseline tumor characteristics; BCR	2008 (37)	1267	Active smoker Nonsmoker	Baseline characteristics: Active smokers (ref: nonsmokers): greater percentage of positive biopsy cores ($p = 0.039$), greater preop. PSA level ($p = 0.003$), more frequent extracapsular extension ($p = 0.003$), and seminal vesicle invasion ($p = 0.029$) BCR (ref: nonsmoker): Univariate analysis: HR 1.19, $p = 0.129$ Multivariate analysis (adjusted for BMI): HR 1.37, $p = 0.008$ Multivariate adjustment for multiple preop. characteristics: HR 1.12, $p = 0.325$ Multivariate adjustment for postop. features: HR 0.91, $p = 0.502$
Rohrmann et al (2013) [24]	European Prospective Investigation into Cancer and Nutrition (EPIC); Europe, 1992–2000	Cohort; CSM	2009 (11.9)	145 112; 432	Never smoker Ever smoker Current smoker	Mortality (ref: never smoker): Ever smoker: HR 1.06 (95% CI: 0.87–1.24) Current smoker: HR 1.27 (95% CI: 0.98–1.65) High-intensity of smoking (≥25 cigarettes/d; ref: nonsmoker): RR 1.81, 95% CI: 1.11–2.93 Long duration of smoking (40+ yr; ref: nonsmoker): RR 1.38, 95% CI: 1.01–1.87 Joint-effect analysis combining smoking status and intensity: clear association between heavy current smoking and CSM with no association for former smokers
Moreira and Aronson (2014) [42]	Shared Equal Access Regional Cancer Hospital (SEARCH); USA, 1995–2010 4 Veteran affairs medical centers (West Los Angeles, CA; Augusta, GA; and Durham and Asheville, NC)	Cohort study; BCR; metastasis, CRPC, OM	2010 (78)	1450 PCa patients	Never smoker Current smoker	Univariate analysis (ref: never smoker): Current smoker: BCR: HR 1.25, $p = 0.024$; metastasis: HR 2.64, $p = 0.026$; CRPC: HR 2.62, $p = 0.021$; OM: HR 2.14, $p < 0.001$ Multivariate analysis (ref: never smoker): Current smoker: BCR: HR 1.10, $p = 0.335$; metastasis: HR 2.51, $p = 0.044$; CRPC: HR 2.67, $p = 0.015$; OM: HR 2.03, $p < 0.001$

Table 1 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Murta-Nascimento et al (2015) [43]	Hospital del Mar Cancer Registry, Barcelona, Spain, 1992–2008	Retrospective cohort study; CSM	2011 (5.8)	1109	Never smoker Ex-smoker Current smoker	CSM (ref: never smoker): Current smoker: 82.9% CSM; ex-smoker: 88.9% CSM; never smoker: 89.6% CSM (difference significantly different; $p = 0.0001$) Multivariate analysis (ref: never smoker): Smoker: HR 1.80 (95% CI: 1.04–3.13) Ex-smoker: very similar CSM to never smokers No statistically significant difference between current, ex, and never smokers for CSM when stratified by stage (I–III and IV)
Wilson et al (2016) [44]	Swedish construction industry organization for working environment, safety and health (Bygghälsan); Sweden	Prospective cohort study of construction workers; retrospective analysis; OM, CSM	NR (4.4)	336 381; 9582	Never user (any tobacco) Ever user (snus only) Exclusive smoker only (cigarette, cigar, pipe) Ever user (both snus and smoking)	OM (ref: never users): Exclusive smokers: HR 1.17, 95% CI: 1.09–1.26 Exclusive snus users: HR 1.19, 95% CI: 1.04–1.37 CSM (ref: never users): Exclusive smokers: HR 1.15, 95% CI: 1.05–1.27 Exclusive snus users: HR 1.24, 95% CI: 1.03–1.49 (all stages); HR 3.17,(95% CI: 1.66–6.06 (nonmetastatic disease) Baseline tumor characteristics: Both snus and smoking users were more likely to be in lower-risk groups at diagnosis (17% of distant metastasis in both users vs 20–22% in all other groups; 24% low risk vs 19–21% in other groups)
Jones et al (2016) [45]	California, Kentucky, Maryland, Utah, USA, 1999–2010	Cohort study (Behavioral Risk Factor Surveillance System; Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research); cumulative smoking prevalence and mortality rates	2010 (NR)	NR	Overall smoking prevalence	California (1999–2010): smoking declined by 3.5%/yr (–4.4% to –2.5%), PCa mortality by 2.5%/yr (–2.9% to –2.2%); Kentucky: smoking declined by 3.0%/yr (–4.0% to –1.9%), PCa mortality by 3.5%/yr (–4.3% to –2.7%); Maryland: smoking declined by 3.0%/yr (–7.0% to 1.2%), PCa mortality 3.5%/yr (–4.1% to –3.0%); Utah: smoking declined by 3.5%/yr (–5.6% to –1.3%), PCa mortality by 2.1%/yr (–3.8% to –0.4%) No corresponding patterns were observed for external causes of death
Studies including patients treated with primary radiotherapy						
Kenfield et al (2011) [41]	The Health Professionals Follow-up Study; USA, 1986–2006	Cohort study; PSA relapse after primary treatment (RP, EBRT)	2008 (8.1)	5366 PCa patient	Never smoker Ever smoker Current smoker	PSA relapse (ref: never smoker): Ever smoker: HR 1.11 (95% CI: 0.96–1.29) Current smoker: HR 1.61 (95% CI: 1.16–2.22)
No significant impact of smoking status and/or smoking habits on mortality/progression/treatment outcome						
Studies including patients treated by surgery and studies including mixed cohorts						
Batty et al (2011) [46]	Whitehall I study; UK, 1967–1970	Cohort; fatal PCa	2007 (NR)	17 934; 551	Never smoker Ever smoker Current smoker	Fatal PCa (ref: never smoker): Ever smoker: HR 1.03 (95% CI: 0.88–1.21) Current smoker: HR 1.14 (95% CI: 0.91–1.44)
Tseng (2012) [47]	Taiwan Insurance; Taiwan, 1995–1998	Cohort; CSM in diabetic PCa patients	2006 (NR)	39 135; 105 diabetic PCa patients	Nonsmoker Smoker	CSM in diabetic PCa patients (ref: nonsmoker): Smoker: HR 1.09 (95% CI: 0.82–1.46)

Table 1 (***Continued***)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Fowke et al (2015) [48]	Asia Cohort Consortium: 18 prospective cohort studies across 6 countries in southern/ eastern Asia (India, China, Taiwan, Japan, South Korea, Singapore), 1993–2006	Multicenter survey study; CSM	NR (9.2)	522 736; 367 PCa deaths	Never smoker Ever smoker (split by 20 PY cutoff)	CSM (multivariate analysis; ref: never smoker): Ever smoker ≤20 PY: HR 1.03 (95% CI: 0.83–1.28) Ever smoker ≥21 PY: HR 0.92; 95% CI: 0.74–1.13 Ever smoker (all): HR 1.00; 95% CI: 0.84, 1.21
Taghizadeh et al (2016) [49]	Vlagtwedde-Vlaardingen; The Netherlands, 1965–1990	Longitudinal cohort study; ACM, CSM	2009 (NR; observational periods 43 yr)	8645 men and women with different tumor diseases	Baseline smoking habits: • Never smoker • Ex-smoker • Current smoker Lifetime smoking habits: • Never smoker • Ex-smoker • Quitter • Persistent smoker • Unstructured smoker Smoking duration and cessation	Higher numbers of PY at baseline were associated with an increased risk of ACM and CSM, but: CSM for smoking status (ref: never smoker): • Ex-smoker: HR 0.96 (95% CI: 0.37–2.50) • Current light smoker: HR 0.78 (95% CI: 0.27–2.23) • Current moderate smoker: HR 0.70 (95% CI: 0.29–1.73) • Current heavy smoker: HR 1.05 (95% CI: 0.42–2.66) CSM for lifetime smoking habits (ref: never smoker): • Persistent ex-smoker: HR 1.04 (95% CI: 0.20–5.37) • Quitter: HR 0.55 (95% CI: 0.11–2.64) • Persistent smoker: HR 0.79 (95% CI: 0.17–3.60) • Unstructured smoker: HR 0.91 (95% CI: 0.13–6.55) CSM—duration of smoking: HR 0.98 (95% CI: 0.89–1.09) CSM—time since smoking cessation: HR 1.03 (95% CI: 0.92–1.14) ACM: declining HR in first 5 r after smoking cessation; this effect was not observed any further with a longer duration (results limited by small sample size)
Case-control studies						
Significant impact of smoking status and/or smoking habits on mortality/progression/treatment outcome						
Studies including patients treated by surgery						
Joshu et al (2011) [52]	Johns Hopkins RP series; USA, 1993–2006	Retrospective CCS; PCa recurrence after RP	2009 (7.3)	1416	Never smoker Ever smoker Current smoker	PCa recurrence (ref: never smoker): Ever smoker: HR 1.16 (95% CI: 0.78–1.74) Current smoker: HR 2.31 (95% CI: 1.05–5.10)
Oh et al (2012) [53]	Korea, 2004–2010	Retrospective CCS; PSA relapse in patients with BMI ≥25 kg/m^2 after RP	2010 (NR)	1165	Nonsmoker Current smoker	PSA relapse (ref: nonsmoker): Current smoker: HR 2.2 (95% CI: 1.04–3.83)
Ngo et al (2013) [54]	Stanford, CA, USA, 1989–2005	CCS; cancer volume in RP specimens	2005 (NR)	630	Never smoker Current smoker PY	Cancer volume (per PY): HR 0.031 (95% CI: 0.015–0.048)

