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# Smoking and Risk of Prostate Cancer and Prostate Cancer Death: A Pooled Study

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**Abstract**

***Background:*** Prospective and detailed investigations of smoking and prostate cancer (PCa) risk and death are lacking.
***Objective:*** To investigate prediagnosis smoking habit (status, intensity, duration, and cessation) as a risk factor, on its own and combined with body mass index (BMI), for PCa incidence and death.
***Design, setting, and participants:*** We included 351 448 men with smoking information from five Swedish cohorts.
***Outcome measurements and statistical analysis:*** We used Cox regression to calculate hazard ratios (HRs) and confidence intervals (CIs) for PCa incidence ($n$ = 24 731) and death ($n$ = 4322).
***Results and limitations:*** Smoking was associated with a lower risk of any PCa (HR 0.89, 95% CI 0.86–0.92), which was most pronounced for low-risk PCa (HR 0.74, 95% CI 0.69–0.79) and was restricted to PCa cases diagnosed in the prostate-specific antigen (PSA) era. Smoking was associated with a higher risk of PCa death in the full cohort (HR 1.10, 95% CI 1.02–1.18) and in case-only analysis adjusted for clinical characteristics (HR 1.20, 95% CI 1.11–1.31), which was a consistent finding across case groups ($p$ = 0.8 for heterogeneity). Associations by smoking intensity and, to lesser degree, smoking duration and cessation, supported the associations for smoking status. Smoking in combination with obesity (BMI $\geq$30 kg/m$^2$) further decreased the risk of low-risk PCa incidence (HR 0.40, 95% CI 0.30–0.53 compared to never smokers with BMI <25 kg/m$^2$) and further increased the risk of PCa death (HR 1.49, 95% CI 1.21–1.84). A limitation of the study is that only a subgroup of men had information on smoking habit around the time of their PCa diagnosis.
***Conclusions:*** The lower PCa risk for smokers in the PSA era, particularly for low-risk PCa, can probably be attributed to low uptake of PSA testing by smokers. Poor survival for

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smokers, particularly obese smokers, requires further study to clarify the underlying causes and the preventive potential of smoking intervention for PCa death.

***Patient summary:*** Smokers have a higher risk of dying from prostate cancer, which further increases with obesity.



## 1. Introduction

Tobacco smoking is an established risk factor for many cancers [1] but its relationship to prostate cancer (PCa), the second most common cancer among men worldwide [2], remains unclear. While observational studies have reported a lower risk of any PCa for smokers [3–11], a Mendelian randomisation study found no such association [12]. Only a limited number of studies on smoking and PCa risk by cancer risk category have been published. These found a negative association with localised PCa but no association with advanced PCa [3,4,11], which may be influenced by delayed detection of PCa in smokers owing to their lower prostate-specific antigen (PSA) levels [13] and possibly lower frequency of asymptomatic PSA testing [14,15].

Smoking could promote PCa progression via biological mechanisms or poorer treatment effects in smokers [16]. Both population-based cohort studies and patient studies have suggested that smoking increases the risk of PCa progression and death [10,17-26]. However, patient studies have often been small, and analysis of cases only may cause selection bias (collider bias) if the exposure is related to disease risk [27,28]. Such bias cannot occur in population-based studies of initially cancer-free men, which, however, reflects the association not only with survival after PCa diagnosis but also with PCa risk inherent to follow-up from a cancer-free state. A parallel analysis of the full cohort and of cases only provides a fuller picture of the association of smoking with PCa death.

In this study, we investigated the association between smoking (status, intensity, duration, and cessation) and PCa risk by cancer risk category, and of PCa death in full-cohort and case-only analyses. In a previous study on body mass index (BMI) and PCa [29] we found the same direction of association as in studies of smoking and PCa, so we also examined the combined effect of smoking and BMI on risk.