Table 1 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Rieken et al (2015) [55]	Six US and Austrian centers; 2000–2011	Retrospective CCS, BCR after primary RP without neoadjuvant treatment	2011 (NR)	6538 node-negative PCa patients	Never smoker Former smoker Current smoker	Association between smoking and clinicopathological features: RP Gleason score ($p = 0.3$) Extracapsular extension ($p = 0.2$) Seminal vesicle invasion ($p = 0.8$) Positive surgical margins ($p = 0.9$) Association between smoking status and 5-yr BCR-free survival: Never smoker: 90% Former smoker: 84% Current smoker: 83% BCR (multivariate analysis; ref: never smoker): Former smoker: HR 1.63, 95% CI: 1.30–2.04; $p < 0.001$ Current smoker: HR 1.80, 95% CI: 1.45–2.24; $p < 0.001$ Significant association between smoking and BCR in all RP Gleason score categories Association between cumulative exposure and BCR: no significant differences in 5-yr BCR-free survival among all groups (4 categories) and on multivariable analysis Association between smoking cessation and BCR (multivariate analysis; ref: never smoker): Smoking cessation of $\geq$4.9 yr: HR 1.86, 95% CI: 1.43–2.41; $p < 0.001$ 5–9.9 yr: HR 2.01, 95% CI: 1.50–2.70; $p < 0.001$ $\geq$10 yr: HR 0.96, 95% CI: 0.68–1.37; $p = 0.84$
Froehner et al (2015) [56]	Dresden; Germany, 1992–2007	Retrospective CCS; CSM, competing mortality after RP	NR (9.7 yr)	2818	Nonsmoker Former smoker Smoker	CSM (multivariate models; ref: nonsmoker): Smoker: HR 1.30 (95% CI: 0.80–2.09), $p = 0.29$ Former smoker: HR 0.82 (95% CI, 0.50–1.34), $p = 0.42$ Competing mortality (multivariable models; ref: nonsmoker): Smoker: HR 2.33 (95% CI: 1.77–3.07), $p < 0.0001$ Former smoker: HR 1.12 (95% CI: 0.85–1.46), $p = 0.42$ The impact of current smoking on competing mortality was approximately equivalent to 3 points of the CCI or 10 yr of age
Sato et al (2017) [59]	Fukuoka, Kyushu, Japan, 2003–2013	Retrospective CCS; baseline tumor characteristics on biopsy and RP specimens; BCR	NR (3.3 yr)	1165	Nonsmokers Current smokers	Tumor characteristics on biopsy: Current smokers (ref: nonsmokers): significantly higher PSA levels, higher biopsy and pathological GS, more frequent lymph-node involvement BCR (univariate analysis; ref: nonsmoker): Current smoker: HR 1.31 (95% CI: 1.00–1.72), $p = 0.046$; however, no independent impact on multivariate analysis
Froehner et al (2017) [60]	Dresden, Germany, 1992–2007	Retrospective CCS; OM, competing mortality, OCM, second cancer mortality after RP	NR (10 yr)	2630	Current smoker Nonsmoker	OM (ref: nonsmoker or unknown status): Current smoker: HR 2.12; 95% CI: 1.64–2.73; $p < 0.0001$ Competing mortality (ref: nonsmoker or unknown status): Current smoker: HR 2.29; 95% CI: 1.73–3.02; $p < 0.0001$ OCM (ref: nonsmoker or unknown status): Current smoker: HR 2.16; 95% CI: 1.52–3.07; $p < 0.0001$ Second cancer mortality (ref: nonsmoker or unknown status) Current smoker: HR 2.15; 95% CI: 1.35–3.42; $p = 0.0013$

Table 1 (***Continued***)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Froehner et al (2017) [61]	Dresden, Germany, 1992–2007	Retrospective CCS; competing mortality after RP	NR	2961	Nonsmoker/ex-smoker in one category Current smoker	Competing mortality (multivariate analysis; ref: non-/ex-smoker): Current smoker (all patients): HR 2.18, $p = 0.0098$ ≥70 yr: HR 2.18; 95% CI: 1.21–3.93; $p = 0.0098$ <70 yr: HR 2.06; 95% CI: 1.59–2.6; $p < 0.0001$
Studies including patients treated with primary radiotherapy						
Pantarotto et al (2007) [50]	Canada, 1990–1999	Retrospective CCS; distant failure after EBRT	1999 (NR)	434	Never smoker Ever smoker Current smoker	Distant failure (ref: never smoker): Ever smoker: HR 2.90 (95% CI: 1.09–7.67) Current smoker: HR 5.24 (95% CI: 1.75–15.72)
Steinberger et al (2015) [57] See comment in PubMed Commons	Memorial Sloan Kettering Cancer Center, New York, USA, 1998–2005	Retrospective CCS; BCF, distant metastasis, CSM after primary EBRT (med. dose 81 Gy)	NR (7.9 yr)	2156	Never smoker Current smoker Former smoker Current smoking status unknown Tobacco use (PY) Duration of smoking Time since smoking cessation	BCF (ref: never smoker): Current smoker: HR 1.4, $p = 0.02$ Distant metastasis: Current smoker: HR 2.37, $p < 0.001$ CSM: Current smoker: HR 2.25, $p < 0.001$ All other smoking categories not significantly associated with outcome
Studies including mixed cohorts (eg, RP, radiotherapy, ADT; various tumors)						
Gong et al (2008) [51]	Seattle, WA, USA, 1993–1996	CCS; CSM after RP, EBRT, ADT	1996 (NR)	752	Never smoker Ever smoker (quit >10 yr) Ever smoker (quit <10 yr) Current smoker	CSM: Ever smoker (quit >10 yr): HR 0.45 (95% CI: 0.19–1.05) Ever smoker (quit <10 yr): HR 1.48 (95% CI: 0.50–4.37) Current smoker: HR 2.66 (95% CI: 1.01–3.99)
Ho et al (2016) [58]	Mayo Clinic, Rochester, MN, USA, 2005–2009	Retrospective CCS; OS	NR	163 patients (breast, colorectal, prostate, lung); 26 PCa patients	Smoking history yes/no	OM (all cancers): Multivariate analysis: HR 2.53 (1.36–5.04); $p = 0020$
No significant impact of smoking status and/or smoking habits on mortality/progression/treatment outcome						
Studies including patients treated with primary radiotherapy						
Tendulkar et al (2013) [62]	Cleveland Clinic, OH, USA, 1996–2009	Retrospective single-center CCS; OM and CSM after EBRT plus ADT (med. dose 78 Gy)	NR (6.2)	660 PCa patients	Smoking history yes/no	OM (multivariate analysis; ref: smoking history no): Smoking status was not a significant predictor CSM (cumulative): smoking status was not a significant predictor ($p = 0.60$)
Lee et al (2017) [63]	New York, USA, 2004–2011	CCS, two centers; BCFS, DMFS after EBRT (median dose 76 Gy)	NR (6.3 yr)	500	Never smoker Smoker Former smoker	8-yr BCFS: never smokers: 73.6%; former smokers: 80.2%; current smokers: 73.4% ($p = 0.38$) BCFS (multivariate analysis; ref: never smoker): Former smoker: HR 0.72, $p = 0.19$ Current smoker: HR 1.02, $p = 0.93$ 8-yr DMFS was 92.8%, 96.8%, and 95.3%, respectively, $p = 0.54$ DMFS (multivariate analysis; ref: never smoker): Former smoker: HR 0.71, $p = 0.51$ Current smoker: HR 1.41, $p = 0.52$

Table 1 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, yr)	Total no. of men; prostate cancer patients	Smoking category	Results and main findings
Systematic reviews/meta-analysis						
Huncharek et al (2010) [39]	US, Europe, Asia	MA of 24 cohort studies published between 1966 and 2003; PCa-related death	NR	21 579 PCa patients	Current smoker Former smoker Never smoker	Death from PCa: Former smoker: RR 1.09; 95% CI: 1.02–1.16 (ref: never smoker) Current smoker: RR 1.14; 95% CI: 1.06–1.19 (ref: never smoker) Heaviest smokers had a 24–30% greater risk of death from PCa compared with nonsmokers
Islami et al (2014) [64]	USA, Europe, Asia Pacific	MA of 51 articles/ studies published between 1958 and January 21, 2014	NR	11 823 PCa deaths, 503 49 PCs cases; 4 082 606 cohort participants	Current use Former use Ever use	Current cigarette smoking associated with increased risk of PCa death (RR 1.24; 95% CI: 1.18–1.31; limited evidence for heterogeneity and publication bias) Number of cigarettes/d: dose-response association with PCa mortality (p = 0.02; RR for 20 cigarettes/d: 1.20) PAR for cigarette smoking and PCa deaths in the USA and Europe: 6.7% and 9.5%, respectively
Ordóñez-Mena et al (2016) [38] See comment in PubMed Commons	CHANCES: coordinated multicountry study aiming to facilitate harmonization of data from ongoing prospective cohort studies; Europe, USA	MA of 19 population-based prospective cohort studies; CSM	NR (12 yr)	897 021; 140 205 cancer patients	Never smoker Former smoker Current smoker Years since smoking cessation	Cancer-specific mortality (current smokers; ref: never smokers): HR 1.26 (95%CI: 0.97; 1.64); RAP 1.88 (0.25; 3.51)

AA = African American; ACM = all-cause mortality; ADT = androgen deprivation therapy; BCF = biochemical failure; BCFS = biochemical recurrence-free survival; BCR = biochemical recurrence; BMI = body mass index; CCS = case-control study; CCI = Charlson Comorbidity Index; CI = confidence interval; CRPC = castrate-resistant prostate cancer; CSM = cancer-specific mortality; DM = diabetes mellitus; DMFS = distant metastasis-free survival; EBRT = external beam radiotherapy; EPIC = Expanded Prostate Index Composite Questionnaire; FU = follow-up; Gy = Grey; GS = Gleason score; HGPCA = high-grade prostate cancer; HR = hazard ratio; LGPCA = low-grade prostate cancer; MA = meta-analysis; med. = median; NR = not reported; OR = odds ratio; PAR = population attributable risk; OCM = other-cause mortality; OM = overall mortality; OS = overall survival; PCa = prostate cancer; postop = postoperative; preop = preoperative; PSA = prostate-specific antigen; PY = pack years; RAP = rate advancement periods; ref = reference; RP = radical prostatectomy; RR = risk ratio.

(PA) (RR 0.90; 95% CI: 0.85–0.96). Smoking duration, the number of cigarettes smoked per day, and previous smoking were not significantly associated with PCa risk. However, considerable heterogeneity of study results ($I^2 = 68\%$; $p < 0.001$) was noted, and studies completed until 1995 (prior to prostate-specific antigen [PSA] screening era) indicated a positive association of ever smoking with incident PCa (RR 1.06; 95% CI: 1.00–1.12).

3.1.2. Association of smoking with treatment outcome, progression, and mortality

The association of smoking with treatment outcome, progression, and mortality seems to be robust, and several observational studies have shown an association with worse outcome after radical prostatectomy (RP) and external beam radiation therapy (EBRT), or under medical tumor treatment (Table 1).

Of 13 cohort studies, nine found a significant impact of smoking on CSM in the entire cohort [12,18,24,40–45] or for subgroups of patients, for example, heavy and long-duration smokers [24]. Moreira and Aronson [42] analyzed overall mortality (OM), biochemical recurrence (BCR), development of metastasis, and castrate-resistant PCa (CRPC), and found a significantly increased risk for all end points in current smokers (BCR: HR 1.10; $p = 0.335$; metastasis: HR 2.51; $p = 0.044$; CRPC: HR 2.67; $p = 0.015$; OM: HR 2.03; $p < 0.001$). Jones et al [45] compared PCa death rates in four US states with the smoking prevalence between 1999 and 2010, and indicated a significant and congruent reduction in both smoking prevalence and CSM, while no corresponding patterns were observed for other causes of death. Rohrmann et al [12] analyzed US cohorts started in 1963 and 1975 and did not find a significant impact on CSM in the entire cohorts (HR 0.93; 95% CI: 0.67–1.29 and HR 1.25; 95% CI: 0.84–1.87, respectively); however, smokers consuming ≥20 cigarettes/d (RR 2.38; 95% CI: 0.94–5.99) and former smokers (RR 2.75; 95% CI: 1.13–6.74) had a greater risk of PCa death during the first 10 yr of follow-up, indicating a possible effect of PSA screening and changes in health-related lifestyle.

Four cohort studies were not able to confirm an independent impact of smoking on outcome [46–49]. Batty et al [46] did not find an association between smoking and CSM (current vs never smokers: HR 1.14; 95% CI: 0.91–1.44). However, the results of this study are also somehow surprising, as no impact of diabetes, blood pressure, socioeconomic status, and PA on OM was found, whereas marital status and increased physical stature were associated with CSM [46]. Ordóñez-Mena et al [38] did not find an independent impact of smoking status on CSM in an Asian cohort of diabetic patients (smokers vs non-smokers: HR 1.09; 95% CI: 0.82–1.46). Taghizadeh et al [49] analyzed the impact of smoking in a cohort including men and women with different tumor diseases; a general trend to worse CSM in smokers was not significant. In addition, Fowke et al [48] did not find significant differences in CSM in a summary of 18 Asian cohort studies.

Overall 16 articles (referring to 14 studies) were identified reporting results of CCSs on mortality and/or treatment outcomes assessed by the end point recurrence or distant failure [50–63]. Fourteen articles reported a consistent association between smoking status and cancer-related death or treatment outcomes [50–61].

Froehner et al [56,60,61] have additionally analyzed the impact of smoking on competing mortality (CM). Whereas OM was significantly enhanced in smokers (HR 2.12; 95% CI: 1.64–2.73; $p < 0.0001$), CSM was not (HR 1.30; 95% CI: 0.80–2.09; $p = 0.29$), alongside with significantly increased CM (HR 2.33; 95% CI: 1.77–3.07; $p < 0.0001$) equivalent to three points of the Charlson Comorbidity Index or 10 yr of age [56,60,61]. Ngo et al [54] found a significant difference in tumor volume (2.54 vs 2.16 ml; $p = 0.016$) and high-grade cancer volume (0.58 vs 0.28 ml; $p = 0.004$) when comparing smokers and nonsmokers, and a greater risk of BCR (HR 1.27; 95% CI: 1.03–1.54; $p = 0.02$) with approximately 1% increase in risk per PY. In a study by Sato et al [59], increased BCR in smokers (HR 1.31; 95% CI: 1.00–1.72; $p = 0.046$) and worse tumor baseline characteristics (PSA, Gleason score [GS], and lymph-node involvement) were detected. In contrast, Rieken et al [55] could not confirm significant differences in GS, extracapsular extension, seminal vesicle invasion, and surgical margins; nonetheless, former and current smokers had a significantly increased BCR (former smokers: HR 1.63, 95% CI: 1.30–2.04; $p < 0.001$; current smokers: HR 1.80, 95% CI: 1.45–2.24; $p < 0.001$). The association between prior smoking and outcome was present until 10 yr after smoking cessation and diminished in smokers who had quit smoking >10 yr ago (HR 0.96, 95% CI: 0.68–1.37; $p = 0.84$) [55].

Smoking has also a negative impact on treatment outcome after primary EBRT. A significantly higher proportion of current smokers (24.3%; $p = 0.007$) developed distant failure when compared with never (7.6%) or ever (16.9%) smokers in a study by Pantarotto et al [50] on 434 patients. In another study, smoking was associated with a higher risk of metastasis in both current (HR 5.24; 95% CI: 1.75–15.72) and ever (HR 2.90; 95%CI: 1.09–7.67) smokers [41]. Steinberger et al [57] found that BCR (HR 1.4, $p = 0.02$), metastatic disease (HR 2.37, $p < 0.001$), and CSM (HR 2.25, $p < 0.001$) after EBRT were significantly increased in smokers compared with never smokers. In contrast, two CCSs did not find an adverse impact of smoking on OM, CSM, BCR, and distant failure in patients undergoing primary EBRT [62,63]. The cohort evaluated by Lee et al [63] in this regard mainly comprised AA men (61.9%). Whether the outcomes assessed in this study might have been impacted also by ethnical differences and differential impact of smoking habits remains to be determined.

The abovementioned MAs by Islami et al [64], Huncharek et al [39], and Ordóñez-Mena et al [38] have also analyzed the impact of smoking on CSM. The highest categories of smoking were associated with 24–30% increased CSM; consistently, this association was observed for current, former, and ever smokers and in meta-regression models, suggesting a dose-response association. The results published by Islami et al [64] were further confirmed in subgroup analyses for geographical region or study completion time. Cigarette smoking at baseline was associated with an increased risk of death from PCa (RR 1.24; 95% CI: 1.18–1.31) with little heterogeneity in results ($I^2 = 1\%$; $p = 0.45$), and the amount of cigarette smoking at baseline (cigarettes/d) showed a dose-response association with PCa death ($p = 0.02$; 20 cigarettes/d: RR 1.20). The RR for the association between previous cigarette smoking and PCa mortality was 1.06 (95% CI, 1.00–1.13) [64]. Based on the results published by Huncharek et al [39], current smokers had an increased risk of fatal PCa (RR 1.14; 95% CI: 1.06–1.19) and heaviest smokers up to 30% enhanced CSM compared with nonsmokers. Consistently, Ordóñez-Mena et al [38] reported increased CSM in smokers (HR 1.26; 95% CI: 0.97–1.64).

There is evidence that former smokers may have a modestly increased risk of PCa relative to never smokers, but the literature is inconsistent in this regard. However, studies in which smoking status has also been assessed with the time period from quitting smoking to PCa diagnosis have indicated that an increased risk for PCa development and poorer outcome after RP remains for 10 yr and returns to baseline afterward [10,55].

Different outcomes and impact of smoking have also been shown in different ethnicities, especially when comparing AA versus Caucasian patients [31]. Whether the underlying reasons are related to smoking habits, duration, different rates of quitters, or other factors remains to be determined [68,69]. Both AA and Caucasian men in the USA have a 21% prevalence of cigarette smoking; however, AA men have lower rates of heavy smoking and smoking cessation [74,75]. The association between smoking and PCa might be missed when rates of heavy smokers are lower and the risk of PCa is generally higher in AA men.

3.2. *Sexual activity*

Available evidence suggests that sexual activity might play a role in PCa pathogenesis. The main characteristics of sexual behavior studied are the number of sexual partners, sexual orientation, ejaculation frequency (EF), and age at first intercourse; furthermore, the impact of sexually transmitted infections (STIs) including human papilloma virus (HPV) prevalence in the prostate has been evaluated. The impact of vasectomy on PCa risk and mortality has been studied as well. In this review, prospective articles together with additional selected high-quality retrospective studies published in the last 10 yr, mainly observational CCSs and cohort studies, have been reviewed (Table 2).

3.2.1. *Sexual activity and risk of PCa*

With respect to the number of sexual partners, in a population-based CCS, Spence et al [90] showed that individuals who had had >20 lifetime female sexual partners displayed a decreased risk of PCa and had less aggressive tumors at diagnosis. The protective effect was maintained after adjustment for the number of male partners. The authors suggested that one plausible explanation could be a higher EF, which has been shown to decrease the risk of PCa [91,92]. Nonetheless, it has not been proved that EF is increasing with a higher number of female partners.

EF has been proposed as a modifiable risk factor for PCa; this association has been studied recently by two research groups [91,92]. In a prospective cohort study, Rider et al [91] showed a decreased risk of low-grade PCa in patients with an EF of ≥21/mo at ages 20–29 and 40–49 yr. This observation was corroborated by Papa et al [92] in a CCS that showed an inverse association between PCa risk and EF at ages 30–39 yr when considering the OR per five-unit increase in ejaculation per week.

Different authors have suggested an association between STIs and PCa risk. Two cohort studies meeting the inclusion criteria could not show an association between a history of any STI and PCa [90,93]. This contrasts with an MA that found slightly higher risks in patients with a history of any STI [94]. However, the data display significant heterogeneity, which limits the validity of conclusions. Two cohort studies have suggested that *Neisseria gonorrhoeae* infections increase the risk of PCa [95,96]. In one study, HPV detection was more frequent in PCa specimens compared with specimens retrieved from nonmalignant tissue, which was not confirmed by other authors [97,98].

Concerning the impact of sexual orientation on PCa risk, there is a lack of evidence for the nonheterosexual male population and data are scarce in cancer registries. Spence et al [90] described a slightly increased risk in nonheterosexual men. However, a recent review of quantitative data showed a similar rate of PCa diagnosis in heterosexual and nonheterosexual patients [99].

Vasectomy has been discussed as a putative risk factor for PCa development over recent decades, and some studies have supported an association with lethal PCa [100]. On the contrary, most recent studies found either no or only a weak association between vasectomy and overall PCa risk (closer to the null with increasingly robust study design) and no significant association with HGPCA, advanced-stage PCa, or fatal PCa, finally resulting in currently strong evidence rebutting a relationship between vasectomy and PCa [101–105].

Results from available studies on sexual activity and PCa risk imply several limitations as outlined in section 3.4, and altogether the current evidence cannot be considered authoritative.

3.3. *Sports and PCa*

Several epidemiology studies and CCSs have been published on the topic of exercise and cancer risk. There is evidence that the risk of cancerous lesions is reduced in physically active individuals and that regular PA may reduce the risk for PCa development; however, published results are partially contradictory [135,136,138]. While several studies have evaluated the impact of PA on quality of life in cancer patients after or during treatment, less data are available on the possible impact of PA on CSM. This review focuses on leisure PA, while selected studies addressing both occupational and leisure PA are included (Table 3).

Table 2 – Characteristics of studies evaluating the association between sexual activity and PCa.