## 2. Patients and methods

### 2.1. Study population

Five Swedish cohorts were combined, containing data from health examinations performed between 1974 and 2016 in the Construction Workers Cohort (Bygghälsan) [30], the Västerbotten Intervention Programme [31,32], the Northern Sweden MONICA study [31,33], the Malmö Diet and Cancer Study [34], and the Malmö Preventive Project [35]. Self-reported information on smoking included age of smoking onset and number of cigarettes smoked per day for current smokers, and information on age at smoking cessation for former smokers. Pack-years were calculated by multiplying the number of packs of cigarettes smoked per day by the smoking duration in years. More information on the cohorts is provided in the Supplementary material. The study was approved by the Ethics Committee at Lund University, Sweden (reference numbers 2016/564 and 2020-01571).

### 2.2. Follow-up

The unique personal identification number of all inhabitants in Sweden was used to follow cohort participants in national registers up to December 31, 2016. The Swedish Cancer Register [36] was used to capture diagnoses of PCa (ICD-7 code 177) and other cancers. The Swedish Cause of Death Register [37] was used to obtain information on the primary cause of death and the Total Population Register was used for information on emigration. The National Prostate Cancer Register (NPCR) of Sweden [38] was used to obtain diagnostic information on PCa cases and primary treatment. Since 1998, the NPCR has captured 99% of PCa cases recorded in the Swedish Cancer Register [36]. PCa cases were classified into five risk categories at diagnosis [38]: localised low-risk PCa (T1–2, Gleason score 2–6, and PSA <10 ng/ml), localised intermediate-risk PCa (T1–2, Gleason score 7, and/or PSA 10 to <20 ng/ml), localised high-risk PCa (T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml), regionally metastatic/locally advanced PCa (T4 and/or N1 and/or PSA 50–100 ng/ml in the absence of distant metastases [M0 or Mx]), or distant metastases (M1 and/or PSA ≥100 ng/ml). From 2000 onwards, the NPCR contains information on the main reason for PCa detection: a health check-up involving an asymptomatic PSA test or investigation of lower urinary tract symptoms (LUTS) or other symptoms [39]. We also linked individuals to the Longitudinal Integration Database for Health Insurance and Labour Market Studies for information on socioeconomic factors and country of birth, and to the Patient Register for information on inpatient care, which we used for the Charlson comorbidity index [40].

### 2.3. Statistical analysis

A flowchart for participant selection is provided in Supplementary Fig. 1. Person-years were calculated from the date of health examination until the date of PCa diagnosis, emigration, death, or, for PCa risk, until censoring because of another cancer diagnosis (4.2% of the population) excluding nonmelanoma skin cancer, or until the end of follow-up, whichever occurred first. In the full cohort, Cox regression with attained age as the time scale was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for incident PCa and PCa death according to smoking status (never smoker, former smoker, current smoker), smoking duration, smoking intensity, and pack-years of smoking among smokers, and time since smoking cessation among former smokers. Never smokers were included in all these analyses [41]. We also examined the joint association of BMI (<25, 25–29, or ≥30 kg/m$^2$) and smoking status with PCa risk. All models were stratified by cohort and birth year (<1935, 1935–1939, 1940–1944, 1945–1949, or ≥1950) and were adjusted for study entry information, including age (continuous), geographical region (North, Uppsala-Örebro, Stockholm, West, South-East, or South), country of birth (born in Sweden with both parents born in Sweden, born in Sweden with one parent born in Sweden, born in Sweden with both parents born abroad, or born abroad), education (pre-upper secondary school <9 yr, pre-upper secondary school 9 yr, maximum of 2 yr upper secondary

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**Table 1 – Baseline characteristics of the 351 448 men according to smoking status**

| Characteristic | Never smoker (*n* = 163 453) | Former smoker (*n* = 68 675) | Current smoker (*n* = 119 320) |
|---|---|---|---|
| Cohort (year of health examination), *n* (%) | | | |
| Construction Workers Cohort (1978–1993) | 124 132 (47) | 43 749 (16) | 98 817 (37) |
| Västerbotten Intervention Program (1985–2016) | 29 550 (54) | 16 696 (30) | 8827 (16) |
| Northern Sweden Monica Study (1986–2014) | 1786 (45) | 1445 (37) | 724 (18) |
| Malmö Diet and Cancer Study (1991–1996) | 3137 (29) | 4639 (43) | 3035 (28) |
| Malmö Preventive Project (1974–1984) | 4848 (33) | 2146 (14) | 7917 (53) |
| Mean age at study entry, yr (SD) | 35.0 (13) | 44.3 (12) | 38.3 (12) |
| Age category, *n* (%) | | | |
| <35 yr | 88 869 (54) | 17 307 (25) | 52 798 (44) |
| 35–44 yr | 35 608 (22) | 18 471 (27) | 29 945 (25) |
| 45–54 yr | 21 997 (14) | 16 709 (24) | 22 325 (19) |
| ≥55 yr | 16 979 (10) | 16 188 (24) | 14 252 (12) |
| Smoking intensity, cigarettes per day, *n* (%) | | | |
| <5 | – | – | 10 629 (9.0) |
| 5–14 | – | – | 31 060 (26) |
| 15–24 | – | – | 48 594 (41) |
| ≥25 | – | – | 8591 (7.0) |
| Missing | – | – | 20 446 (17) |
| Smoking duration, *n* (%) | | | |
| <15 yr | – | – | 40 383 (34) |
| 15–24 yr | – | – | 30 672 (26) |
| 25–29 yr | – | – | 16 616 (15) |
| ≥30 yr | – | – | 11 203 (10) |
| Missing | – | – | 20 446 (15) |
| Smoking pack-years, *n* (%) | | | |
| <10 pack-years | – | – | 43 661 (40) |
| 10–19 pack-years | – | – | 28 800 (29) |
| 20–29 pack-years | – | – | 14 587 (15) |
| ≥30 pack-years | – | – | 11 826 (12) |
| Missing | – | – | 20 446 (4.0) |
| Time since smoking, *n* (%) | | | |
| <5 yr | – | 5674 (8.0) | – |
| 5–9 yr | – | 9200 (14) | – |
| 10–14 yr | – | 8391 (12) | – |
| 15–24 yr | – | 17 498 (26) | – |
| ≥25 yr | – | 21 348 (31) | – |
| Missing | – | 6564 (9.0) | – |
| Mean body mass index, kg/m$^2$ (SD) | 24.6 (3.3) | 25.8 (3.4) | 24.4 (3.3) |
| Body mass index category, *n* (%) | | | |
| <25 kg/m$^2$ | 96 476 (59) | 29 846 (44) | 71 880 (60) |
| 25–29.9 kg/m$^2$ | 53 721 (33) | 30 184 (44) | 38 029 (32) |
| ≥30 kg/m$^2$ | 10 365 (6.0) | 7008 (10) | 6625 (6.0) |
| Missing | 2891 (2.0) | 1637 (2.0) | 2786 (2.0) |
| Education, *n* (%)[a] | | | |
| Pre-upper secondary school <9 yr | 28 329 (17) | 20 736 (29) | 33 722 (28) |
| Pre-upper secondary school 9 yr | 14 140 (9.0) | 6124 (10) | 14 727 (12) |
| Maximum of 2 yr of upper secondary school | 77 761 (48) | 22 810 (33) | 45 936 (39) |
| 3 yr of upper secondary school | 18 104 (11) | 9142 (13) | 12 141 (10) |
| Post-upper secondary school <3 yr | 12 988 (8.0) | 4179 (6.0) | 4349 (4.0) |
| Post-upper secondary school ≥3 yr | 8985 (6.0) | 3563 (5.0) | 2152 (2.0) |
| Missing | 3146 (2.0) | 2121 (3.0) | 6293 (5.0) |
| Marital status, *n* (%) | | | |
| Unmarried | 71 067 (43) | 12 224 (18) | 34 374 (29) |
| Married | 79 843 (49) | 47 298 (69) | 63 985 (54) |
| Divorced | 8291 (5.0) | 6038 (9.0) | 13 620 (11) |
| Widower | 1514 (1.0) | 1220 (2.0) | 1783 (1.0) |
| Missing | 2738 (2.0) | 1895 (3.0) | 5558 (5.0) |
| Country of birth, *n* (%) | | | |
| Born in Sweden with both parents born in Sweden | 146 941 (90) | 61 047 (89) | 102 892 (86) |
| Other | 16 512 (10) | 7628 (11) | 16 428 (14) |
| First-degree family history of prostate cancer, *n* (%) [b] | | | |
| No | 131 624 (80) | 44 321 (64) | 82 408 (69) |
| Yes | 3168 (2.0) | 1841 (3.0) | 1776 (2.0) |
| Missing | 28 661 (18) | 22 513 (33) | 35 136 (29) |

SD = standard deviation.