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, years)	Total no. of men; prostate cancer patients	Patient category	Results and main conclusions
Cohort studies						
Impact of STIs on prostate cancer risk						
Cheng et al (2010) [93]	The California Men's Health Study; USA, 2002–2003	Cohort, association between prostatitis, STIs, and PCa incidence	2006 (NR)	68 675; 1658	any STD and each specific STD (no/yes/ missing)	No overall association between history of any STDs and PCa; inverse association of genital warts with PCA risk (RR 0.77; 95% CI: 0.60–0.99)
Wang et al (2016) [95]	Taiwan National Health Insurance Research Database; Taiwan, 2000–2010	Cohort, incidence of PCa in patients with gonorrhea	2010 (10)	1775; 11	History of gonorrhea (yes/no)	Significant association of gonorrhea with PCa risk (adjusted HR 5.66, 95% CI: 1.36–23.52)
Vázquez-Salas et al (2016) [96]	Six public hospitals in Mexico City; Mexico, 2011–2014	Cohort, face-to-face interview, association between history of STI and PCa risk, incidence	2011 (17.3)	1207; 402	Gonorrhea infection status (with/ without)	• Association of history of STI with PCa risk (OR 2.67; 95% CI: 1.91–3.73) • Association of gonorrhea with PCa risk (OR 3.04; 95% CI: 1.99–4.64)
Impact of ejaculatory frequency on prostate cancer risk						
Rider et al (2016) [91]	Health Professionals Follow-up Study; USA, 1992–2010	Cohort, association between EF and PCa incidence	2010 (NR)	31 925; 3839	EF/mo at ages 20–29 and 40–49 yr (1–3, 4–7, 8–12, 13–20, and >20)	Decreased risk of low-grade PCa in patients with EF ≥21/ mo at ages 20–29 and 40–49 yr
Case-control studies						
Impact of number of sexual partners on prostate cancer risk						
Spence et al (2014) [90]	Prostate Cancer & Environment Study (PROtEuS); Canada, 2005–2009	CCS, face-to-face interview; association between number and gender of sexual partners, STIs, and PCa risk; incidence	2014; single assessment, no FU	1590 PCa patients; 1618 controls	-No. of sexual partners (female and/or male); (1/2–3/4–7/8–20/≥21) -Self-identified sexual orientation (heterosexual/homosexual/bisexual) -Ever had male sexual partner (ever/ never) -Ever infected with any STIs (no/yes)	• Association of >20 female sexual partners and a reduced risk of PCa overall (OR 0.72, 95% CI: 0.56–0.94) and less aggressive PCa (OR 0.68, 95% CI: 0.52–0.91). Results were unchanged when adjusted for the number of male partners • Homosexual or bisexual men with slightly enhanced PCa risk (data not shown), similar results for cancer aggressiveness • No association between specific STI and any STI with overall PCa risk or cancer aggressiveness
Impact of STIs on prostate cancer risk						
Singh et al (2015) [97]	India, NR	CCS, frequency of HPV infection in PCa (PCR confirmation in prostate biopsies)	NR, single assessment, no FU	95 PCa patients; 55 controls	HPV status (positive/negative)	Highly significant correlation between HPV detection and PCa stage (41% of HPV infection in prostate tumor biopsies and 20% in BPH; $p < 0.0004$)
May et al (2008) [98]	Germany, 2008	CCS, HPV detection by PCR and DNA sequencing in prostate biopsies and association with PCa	2008, single assessment, no FU	50 PCa patients, 163 controls		• 145 patients (68.1%) with HPV DNA; 137 patients (64%) with high-risk HPV (18% HPV 16/18) • No significant correlation between HPV and PCa ($n = 50$; OR 1.45; 95% CI: 0.71–0.91)
Impact of ejaculatory frequency on prostate cancer risk						

Table 2 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, years)	Total no. of men; prostate cancer patients	Patient category	Results and main conclusions
Papa et al (2017) [92]	Victoria, Australia, following identification through the Victorian Cancer Registry; 2010–2014	CCS, self-reported questionnaires; relationship between EF at 20–50 yr and subsequent aggressive PCa	2017; single assessment, no FU	1236 high-risk PCa patients; 905 controls	-No. of ejaculations: $<$7 per week $>$7–$\leq$14 per week $>$14 per week	Decreased risk of high-risk PCa considering ORs per five-unit increase in EF/wk (OR 0.83, 95% CI: 0.72–0.96)
Impact of vasectomy on prostate cancer risk						
Siddiqui et al (2014) [100]	USA	Cohort (Health Professionals Follow-Up Study)		49 405 men; 6023 PCa cases, 811 PCa deaths	Vasectomy yes vs no	• PCa risk: RR 1.10; 95% CI: 1.04–1.17 • HGPCA: RR 1.22; 95% CI: 1.03–1.45 • PCa death or distant metastasis: RR 1.19; 95% CI: 1.00–1.43 • Association with lethal PCa among men receiving regular PSA screening: RR 1.56; 95% CI: 1.03–2.36 No association with low-grade or localized disease
Nayan et al (2016) [101]	Ontario, Canada	Cohort study (healthcare databases); association between vasectomy and PCa risk	2012 (10.9)	326 607 men (20–65 yr) after vasectomy matched 1:1 on age, year of cohort entry, comorbidity, geographical region to men without vasectomy; 3462 incident PCa cases	Vasectomy yes vs no	PCa risk: • 1843 incident PCa cases (53.2%) in vasectomy group and 1619 (46.8%) in nonvasectomy group • Unadjusted analysis: vasectomy was associated with a slightly increased risk of incident PCa (HR 1.13, 95% CI: 1.05–1.20) • Results after adjustment for measures of health-seeking behavior: HR 1.02, 95% CI: 0.95–1.09 Risk of HGPCA: adjusted OR: 1.05, 95%CI: 0.67–1.66 Risk of advanced PCa: adjusted OR: 1.04, 95% CI: 0.81–1.34 Mortality: adjusted HR: 1.06, 95% CI: 0.60–1.85
Jacobs et al (2016) [102]	USA	Cohort (cancer prevention study); association with PCa risk and PCa mortality	Cohort 1: 1982–2012 (NR) Cohort 2: 1992–2011 (NR)	Cohort 1: 363 726 men (7451 PCa-related deaths) Cohort 2: 66 542 men (9133 PCa cases)	Vasectomy yes vs no	• PCa mortality: HR 1.01; 95% CI: 0.93–1.10 • PCa risk: HR 1.02; 95% CI: 0.96–1.08 • HGPCA: HR 0.91; 95% CI: 0.78–1.07
Shoag et al (2017) [103]	USA	Randomized screening trial (Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial)	Overall 13-yr FU (NR)		Vasectomy yes vs no	PCa risk: • Men in usual care arm: adjusted HR: 1.11; 95% CI: 1.03–1.20; $p = 0.008$ • Men in screening arm: no association between vasectomy and PCa diagnosis • Men with vasectomy at an older age in the usual care arm had an increased risk of PCa, but those not in the screening arm were at increased risk of PCa

Table 2 (*Continued*)

Study	Study name/ description; country/region, assessment date/ recruitment period	Study design, outcome parameters	Last FU (mean or median FU, years)	Total no. of men; prostate cancer patients	Patient category	Results and main conclusions
Smith et al (2017) [104]	Europe	European Prospective Investigation Into Cancer and Nutrition (EPIC) study	NR (15.4)	84 753 men (15% with vasectomy); 4377 PCa cases	Vasectomy yes vs no	• PCa risk: HR 1.05; 95% CI, 0.96–1.15; no evidence for heterogeneity observed by stage of disease or years since vasectomy • Association with tumor grade: $p = 0.02$ • Risk of low–intermediate-grade PCa: HR 1.14; 95% CI: 1.01–1.29 • Risk of HGPCA: HR 0.83; 95% CI: 0.64–1.07 • PCa-related death: HR 0.88; 95% CI: 0.68–1.12
Data from systematic review and meta-analysis						
Caini et al (2014) [94]	MA of 47 studies; 34 CCS, 10 nested CCS, and 3 cohort studies published between 1971 and 2011	MA, association between history of STI and PCa incidence	NR	17 679 PC patients; 133 667 controls	any STI and specific STIs (no/yes)	• Association of any STI history with PCa risk (SRR 1.49, 95% CI 1.19–1.92) • Association of gonorrhea with PCa risk (SRR 1.20, 95% CI 1.05–1.37); no other specific STI significantly associated with PCa
Rosser et al (2016) [99]	Systematic review of 30 studies published between 2000 and 2015	Systematic review, summarizing literature on PCa in GBM, including its epidemiology, clinical studies, and anecdotal reports	NR	NR	Sexual orientation (GBM)	GBM less screened for PCa than heterosexual men, similarly often diagnosed with PCa, but poorer sexual function and quality-of-life outcomes
Bhindi et al (2017) [105]	Systematic review and MA of cohort, case-control and cross-sectional studies	MA on 16 cohort studies, 33 CCS, 4 cross-sectional studies; association between vasectomy and diagnosis of PCa, with high-grade, advanced, and fatal PCa	NR	2 563 519 participants (cohort studies); 44 536 (CCS); 12 098 221 (cross-sectional studies)	Vasectomy yes vs no	PCa risk (based on studies with low risk of bias): • Weak association between vasectomy and PCa based on 7 cohort studies: adjusted RR: 1.05; 95% CI: 1.02–1.09; $p < 0.001$; $I^2 = 9\%$ • Similar but insignificant association based on 6 CCSs: adjusted RR: 1.06; 95% CI: 0.88–1.29; $p = 0.54$; $I^2 = 37\%$ • Effect estimates were insignificant when studies with a moderate to high risk of bias were included Risk of HGPCA (6 studies; adjusted RR: 1.03; 95% CI: 0.89–1.21; $p = 0.67$; $I^2 = 55\%$) Risk of advanced PCa (6 studies; adjusted RR: 1.08; 95% CI: 0.98–1.20; $p = 0.11$; $I^2 = 18\%$) Risk of fatal PCa (5 studies; adjusted RR: 1.02; 95% CI: 0.92–1.14; $p = 0.68$; $I^2 = 26\%$) were not significant (all cohort studies). Overall: 0.6% (95% CI: 0.3–1.2%) absolute increase in lifetime PCA risk

CI = confidence interval; CCS = case-control study; EF = ejaculation frequency; FU = follow-up; GBM = gay, bisexual and other men who have sex with men; HGPCA = high-grade prostate cancer; HPV = human papilloma virus; HR = hazard ratio; MA = meta-analysis; NR = not reported; OR = odds ratio; PCa = prostate cancer; PCR = polymerase chain reaction; RR = risk ratio; SRR = residual sum of squares; STD = sexually transmitted disease; STI = sexually transmitted infection.

Table 3 – Impact of sports and exercise on prostate cancer risk and treatment outcome/mortality/progression.