[a] Data from the Swedish longitudinal integration database for health insurance and labour market studies.

[b] Determined from the Swedish Multi-generation Register and the Swedish Cancer Register. The Swedish Multi-generation Register has virtually complete coverage of first-degree biological family for individuals born in or after 1932, registered in Sweden in 1961 or later. Tracked biological fathers and brothers of study participants were linked to the Cancer Register to obtain information on prostate cancer diagnosis. Missing data are because of parents being born too early for inclusion in the Swedish Multi-generation Register, or because they never lived in Sweden.

school, 3 yr upper secondary school, <3 yr post-upper secondary school, post-upper secondary school ≥3 yr including university, or missing), and marital status (unmarried, married, divorced, widower, or missing). First-degree family history of PCa was missing for 25% of the population and thus was not included as an adjustment factor; however, among men with this information available, additional adjusting for first-

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**Table 2 – Clinical characteristics of the 21 926 incident prostate cancer cases identified in the National Prostate Cancer Register of Sweden**

| Characteristic | Never smoker (*n* = 9106) | Former smoker (*n* = 5873) | Current smoker (*n* = 6947) |
|---|---|---|---|
| Mean age at diagnosis, yr (SD) | 68.9 (8.6) | 70.0 (7.8) | 68.3 (7.8) |
| Age category, *n* (%) | | | |
| <65 yr | 2953 (32) | 1574 (27) | 2384 (34) |
| 65–70 yr | 2132 (24) | 1442 (24) | 1732 (25) |
| 70–75 yr | 1793 (20) | 1292 (22) | 1427 (21) |
| ≥75 yr | 2228 (24) | 1565 (27) | 1404 (20) |
| Charlson comorbidity index, *n* (%) [a] | | | |
| 0 (no comorbidity) | 7801 (86) | 4802 (82) | 5662 (82) |
| 1 (mild comorbidity) | 744 (8.0) | 623 (11) | 754 (11) |
| ≥2 (severe comorbidity) | 561 (6.0) | 448 (7.0) | 531 (7.0) |
| Mode for prostate cancer detection, *n* (%) | | | |
| Asymptomatic health check-up | 3556 (40) | 2092 (36) | 2576 (36) |
| Lower urinary tract symptoms | 2580 (28) | 1658 (28) | 1950 (28) |
| Other symptoms | 2012 (22) | 1399 (24) | 1638 (24) |
| Missing | 958 (10) | 724 (12) | 783 (11) |
| Local clinical tumour stage, *n* (%) | | | |
| T1a–b | 425 (5.0) | 285 (5.0) | 280 (4.0) |
| T1c | 3994 (44) | 2410 (41) | 2775 (40) |
| T2 | 2777 (30) | 1900 (32) | 2200 (32) |
| T3–4 | 1799 (20) | 1192 (20) | 1581 (23) |
| Missing | 111 (1.0) | 86 (2.0) | 111 (1.0) |
| Lymph node metastasis, *n* (%) | | | |
| N0 | 1729 (19) | 1080 (18) | 1355 (20) |
| N1 | 312 (3.0) | 186 (3.0) | 242 (3.0) |
| Nx/missing | 7065 (78) | 4607 (79) | 5350 (77) |
| Bone metastasis, *n* (%) | | | |
| M0 | 5208 (57) | 3244 (55) | 3783 (55) |
| M1 | 775 (8.0) | 549 (9.0) | 698 (10) |
| Mx/missing | 3123 (35) | 2080 (36) | 2466 (35) |
| Gleason score, *n* (%) | | | |
| ≤6 | 3791 (42) | 2300 (39) | 2670 (38) |
| 7 | 2841 (31) | 1862 (32) | 2269 (33) |
| 8–10 | 1675 (18) | 1092 (19) | 1365 (20) |
| Gx/missing | 799 (9.0) | 619 (10) | 643 (9.0) |
| PSA at diagnosis, *n* (%) | | | |
| <4 ng/ml | 840 (9.0) | 497 (8.0) | 626 (9.0) |
| 4–9 ng/ml | 3793 (41) | 2340 (40) | 2789 (40) |
| 10–49 ng/ml | 3055 (34) | 2155 (37) | 2338 (34) |
| ≥50 ng/ml | 1328 (15) | 827 (14) | 1108 (16) |
| Missing | 90 (1.0) | 54 (1.0) | 86 (1.0) |
| Cancer risk category, *n* (%) [b] | | | |
| Localised low-risk | 2731 (30) | 1579 (27) | 1848 (27) |
| Localised intermediate-risk | 2671 (30) | 1778 (30) | 2080 (30) |
| Localised high-risk | 1949 (21) | 1405 (24) | 1544 (22) |
| Regionally metastatic/locally advanced | 622 (7.0) | 343 (6.0) | 502 (7.0) |
| Distant metastases | 1133 (12) | 768 (13) | 973 (14) |
| Primary treatment, *n* (%) [c] | | | |
| Conservative | 2526 (28) | 1523 (26) | 1741 (25) |
| Curative | 3889 (43) | 2498 (43) | 2965 (43) |
| Noncurative | 2362 (26) | 1670 (28) | 1984 (29) |
| Missing | 329 (3.0) | 182 (3.0) | 257 (3.0) |