Study	Study design, outcome parameters	Country/region; FU information	Total no. of men; PCa patients; controls	PA categories	Results and main findings
Cohort studies					
No impact on PCa risk and/or outcome					
Platz et al (2003) [106]	Cohort; incidence	USA; 14 yr overall FU	46 786 health professionals; 2896	Vigorous leisure activity <3 vs >3 MET-h/wk	Incidence (multivariate analysis adjusted for age, family history, BMI, DM, smoking, diet): No significant relationship to PCa
Zeegers et al (2005) [107]	Cohort; incidence	The Netherlands; 9.3 yr overall FU	58 279; 1386	Cycling/walking (min/d)	Incidence (multivariate analysis adjusted for age, alcohol consumption, BMI, energy intake, family history, gardening, sport involvement; ref: <10 min/d): Cycling/walking >60 min/d: RR 0.85 (95% CI: 0.69–1.05)
Crespo et al (2008) [108]	Cohort; CSM	Puerto Rico; last FU 2002	9824 overall	Framingham index (quartiles)	CSM (multivariate analysis adjusted for age, education, urban residence, smoking, BMI): No independent association between PA and PCa mortality
Johnsen et al (2009) [109]	Cohort; incidence	USA; 8.5 yr overall FU	127 923; 2458	Quartiles of leisure activity (<25 to >71 MET-h/wk)	Incidence (multivariate analysis adjusted for occupational activity, height, weight, marital status, education; ref: lowest quartile): Leisure activity unrelated to incident PCa
Parent et al (2011) [110]	Cohort; incidence	Canada; 14 yr overall FU	3730; 449	Involvement in sports and outdoor activities—never vs not often vs often	Incidence (multivariate analysis adjusted for age, SES, education, ethnicity, smoking, BMI): No independent effect on PCa risk
Hrafnkelsdóttir et al (2015) [111]	Cohort; incidence	Iceland; overall 24 yr FU	8221; 1052	Regular PA from age of 20 yr vs sedentary	Incidence (multivariate analysis adjusted for age, height, BMI, DM, family history, education, medical checkups; ref: sedentary): Regular PA: HR 0.93 (95% CI: 0.83–1.07) Regular PA (incidence of advanced tumors): HR 0.82 (95% CI: 0.63–1.06)
Grotta et al (2015) [112]	Cohort; incidence	Sweden; 13 yr overall FU	13 109	Low vs high leisure activity	Incidence (multivariate analysis adjusted for age, education, smoking, BMI, alcohol consumption, DM; ref: low leisure activity): High leisure activity: OR 0.93 (95% CI: 0.76–1.14)
Positive or adverse impact on PCa incidence					
Giovannucci et al (2005) [113]	Cohort; incidence, incidence of advanced PCa	USA; 14 yr overall FU	47 620 health professionals; 2892	Vigorous PA, 0 vs >29 MET-h/wk	Incidence (multivariate analysis adjusted for age, BMI, smoking, height, family history, DM, race, energy intake, diet; ref: nonvigorous activity; ref: no PA): Vigorous PA (PCa overall): no independent impact Men <65 yr (incidence of advanced PCa): OR 0.33 (0.17–0.62)
Patel et al (2005) [114]	Cohort; incidence	USA; 9 yr overall FU	72 174; 5503	MET-h/wk (<0.7–35) at age 40 yr and in 1992	Incidence (multivariate analysis adjusted for age, ethnicity, BMI, weight change, energy intake, diet and vitamin use, DM, family and medical history; ref: lowest category): Highest category: no significant effect on overall incidence Highest category: reduced risk for aggressive tumors: RR 0.69 (95% CI: 0.52–0.92)
Littman et al (2006) [115]	Cohort, questionnaire; incidence	USA; questionnaire assessment 2000–2002	34 757; 583	MET-h/wk Walking pace Stair climbing High-intensity activity Activity at earlier ages	Incidence (multivariate analysis adjusted for family history, BMI, income): No association with PCa risk in entire cohort ≥10.5 MET-h/wk (median level) in normal-weight patients (ref: no activity): HR 0.69 (95% CI 0.46-1.0) Enhanced activity in men ≥65 yr at diagnosis: HR 0.75, 95% CI 0.55–1.0
Nilsen et al (2006) [116]	Cohort; incidence	Norway; 7 yr overall FU	29 110; 957	Low vs high activity score based on frequency, intensity, activity duration	Incidence (multivariate analysis adjusted for age, marital status, education, BMI, smoking, alcohol consumption; ref. low score): High activity score: No significant impact on overall PCa incidence (RR 0.86) Significant impact on incidence of advanced cancer: RR 0.64 (95% CI: 0.43–0.95); $p = 0.02$
Darlington et al (2007) [117]	Cohort; telephone questionnaire; incidence	Canada; enrollment 1995–1998	752 PCa patients, telephone listing controls	Strenuous activity at mid-teens, early 30s, early 50 s (yes/no)	Incidence (multivariate analysis adjusted for age, education, BMI, family history, occupation): Strenuous activity mid-teens: OR 1.0 (95% CI: 0.8–1.2) Strenuous activity early 30s: OR 0.9 (95% CI: 0.7–1.0) Strenuous activity early 50s: OR 0.8 (95% CI: 0.6–0.9)

Table 3 (*Continued*)

Study	Study design, outcome parameters	Country/region; FU information	Total no. of men; PCa patients; controls	PA categories	Results and main findings
Moore et al (2008) [118]	Cohort; incidence	USA; 8.2 yr overall FU	293 902; 17 872	Exercise at baseline and in adolescence: never/rarely to >5 times/wk	Incidence (multivariate analysis adjusted for age, marital status, education, smoking, medical history, BMI, waist circumference, family history, diet, supplements): Frequent activity during adolescence with significant positive impact on PCa risk ($p = 0.03$) Exercise habits at baseline: RR 0.97 (0.91–1.03)
Moore et al (2009) [119]	Cohort, questionnaire; National Institutes of Health-AARP Diet and Health Study; incidence	USA; 7 yr overall FU	160 006 white men; 3671 black men; 9624 PCa (white men), 371 PCa (black men)	Time spent on PA/wk (categorized by intensity (moderate, vigorous, light, total), during ages 15–18, 19–29, and 35–39 yr, during past 10 yr	Incidence—white men: • No positive association of PA with PCa regardless of age period or activity intensity • Frequency of activity in the past 10 yr prior to PCa diagnosis adjusted for different MET categories (ref: ≤11.5 MET-h/wk): 11.6–26.5: RR 1.05 (95% CI: 0.99–1.12); 26.6–41.5: RR 1.13 (95% CI: 1.05–1.21); 41.6–51.5: RR 1.10 (95% CI: 1.03–1.17); ≥51.5: RR 1.07 (95% CI: 1.00–1.14); $p = 0.02$ Incidence—black men: • ≥4 h moderate/vigorous-intensity PA (ref: infrequent activity) during ages 19–29 yr: RR 0.65; 95% CI: 0.43–0.99; $p = 0.01$ • MET-h at age 19–29 yr (ref: ≤11.5): 11.6–26.5: RR 0.93 (95% CI: 0.66–1.319; 26.6–41.5: RR 0.81 (0.57–1.16); 41.6–51.5: RR 0.72 (95% CI: 0.51–1.02); ≥51.6: RR 0.75 (95% CI: 0.54–1.05); $p = 0.045$ • Frequency of activity (ref: infrequent activity): Frequency of activity at age 19–29 yr: RR 0.61 (95% CI: 0.40–0.95)
Orsini et al (2009) [120]	Cohort; incidence	USA; 8 yr overall FU	45 887; 2735	Walking or cycling, 5 categories (hardly ever to >60 min/d)	Incidence (multivariate analysis adjusted for occupational activity, age, smoking, alcohol consumption, education, diet, energy intake, waist/hip ratio, DM; per category): RR 0.86 (95% CI: 0.76–0.98); $p = 0.028$ Effects greater for advanced (RR 0.74) and fatal cancers (RR 0.72)
Richman et al (2011) [121]	Cohort; substudy of CaPSURE study (questionnaire study 2004/2005); risk of PCa progression and mortality	USA; enrollment 1995–2004/2005	2134 PCa patients; 1455 men diagnosed with localized PCa	Examination of vigorous PA, nonvigorous activity, walking duration, walking pace after PCa diagnosis	Briskly walking ≥3 h/wk: 57% reduced progression rate (ref: <3 h/wk): HR 0.43 (95% CI: 0.21–0.91; $p = 0.03$) Walking pace: associated with decreased progression risk independent of duration (ref: easy pace: HR 0.52; 95% CI: 0.29–0.91; $p = 0.01$
Bonn et al (2015) [122]	Cohort; OS, CSM	Last FU 2012	4623 PCa patients	Postdiagnosis recreational MET-h/d, time spent walking/bicycling, performing household work, or exercising	OM (ref: less active men within each activity type): Patients ≥5 recreational MET-h/d: HR 0.63; 95% CI: 0.52–0.77 Walking/bicycling ≥20 min/d: HR 0.70; 95% CI: 0.57–0.86 Household work ≥1 h/d: HR 0.71; 95% CI: 0.59–0.86 Exercising ≥1 h/wk: HR 0.74; 95% CI: 0.61–0.90 CSM (ref: less active men within each activity type): Walking/bicycling ≥20 min/d: HR 0.61; 95% CI: 0.43–0.87 Exercising ≥1 h/wk: HR 0.68; 95% CI: 0.48–0.94
Kenfield et al (2015) [123]	Cohort (Health Professionals Follow-up Study, 1986–2010; Physicianś Health Study followed from 1982 to 2010	USA; 15 yr overall FU (1996–2010	Development of lifestyle score on 42 701 men (HPFS); application of score in 20 342 men (PHS); 576 lethal PCa events (HFPS); 337 lethal PCa events in PHS	Vigorous PA Low versus high	Lethal PCa (multivariate analysis adjusted for smoking status, diet, BMI; low PA): High PA: HR 0.64 (95% CI: 0.50–0.82) High PA: HR 0.80 (95% CI: 0.64–1.00; based on exposure update until date of diagnosis of PCa)
Case-control studies					
No impact on PCa incidence					
Sanderson et al (2004) [124]	CCS; cohort (Medicare beneficiary); incidence	USA; assessment 2000–2002	416 PCa patients; 429 controls	Tertiles of strenuous and of moderate PA (h/wk)	Incidence (multivariate analysis adjusted for age, geographic region, family history): no relationship to PCa in either AA or Caucasian men

Table 3 (*Continued*)