SD = standard deviation; PSA = prostate-specific antigen.
[a] According to discharge diagnoses in the Swedish Patient Register.
[b] Localised low-risk: T1–2, Gleason score 2–6, and PSA <10 ng/ml; localised intermediate-risk: T1–2, Gleason score 7, and/or PSA 10 to <20 ng/ml; localised high-risk: T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml; regionally metastatic/locally advanced: T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases; distant metastases: M1 and/or PSA ≥100 ng/ml.
[c] Conservative treatment includes watchful waiting and active surveillance; curative treatment includes radical prostatectomy and radiotherapy; noncurative treatment includes all androgen deprivation therapies such as orchiectomy, gonadotropin-releasing hormone agonists and antagonists, and antiandrogens.

degree family history of PCa only changed the third decimal place of the estimate of the association of smoking with PCa risk. In response to findings of lower risk of any PCa and localised PCa for smokers, we investigated the potential influence of PSA testing on these findings by calculating the association of smoking status with PCa risk before 1997 versus 1997 onwards (proxy for the start of opportunistic PSA testing in Sweden), and for PCa detected via an asymptomatic PSA test versus investigation for LUTS or other symptoms.

We conducted case-only analyses for smoking and PCa death using Cox regression with time since PCa diagnosis as the time scale and the same model stratifications as in the full-cohort analyses. These models were adjusted for factors at the time of diagnosis, including age (continuous), education, marital status, source of income (work, studies, care of child or family, sick, unemployed, early retirement, social benefits, labour market policy activity, pensioner, no income, or missing), Charlson comorbidity index (none, mild, or severe) [40], primary treatment (conservative, curative, noncurative, or missing), geographical region, country of birth, and PCa risk category (for total PCa). Among cases, we compared PSA level and Gleason score between smoking status categories, separately by PCa risk category, using the Kruskal-Wallis test.

The proportional hazards assumption was tested with Schoenfeld residuals. The heterogeneity between PCa risk categories was calculated using the Lunn and McNeil method [42]. We also investigated the interaction between smoking status and subcohort using the likelihood ratio

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test for a product term of cohort and smoking status on PCa risk and death. We found no indication of interaction ($p \geq 0.2$ for all), which supported the pooling of our data. An additional analysis was performed in which repeat smoking data were included in a time-updated Cox model, as described in the Supplementary material.

We estimated the population attributable fraction (PAF) [43] of PCa deaths attributable to smoking, and to smoking combined with overweight (BMI 25–29.9 kg/m$^2$) and obesity (BMI ≥30 kg/m$^2$), on the basis of the prevalence and HRs (Supplementary material).

All statistical tests were two-sided and performed with STATA v17.

## 3. Results

Baseline characteristics according to smoking status for the 351 448 men are shown in Table 1. For the 326 717 men without a PCa diagnosis during follow-up, the median follow-up was 28 yr. Of 24 731 men diagnosed with PCa, 4322 died from the disease. Clinical characteristics were available for 21 926 PCa cases (Table 2).

Smoking was associated with a lower risk of any PCa (HR 0.89, 95% CI 0.86–0.92) and of localised PCa (HR 0.83, 95% CI 0.80–0.86), which was more pronounced for the lower risk categories (Table 3). No association was found for more advanced PCa. The associations between smoking intensity and pack-years of smoking supported the finding for smoking status and localised disease, whereas the associations for smoking duration and time since cessation and PCa risk were less clear (Supplementary Table 1).

The lower risk of any PCa among smokers was only evident in the PSA era (HR 0.87, 95% CI 0.85–0.91) and the association within this period was more pronounced when the PCa had been detected via an asymptomatic PSA test (HR 0.80, 95% CI 0.75–0.84) than when it had been detected via investigation for LUTS or other symptoms (HR 0.91, 95% CI 0.83–0.92; $p$ for difference <0.001 and 0.02, respectively; Supplementary Table 2).

The lower risk of localised PCa and the higher risk of PCa death for smokers in the full population were further affirmed when smoking status was combined with overweight and obesity (Table 4). The HR for current smokers with BMI ≥30 kg/m$^2$ versus never smokers with BMI <25 kg/m$^2$ was 0.63 (95% CI 0.55–0.72) for all localised PCa, with stronger negative associations for the lower PCa risk categories, and 1.49 (95% CI 1.21–1.84) for PCa death.

In contrast to PCa risk, smoking was associated with a higher risk of PCa death; the HR for current smokers versus never smokers was 1.10 (95% CI 1.02–1.18) in the full-cohort analysis (Table 3) and 1.20 (95% CI 1.11–1.31) in the case-only analysis, with HRs ranging between 1.15 and 1.24 in separate PCa risk categories (Table 5). When restricting the case-only analysis to men with information on smoking status no longer than 10 yr before PCa diagnosis, the effect size was similar but the CI crossed unity (HR 1.17, 95% CI 0.89–1.57). For each PCa risk category, PSA levels and Gleason score did not differ by smoking status ($p$ for difference >0.05 for all; Supplementary Table 3). Smoking intensity and duration and pack-years of smoking were not associated with PCa death in the full-cohort analysis (Table 3), but showed positive associations in the case-only analysis (HR per 10 cigarettes/d 1.09, 95% CI 1.01–1.20; HR per 10 yr of smoking 1.06, 95% CI 1.00–1.16; HR per 10 pack-years 1.07, 95% CI 1.00–1.13).

The PAF of smoking to PCa death for smokers compared to never smokers was 3% (95% CI 0.3–6.4%). For overweight/obesity, the PAF was 8% (95% CI 4.7–11%) and the joint PAF for smoking and overweight/obesity was 11% (95% CI 6.7–14.8%). These proportions were 3% (95% CI 0.0–6.5%), 8% (95% CI 5.0–11%), and 11% (95% CI 6.8–15%), respectively, when PAF calculations were based on a smoking prevalence of 24% and an overweight/obesity prevalence of 57% among men in the population-based cohorts (ie, excluding the Construction Workers Cohort).

All primary analyses were based on smoking information at study entry. However, among the 203 151 men with subsequent smoking data, 39 797 (20%) had changed their smoking status. Among PCa cases, 16 957 had two or more smoking data recording points before their PCa diagnosis, of whom 2034 (12%) had changed their smoking status before PCa diagnosis. In the time-updated analysis for men with repeat measurements, the HR for current smokers versus never smokers was 0.89 (95% CI 0.85–0.92) for any PCa, while the HR for PCa death was 1.10 (95% CI 1.00–1.20) in the full-cohort analysis and 1.24 (95% CI 1.12–1.38) in the case-only analysis.