Study	Study design, outcome parameters	Country/region; FU information	Total no. of men; PCa patients; controls	PA categories	Results and main findings
Pierotti et al (2005) [125]	CCS; incidence	Italy; 12 yr overall FU (1991–2002)	1294 PCa patients; 1451 controls	3-Level categorization of PA at ages 12, 15–19, 30–39, and 50–59 yr	Incidence (multivariate analysis adjusted for age, test center, education, SES, BMI, total energy intake, smoking, alcohol consumption, family history): No effect on risk of PCa at any age
Strom et al (2008) [126]	CCS; incidence	USA; no specific FU information	176 PCa patients (Mexican American men); 176 controls	Leisure activity (<1/wk vs >1/week)	Incidence (multivariate analysis adjusted for age, education, screening, occupational activity; ref: <1/wk): >1/wk: no independent impact on PCa risk
Positive or adverse impact on PCa incidence and/or outcome					
Friedenreich et al (2004) [127]	Population-based CCS; incidence	Canada; 1997–2000	988 PCa patients (stage ≥T2); 1063 population controls	MET-h/wk; intensity of activity (ie, low, <3; moderate, 3–6; and vigorous, >6 metabolic equivalents)	Incidence (multivariate analysis adjusted for age, region, education, BMI, waist/hip ratio, energy intake, alcohol consumption, family and medical history; ref: <115 MET-h/wk): Total lifetime PA ≥203 MET-h/wk: OR 0.87, 95% CI: 0.65–1.17 Vigorous activity (categories low vs moderate vs vigorous): OR 0.70, 95% CI: 0.54–0.92 Type of activity (comparing lowest and highest intensity): • Occupational PA (OR 0.90, 95% CI: 0.66–1.22) • Recreational PA (OR 0.80, 95% CI: 0.61–1.05) • Household PA (OR 1.36, 95% CI: 1.05–1.76)
Jian et al (2005) [128]	CCS; incidence	China; no specific FU information available	130 PCa patients, 274 controls	Reported MET hours of moderate and total activity categories	Incidence (multivariate analysis adjusted for age, area of residence, education, income, marital status, number of children, years in work force, family history, BMI, energy intake; ref: moderate activity <40 MET): <80: OR 0.47 (95% CI: 0.22–1.02) <120: OR 0.46 (95% CI: 0.21–0.99) >120: OR 0.20 (95% CI: 0.07–0.62); overall $p = 0.015$ Total activity (ref: total activity <44 MET): <90: OR 0.42 (95% CI: 0.18–0.99) <135: OR 0.36 (95% CI: 0.16–0.86) >135: OR 0.39 (95% CI 0.15–0.99)
Chen et al (2005) [129]	CCS; incidence	Taiwan; conduction between 1996 and 1998	237 PCa patients, 481 controls	4-Level categorization of PA; primarily a dietary study	Incidence (multivariate analysis adjusted for age, BMI, income, marriage, dietary variables; ref: moderate exercise): High exercise: OR 1.84 (95% CI: 1.01–3.34)
Wiklund et al (2008) [130]	CCS, cohort; incidence	Sweden; no specific FU information available	1449 PCa patients; 1118 population controls	MET-h/d lifetime recreational activity, <7.4 to >13.5	Incidence (multivariate analysis adjusted for age, region, education, BMI, alcohol consumption, family history, DM, energy intake; ref: <7.4): <10.2: OR 1.33 (95% CI: 1.00–1.78) <13.5: OR 1.43 (95% CI: 1.07–1.91) >13.5: OR 1.56 (95% CI: 1.16–2.10); overall $p = 0.006$
Hvid et al (2016) [131]	CCS/RCT; PSADT; changes in aerobic fitness, body composition, insulin sensitivity, biomarkers	Denmark; no specific FU information available	25 PCa patients with BCR after RP or managed by AS; 19 PCa patients completed study	Randomization to either 24 mo (3 times/wk) of home-based endurance training or usual care Measurement: aerobic fitness, body composition, insulin sensitivity, biomarkers at 0, 6, and 24 mo of intervention, PSADT (monthly measurements)	PSADT: increased training group from 28 to 76 mo ($p < 0.05$) during first 6 mo; correlated with changes in VO2max ($p < 0.01$, $r(2) = 0.41$) Body composition: training group lost 3.6 ± 1.0 kg ($p < 0.05$) fat mass, but change in body composition not associated with PSADT Biomarkers: significant improvements in plasma triglycerides, adiponectin, IGF-1, IGFBP-1, fasting glucose levels in training group; no change in insulin sensitivity, testosterone, cholesterols, fasting insulin, plasma TNF-alpha, IL-6, leptin in intervention group, but not in control group
Rief et al (2016) [132]	CCS, RCT; bone survival, local bone progression, OS, PFS	Germany; conduction 2011–2013; median FU 10 mo (range 2–35)	60 cancer patients receiving RT for spinal bone metastases (median total dose 30 Gy); 5 and 9 PCa patients in groups A and B	Two groups: resistance training (group A); passive physical therapy (group B)	Bone survival (ref: group B): significant difference in bone survival ($p = 0.303$) OS (ref: group B): no difference ($p = 0.688$) PFS (ref: group B): no difference ($p = 0.295$) Local bone progression: 16.7% in group B, 0% in group A over the course ($p = 0.019$)

Table 3 (***Continued***)

Study	Study design, outcome parameters	Country/region; FU information	Total no. of men; PCa patients; controls	PA categories	Results and main findings
Friedenreich et al (2016) [133]	Prospective CCS; CSM	Canada; PCa diagnosis between 1997 and 2000; FU until 2014	830 stage II–IV PCa patients	Prediagnosis lifetime activity self-reported at diagnosis; postdiagnosis activity self-reported up to three times during FU	Postdiagnosis total PA (>119 vs ≤42 MET-h/wk/yr) was associated with a significantly lower ACM (HR 0.58; 95% CI: 0.42–0.79; $p < 0.01$) Postdiagnosis recreational PA (>26 vs ≤4 MET-h/wk/yr) was associated with a significantly lower CSM (HR 0.56; 95% CI: 0.35–0.90; $p = 0.01$) Sustained recreational activity before and after diagnosis (>18–20 vs <7–8 MET-h/wk/yr) was associated with a lower risk of ACM (HR 0.66; 95% CI: 0.49–0.88)
Systematic reviews/meta-analyses					
Oliveira and Lee (1997) [134]		17 epidemiological investigations of exercise and prevention of PCa		Exercise (various definitions and categories)	9/17 studies: significant benefit of active lifestyle with reduced risk for PCa 5/17: no impact 3/17: adverse effects from an active lifestyle
Friedenreich and Thune (2001) [135]		24 studies; incidence		Exercise (various definitions and categories)	14/24 studies: suggestion of an inverse trend between PA and PCa risk 6/24: no effect 4/24: increased risk of PCa in most active men
Torti and Matheson (2004) [136]		Studies included published between 1976 and 2002; 13 cohort studies (1989–2001), 11 CCS (1988–2002), 27 studies overall (1976–2002); USA and international; incidence		Exercise (various definitions and categories)	9/13 cohort studies: Positive association between exercise and decreased prostate cancer risk 5/11 case-control studies: Association between decreased risk of PCa and high activity levels All studies: 16/27: reduced PCa risk in men who were most active 9/16: statistically significant reduction of PCa risk with an average risk reduction between 10% and 30%
Liu et al (2011) [137]		19 cohort studies; 24 case-control studies; incidence	88 294 cases	Exercise (various definitions and categories)	Combined data: Total PA was significantly associated with a decreased risk of PCa: RR 0.90; 95% CI: 0.84–0.95 Pooled RR for occupational PA: 0.81 (95% CI: 0.73–0.91) Pooled RR for recreational PA: 0.95 (95% CI, 0.89–1.00) Total PA was associated with a significant PCa risk reduction for individuals between 20 and 45 yr (RR 0.93; 95% CI: 0.89–0.97) and between 45 and 65 yr of age (RR 0.91; 95% CI: 0.86–0.97), but not for individuals <20 or >65 yr of age

ACM = all-cause mortality; AS = active surveillance; BCR = biochemical recurrence; BMI = body mass index; CCS = case-control study; CI = confidence interval; CSM = cancer-specific mortality; FU = follow-up; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; IL–6 = interleukin 6; MET = metabolic equivalent; OM = overall mortality; OR = odds ratio; OS = overall survival; PA = physical activity; PCa = prostate cancer; PFS = progression-free survival; PHS = Physicians' Health Study; PSADT = prostate-specific antigen doubling time; RCT = randomized controlled trial; ref = reference; RP = radical prostatectomy; RR = risk ratio; RT = radiotherapy; SES = socioeconomic status; TNF-alpha = tumor necrosis factor alpha.

3.3.1. Impact of sports and exercise on PCa incidence

14 cohort studies were identified analyzing the impact of PA on PCa risk [106,107,109–120]; additional four cohort studies evaluated the impact on CSM and fatal PCa [118,121,122,123].

Six cohort studies did not confirm a significant impact of leisure activity on PCa risk, while in some an insignificant trend toward a risk reduction was observed [106,107,109–112]. Platz et al [106] did not find a significant impact of exercise on PCa risk in the entire cohort, but commented on an increased risk in individuals with high-energy intake, suggesting the possibility that excess energy intake may impact tumor growth rather than fat formation. Adjusted for several covariates, further eight studies showed a significant benefit from PA and a reduced PCa incidence [113–120]. Nilsen et al [116] reported a significant reduction of advanced tumors (RR 0.64, 95% CI: 0.43–0.95; $p = 0.02$); also, Orsini et al [120] found greater benefits for advanced (RR 0.74) and fatal cancers (RR 0.72). Giovannucci et al [113] detected a reduced incidence of advanced PCa in men younger than 65 yr (OR 0.33; 95% CI: 0.17–0.62), while no significant impact was identified in the entire cohort.

Besides the abovementioned cohort studies, 10 relevant CCSs were identified, of which three did not find a significant impact on PCa risk [124–126], while seven studies identified leisure activity as an independent predictor for PCa risk or treatment outcomes [127–133]. Whereas total lifetime PA did not have an independent impact in a study by Friedenreich et al [133], vigorous PA significantly reduced the incidence of PCa (OR 0.70, 95% CI: 0.54–0.92). When split by the type of activity, occupational and recreational PA resulted in a risk reduction, while household PA was associated with an enhanced risk (OR 1.36, 95% CI: 1.05–1.76) [133]. Whether this result is impacted by a bias, a limited number of men exposed to household work, or other confounding factors remains unclear. In a Chinese cohort, moderate activity was associated with a reduction of PCa risk, further reduced with the amount of moderate PA (>120 metabolic equivalent of task hours [MET-h]: OR 0.20; 95% CI: 0.07–0.62; $p = 0.015$) and total activity regardless of intensity (>135 MET-h: OR 0.39; 95% CI 0.15–0.99) [128]. In contrast, Chen et al [129] reported an increased risk for PCa in men with high-level exercise compared with those with moderate levels (OR 1.84; 95% CI: 1.01–3.34). Wiklund et al [130] detected a negative impact of high-intensity training; compared with <7.4 MET-h/d lifetime recreational activity, for men with >13.5 MET-h/d lifetime PA an OR of 1.56 (95% CI: 1.16–2.10; $p = 0.006$) was found.

An MA conducted by Oliveira and Lee [134] in 1997 identified 17 investigations of exercise and prevention of PCa, nine pointing to a significant benefit of an active lifestyle, while three studies showed an adverse effect and five studies no impact. A systematic review of 24 studies by Friedenreich and Thune [135] published in 2001 found some suggestion of an inverse trend between PA and PCa risk in 14 studies, while six reports did not show an effect and four studies showed an increased risk in most active men. Another systematic review found a positive association between exercise and decreased PCa risk in nine of 13 cohort studies, and an association between decreased risk and high activity levels in five of 11 CCSs with an average risk reduction between 10% and 30% [136]. Liu et al [137] reported that total PA was significantly associated with decreased PCa risk (RR 0.90; 95% CI: 0.84–0.95), predominantly for individuals being active between 20 and 45 yr (RR 0.93; 95% CI: 0.89–0.97) and 45 and 65 yr of age (RR 0.91; 95% CI: 0.86–0.97), but not for individuals <20 or >65 yr of age.

3.3.2. *Impact of sports and exercise on treatment outcome, progression, and mortality*

At least seven studies have been looking at the value of PA in preventing disease recurrence and reducing CSM after primary treatment [108,121–123,131–133]. Kenfield et al [123] developed a lifestyle score in more than 42 000 men and applied this score in another cohort of 23 324 men. Contrasting to the results of Crespo et al [108], who found a comparable CSM regardless of the amount of PA, Kenfield et al [123] reported that men with high PA had a reduced risk for fatal PCa (HR 0.64; 95% CI: 0.50–0.82), a relationship still provable when the exposure was updated until the date of PCa diagnosis (HR 0.80; 95% CI: 0.64–1.00). Hvid et al [131] and Rief et al [132] analyzed the impact of leisure activity on mortality and treatment outcomes in two European patient groups. Hvid et al [131] randomized 25 PCa patients with BCR after RP or managed by active surveillance to either 24-mo endurance training or usual care. Patients in the training group had a significant positive impact on most parameters measured. An increasing PSA doubling time (PSA-DT; from 28 to 76 mo over 6 mo) was correlated with changes in VO2max ($p < 0.01$). Besides further significant improvements in biomarkers (eg, IGF-1, IGFBP-1), the training group lost 3.6 ± 1.0 kg ($p < 0.05$) fat mass, while this change was not associated with PSA-DT [131]. Rief et al [132] randomized 60 cancer patients (including 14 PCa patients) receiving radiotherapy for spinal bone metastases to resistance training or passive physical therapy, and analyzed bone survival. While they did not find significant differences in bone survival ($p = 0.303$), overall survival ($p = 0.688$), and progression-free survival ($p = 0.295$), local bone progression was significantly reduced in the resistance training group (0% vs 16.7%; $p = 0.019$) [132]. Friedenreich et al [133] conducted a prospective CCS in 840 PCa patients, and analyzed the impact of pre- and postdiagnosis activity on OM and CSM. Postdiagnosis total PA (>119 vs ≤42 MET-h/wk/yr) was associated with significantly lower OM (HR 0.58; 95% CI: 0.42–0.79; $p < 0.01$) and postdiagnosis recreational PA (>26 vs ≤4 MET-h/wk/yr) was associated with significantly reduced CSM (HR 0.56; 95% CI: 0.35–0.90; $p = 0.01$). Finally, sustained recreational activity before and after diagnosis (>18–20 vs <7–8 MET-h/wk/yr) resulted in a lower risk of OM (HR 0.66; 95% CI: 0.49–0.88) [133]. Richman et al [121] analyzed the impact of PA on PCa progression in 1455 US men with primarily localized disease participating in the CaPSURE study and found that briskly walking ≥3 h/wk resulted in a 57% reduced progression rate (HR 0.43; 95% CI: 0.21–0.91; $p = 0.03$). In a cohort of 4623 PCa patients, Bonn et al [122] found significantly reduced OM and CSM rates in patients with higher levels of PA (HRs 0.61–0.74). These findings support the inference that PA is a useful factor in the prevention of PCa progression and improvement of outcome after primary tumor treatment.

3.3.3. *Optimal pattern and age of PA*

Numbers of articles have provided conflicting and inconsistent evidence on the optimal age and pattern in terms of frequency, intensity, and overall volume of preventive PA.

While some studies have suggested the highest benefit for men being active during adolescence and puberty [118,140–142] or over the age of 65 yr [116], the MA conducted by Liu et al [137] indicated a benefit in individuals between 20–45 and 45–65 yr of age, but not for individuals <20 or >65 yr of age. Darlington et al [117] observed a lower risk of PCa in those who had undertaken strenuous PA in their 50 s only (OR 0.8; 95% CI: 0.6–0.9) and saw no significant benefit for activity taken at earlier ages; Giovannucci et al [113] reported a significantly reduced incidence of advanced PCa in men younger than 65 yr only (OR 0.33; 95% CI: 0.17–0.62). Other authors, however, did not observe differences in different age categories [143].

In several studies, assessment of dose-response relationships remained challenging mainly due to semantic rather than linear categorizations of PA intensity. Two investigations found the largest effect at the second of three PA levels [110,140], while other reports have shown a progressive risk decrease over three or four gradations [113,118,120,142,146,147] or at the highest activity level [113,114,146–148]. Jian et al [128] noted that prostate tumors were more closely related to a low volume of moderate activity (<40 vs >120 MET-h/wk) than to a low total volume of PA (<44

Table 4 – Hypotheses and possible biological mechanism whereby cigarette smoking, sexual activity, and physical activity modify carcinogenesis or tumor progression.

Smoking	
Adherence to PSA screening	• Adherence to PSA testing seems to be negatively associated with smoking, and PSA screening is more common in nonsmokers; smoking has also been linked to poorer compliance with prostate biopsy [32,64]. Rolison et al [75] observed that nonsmokers were 1.95 times more likely to be screened for PCa than smokers; furthermore, smokers were most likely just screened once and were 36% less likely to receive a second on-study biopsy ($p < 0.001$) [73,32]. Less screening and fewer biopsies might result in the detection of fewer nonaggressive PCa screen-detected cancers [32]. • Finally, screening differences might contribute to inferior outcomes, but they are unlikely to explain the enhanced PCa mortality completely. PSA screening reduces PCa death by approximately 21% [89], but differences would need to be considerable to explain the significantly increased CSM [75]. • PSA testing could possibly also be influenced by changes in PSA levels; data from a nationwide survey have shown approximately 8–12% lower PSA values in current and former smokers [74]. • Additionally, PSA tests have never been assessed for accuracy in smokers and nonsmokers.
Advanced baseline disease stages and aggressive tumor characteristics	• Several studies indicated more advanced baseline disease stages and aggressive tumor characteristics [42,74]. These differences may be related to a possibly delayed diagnosis in smokers due to lower screening rates, and an association of smoking with progression and impaired treatment outcome rather than PCa development as more aggressive cancers are promoted [32,64].
Poorer response to treatment	• Experimental studies and in vitro models have shown possible mechanisms linking smoking and PCa progression, such as increased heme-oxygenase-1 messenger RNA expression, which may play a role in tumor angiogenesis [50,64,73,78,79,95]. An effect of smoking on tumor progression through hypermethylation of genes has also been suggested [80,97]. • The presence of more aggressive cancers in smokers together with reduced tissue oxygenation might impair radiotherapy efficacy. • Smoking increases carboxyhemoglobin, which has been shown to decrease tumor oxygenation and increase radiation resistance [64].
Impact on mutations and functional polymorphisms	• Constituents of cigarette smoke such as polycyclic aromatic hydrocarbons require metabolic activation or detoxification, and subsequent DNA binding to exert carcinogenetic action. Smoking may impact mutations or functional polymorphisms in genes involved in these progresses [50,81].
Alternative mechanisms for PCa carcinogenesis	• Exposure to carcinogenic substances found in cigarettes (eg, cadmium) has been proposed as an alternative mechanism for PCa carcinogenesis. Ye et al [82] have reported that cadmium can activate the androgen receptors in human PCa cell lines in the absence of androgen and enhance androgen-mediated transcriptional activity in the prostate when applied in combination with the androgen [56].
Impact on glutathione-S-transferases	• Glutathione-S-transferases (GSTs) are involved in detoxification of tobacco-induced carcinogenesis. Loss of GST-P1 expression in human prostatic epithelium and presence of GST variants have been observed as one of the earliest events in prostate carcinogenesis [51,86]. Among men with genotype GST-P1 Ile/Ile, smoking was associated with an increased risk of PCa (OR 4.09; 95% CI: 1.25–13.35) in an exploratory CCS [51,84]. In a family-based CCS, heavy smoking increased PCa risk nearly twofold in white men with the GST-M1 null genotype (OR 1.73; 95% CI: 0.99–3.05) [66], while this risk was not observed in heavy smokers who carried the GST-M1 nondeleted allele (OR 0.95%; 95% CI, 0.53–1.71) [50,85].
p53 mutations	• Mutations in the *p53* gene, one of the most mutated tumor-suppressor genes in human neoplasms, or in cytochrome P450, which is involved in the metabolic pathways of several endogenous and exogenous compounds such as steroids, may modify PCa risk in smokers [52,85].
Induction of tumor angiogenesis	• Although not studied in the prostate, nicotine can induce angiogenesis in tissues promoting faster cancer progression [98] and inhibit immune reactions, potentially resulting in faster progression and worse prognosis [12,50,79].
Enhanced inflammation	• Smoking results in increased prostatic tissue inflammation [104]. Chronic prostatic inflammation is associated with the presence of proinflammatory cytokines, inflammatory mediators, and growth factors that may lead to uncontrolled proliferative response [13,86–88]
Changes in sex steroid pathway	• Smoking may alter testosterone secretion or inhibit aromatase, resulting in higher concentrations of free and total testosterone; higher daily numbers of cigarettes and PY are also associated with greater concentrations of estradiol [57,89]. Testosterone may exert a differentiating effect on PCa, while estrogens may promote carcinogenesis and result in higher-volume and more aggressive PCa [3,5,89].
Involvement of melanin in nicotine binding	• Melanin-containing tissue binds nicotine, which is associated with enhanced dependence and accumulation of nicotine and associated carcinogens [67]. This effect may imply a greater exposure to nicotine and tobacco-specific toxins and susceptibility to tobacco-related carcinogens, and may contribute to an enhanced PCa risk in AA men [81].
Sexual activity	
Enhanced inflammation	• STI might result in chronic inflammation, which is associated with proinflammatory cytokines, inflammatory mediators, and growth factors that may lead to uncontrolled proliferative response.
Increased ejaculation frequency	• A potential inverse association of EF with PCa risk seems to be driven mainly by low-risk disease, which could indicate that more sexually active men might undergo less screening and follow-up testing (which, however, has not been detected in studies). • In addition to the prostate stagnation hypothesis, there is the consideration that more frequent ejaculation may influence the function of peripheral-zone epithelial cells, hindering the metabolic switch from citrate secretion to citrate oxidation, which occurs early in tumorigenesis [91]. • Increased EF may reduce the development of prostatic intraluminal crystalloids, which have been associated with a higher risk of PCa [91]. • A higher EF may be linked to lowering of psychological tension and central sympathetic nervous system suppression, which could reduce stimulation of prostate epithelial cell division [91].
Sports and physical activity	
Modulation of immune responses	• Sports and exercise enhances immune surveillance mitigated by an increased number of cytotoxic T cells [139,154–156].
Reduction of oxidant stress	• PA results in a greater ability to counter oxidant stress [139,154–156].

Impact on hormonal levels	• Exercise decreases circulating levels of testosterone and IGF, thus reducing stimulants to growth and proliferation of neoplastic cells [139,152,153,157,158]. • As testosterone levels are also modulated by diet, this may contribute to differences in exercise response between populations [158,159]. Barnard et al [160] have provided experimental evidence on putative hormonal involvement. They applied serum from men undertaking an hour of aerobic exercise five times per week and from sedentary controls to lymph nodes infiltrated with PCa cells. Serum of exercise-trained men had decreased levels of IGF and increased IGF-binding protein; subsequently, tumor cell apoptosis in lymph nodes was increased [160,161].
Reduction of overweight and obesity	• Evidence suggests that the greatest protection against PCa is associated with moderate to high intensities of PA; hence, a decrease of adiposity may also be involved in potential protective mechanisms. Finally, it is difficult to untangle the respective contributions of exercise and weight decrease, but there is growing evidence of the importance of adipose tissue-derived cytokines to the microenvironment favoring tumor growth [162–164].

AA = African American; CCS = case-control study; CI = confidence interval; CSM = cancer-specific mortality; EF = ejaculation frequency; OR = odds ratio; PA = physical activity; PCa = prostate cancer; PSA = prostate-specific antigen; PY = pack years; STI = sexually transmitted infection.

vs >135 MET-h/wk), with respective ORs for more active individuals of 0.20 (0.07–0.62, $p = 0.015$) and 0.39 (0.15–0.99, $p = 0.50$). Wannamethee et al [147] observed a decreased risk with an increase in the frequency of participation in sports. In an exhaustive study of leisure behaviors, looking at MET-h/wk of PA, typical walking pace, stair climbing, amount of high-intensity activity, and activity at earlier ages, Littman et al [115] saw the highest benefit in normal-weight patients with a medium level of PA (HR 0.69; 95% CI 0.46–1.0), while active older individuals who were overweight had an increased risk of PCa.

Differential effects of PA might be observed in different ethnical groups. Moore et al [118,119] found no association of PA with the overall PCa risk in white US men, while a significantly enhanced PCa risk was shown in men active over the past 10 yr prior to PCa diagnosis. On the contrary, black men had a significant benefit from PA, especially in the subgroup of patients who were frequently active with moderate intensity at the age of 19–29 yr (RR 0.65; 95% CI: 0.43–0.99; $p = 0.01$). Consistently, a cohort study published in 1999 displayed ethnical differences: the trend towards a high risk among sedentary individuals was confined to AA men (RR 3.17; 95% CI: 0.96–10.46, $p = 0.08$), while no effect was detected in white men (RR 0.98; 95% CI: 0.64–01.49). These results could simply reflect the smaller number of AA men in the sample, but also hint at genetic and dietary differences among two ethnic groups [140].

3.4. *Possible biological mechanisms*

Hypotheses whereby cigarette smoking, sexual activity, and PA modify carcinogenesis or tumor progression comprise, for example, aspects of health-related behavior, different response to treatments, initiation of mutations, functional polymorphisms and alternative carcinogenesis pathways, changes in sex steroid pathways, impact on oxidative stress, and modification of immune responses. Table 4 summarizes the main hypotheses and likely biological mechanisms.

3.5. *Limitations*

Several limitations of this review should be considered. Studies addressing the association of smoking and PCa included a heterogeneity concerning study type, categorical assessment of smoking habits, and time period of conduction (pre-PSA versus PSA era); additionally, several studies are limited to a specific geographical region. Cumulative smoking doses and time since quitting smoking have rarely been evaluated. In most studies, CM has not been evaluated, which may result in an underestimation of the association between smoking and PCa incidence or mortality as most smoking-related deaths are more likely to happen at earlier ages compared with PCa deaths. Concerning sexual activity, there is a general lack of high-quality evidence. Most studies either are retrospective or suffer from a selection bias; longitudinal assessments are largely missing. Several limitations need to be considered for studies evaluating the impact of PA on PCa, namely, inconsistency in outcome parameters, weakness in PA assessments, and various categories of PA measurement. Further limitations include potential associations between occupation, socioeconomic status, exposure to toxins, disparate responses in subgroups, and frequencies of medical examinations and screening. Patterns of exercise could generally be ascertained by interview or personal monitoring; however, the predominant resource in most studies is self-reported questionnaires implying limited reliability and validity, and problems of commemoration, especially for an individual's behavior 10–30 yr previously, when carcinogenesis possibly started [149]. Looking at the attained level of aerobic power might provide a more objective method; nonetheless, the individual's maximal oxygen intake is heavily influenced by body fat accumulation. Additionally, patterns of PA are influenced by age, time, and opportunity for leisure activity, which are strongly linked to social class [150]. Comparisons with nonathletes are further complicated by the fact that for many types of sports, athletes are selected based on their body build, which might represent a confounding factor due to a genetically determined body composition and cancer risk [151]. Quite a substantial portion of athletes have been involved in androgenic steroid abuse, which may impact PCa development [152,153]. Established or putative risk factors for PCa such as diet, obesity, smoking, alcohol consumption, history of STI, vasectomy, and exposure to occupational toxins have been included as covariates for multivariate adjustment; nonetheless, it remains possible that their influence was not eliminated completely and other unknown confounders impacted the results. Finally, also dietary aspects that are often related to PA would need to be considered to completely address the impact on PCa risk and prognosis. Furthermore, studies evaluating variations of factors associated with metabolic syndrome (such as

Table 5 – Conclusions: impact of the modifiable risk factors smoking, sexual activity, and sports on prostate cancer risk, progression, treatment outcome, and cancer-related mortality.

Association of smoking with prostate cancer risk, tumor progression, treatment outcome, and cancer-related mortality	• There is conflicting evidence about the association of smoking with overall prostate cancer incidence. While several cohort studies have indicated reduced risks for prostate cancer diagnosis in smokers, most case-control studies show an increased risk. Potential confounders including lead-time bias due to different time points of diagnosis and different screening patterns need to be considered. • Available evidence indicates an increased risk of more advanced tumor stages and more aggressive baseline disease characteristics in smokers and former smokers. • Current epidemiological evidence suggests a robust and dose-response association between smoking and cancer-related death, which is observed in current and former smokers. Residual confounding cannot be excluded completely, but the association seems not to be related to publication bias. • There is reliable evidence that smoking is associated with adverse pathological features and a higher risk of BCR in patients undergoing RP or EBRT, which is maintained for 10 yr after smoking cessation. • Smoking status and anamnesis should be considered an important and modifiable risk factor in prostate cancer patients, and accordant advice to quit smoking should be given to patients to improve their individual prognosis. Furthermore, increased competing mortality in smokers should be considered.
Association of sexual activity with prostate cancer risk	• Results from available studies on sexual activity and prostate cancer risk imply several limitations, and overall the current evidence cannot be considered authoritative. • Further investigations are clearly necessary to establish the role of STIs in the etiology of prostate cancer and to evaluate whether the suggested associations between prostate cancer risk and sexual behavior are real or spurious. Recent studies found either no or just a weak association between vasectomy and overall prostate cancer risk, and no significant association with high-grade, advanced-stage, or fatal prostate cancer, finally rebutting a relationship between vasectomy and prostate cancer.
Association of physical activity with prostate cancer risk, tumor progression, treatment outcome, and cancer-related mortality	• Despite a considerable volume of research addressing this topic, the value of regular physical activity on prostate cancer risk is not unequivocally established. Many investigators have drawn conflicting inferences based upon small subgroups or by reporting an impact without the accordantly needed statistical power or results. • Studies have shown significant benefits arising from regular physical activity in terms of disease progression, treatment outcome, and mortality, even though this has yet to be proved conclusively. • While the focus of this article was not occupational physical activity, aspects related to occupational activity, including exposure to chemicals, and socioeconomic and dietary differences between men with sedentary versus physical work, also need to be considered. • There remains a need for large and well-designed studies with improved and objective assessment of habitual physical activity at various ages under consideration of important covariates. • Long-term interventions testing possible risk modifications by exercise programs and further exploring possible underlying mechanisms are required to answer the question why susceptibility seems to be influenced by tumor aggressiveness and individuals' age. • The majority of data suggest a favorable impact of physical activity on several health problems; besides a potential preventive impact for cancer development might be assumed. Hence, it is certainly reasonable to advocate an active lifestyle as a potentially useful measure for prostate cancer prevention.

BCR = biochemical recurrence; EBRT = external beam radiotherapy; RP = radical prostatectomy; STI = sexually transmitted infection.

overweight) by physical exercise have not been reviewed [165]. While an adjustment to diet has partially been performed in individual studies and some studies have focused on patients with metabolic syndrome, this systematic review did not specifically consider these aspects due to the overall extensiveness of the subtopics. Additionally, the review process might not have captured all relevant studies. Besides original studies MAs were also considered, possibly impacting overall interpretation of study results. Moreover, due to the nature of topics and the high heterogeneity of both study quality and design, the selection process and interpretation of study findings might have included elements of subjectivity. However, use of standardized methods for the conduction of the review process according to the latest European Association of Urology methodology and PRISMA statement recommendations and extensive revision of the study findings by several experts within the review panel might attenuate these limitations.

4. Conclusions

Owing to several confounding factors, detecting effects of modifiable lifestyle parameters on PCa development and disease-related prognosis remains challenging. Main conclusions drawn from the selected studies are outlined in Table 5.

While data concerning the impact of smoking on PCa development remain conflicting, there is increasing evidence that smoking is associated with aggressive tumor features at baseline and worse cancer-related prognosis, which seems to be maintained for 10 yr after smoking cessation. Subsequently, men should be advised by urologists to quit smoking latest at the time of PCa diagnosis to improve their individual prognosis.

Although strong evidence is available that vasectomy is not associated with PCa risk, limited convincing evidence exists for other aspects of sexual activity on PCa risk; well-conducted and longitudinal studies are necessary to evaluate whether the suggested associations between PCa risk and sexual behavior are real or spurious.

A considerable volume of research indicates an effect of regular PA on PCa risk, disease progression, and mortality, while the specific conditions under which PA might be protective against disease development are not yet defined. As majority of data suggest a favorable impact of PA on several health problems, an active lifestyle is certainly advisable as a potentially useful measure for PCa prevention.

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Study concept and design: Brookman-May, Minervini, Campi, Rodriguez-Faba.
Acquisition of data: Brookman-May, Minervini, Campi, Rodriguez-Faba, Henríquez.
Analysis and interpretation of data: Brookman-May, Minervini, Campi, Rodriguez-Faba, Henríquez.
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Appendix A. Supplementary data

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