## 4. Discussion

In this study, we found a lower PCa risk for smokers and by higher smoking intensity driven by the results for localised PCa. The associations were stronger for localised low-risk PCa and for PCa diagnosed in the PSA era, especially if the PCa was detected via an asymptomatic PSA test. No associations were observed for more advanced PCa at diagnosis, but smokers had a higher risk of dying from PCa, especially if they were also overweight or obese.

In Sweden, opportunistic PSA testing as part of a general health check-up has increased since the mid-1990s, as evidenced by the steep increase in PCa incidence around that time [44]. Our study revealed that the lower risk for smokers was only evident during the PSA era, and the risk further decreased with decreasing risk category for localised PCa. We also investigated the diagnostic pathway leading to a diagnosis of PCa. These data in the NPCR have lower validity than those on clinical characteristics [38], but we do not expect misclassification to be related to smoking habits. The results show that smokers had a more pronounced lower risk of PCa when the diagnostic work-up leading to the PCa diagnosis was initiated by PSA testing than when detection was initiated by investigation of LUTS or other symptoms. Our results support the prevailing hypothesis that the lower risk of localised PCa for smokers may be partly driven by smokers undergoing less asymptomatic PSA testing than their nonsmoking counterparts [14,15]. The more pronounced lower risk for smokers combined with overweight and obesity suggests a behaviour linked to general health consciousness.

In the full-cohort and case-only analyses, smokers had a higher risk of dying from PCa, which confirms the findings from previous studies [10,17-26]. While later detection and more severe PCa at diagnosis among smokers could

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**Table 3 – Hazard ratios for incident prostate cancer and prostate cancer death according to smoking habits in the full cohort**

| Smoking exposure | Localised low-risk [a] | | Localised intermediate-risk [a] | | Localised high-risk [a] | | Regionally metastatic [a] | | Distant metastases [a] | | All prostate cancer [b] | | Prostate cancer death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Events (*n*) | HR (95% CI) [c] | Events (*n*) | HR (95% CI) [c] | Events (*n*) | HR (95% CI) [c] | Events (*n*) | HR (95% CI) [c] | Events (*n*) | HR (95% CI) [c] | Events (*n*) | HR (95% CI) [c] | Events (*n*) | HR (95% CI) [c] |
| Smoking status | *n* = 319 926 [d] | | | | | | | | | | *n* = 351 448 [d] | | | |
| Never smoker | 2631 | Reference | 2567 | Reference | 1814 | Reference | 574 | Reference | 1012 | Reference | 10 076 | Reference | 1646 | Reference |
| Former smoker | 1516 | 0.90 (0.85–0.96) | 1692 | 1.00 (0.94–1.07) | 1275 | 1.01 (0.94–1.09) | 294 | 0.74 (0.64–0.86) | 676 | 0.97 (0.88–1.07) | 6658 | 0.97 (0.94–1.00) | 1224 | 1.03 (0.96–1.11) |
| Current smoker | 1782 | 0.74 (0.69–0.79) | 1963 | 0.87 (0.82–0.92) | 1424 | 0.93 (0.86–0.99) | 454 | 0.96 (0.85–1.09) | 855 | 1.02 (0.93–1.12) | 7997 | 0.89 (0.86–0.92) | 1452 | 1.10 (1.02–1.18) |
| *p* for trend | <0.001 | | <0.001 | | 0.05 | | 0.4 | | 0.7 | | <0.001 | | 0.01 | |
| | *p* = 0.003 for heterogeneity between risk categories [f] | | | | | | | | | | | | | |
| Smoking intensity (per 10 cigarettes/d) [e] | 1495 | 0.82 (0.77–0.88) | 1614 | 0.94 (0.88–1.00) | 1107 | 0.99 (0.92–1.07) | 340 | 0.98 (0.84–1.11) | 643 | 1.06 (0.96–1.17) | 6277 | 0.94 (0.91–0.97) | 1049 | 1.02 (0.94–1.10) |
| | *p* = 0.10 for heterogeneity between risk categories [f] | | | | | | | | | | | | | |
| Smoking duration (per 10 yr of smoking) [e] | 1403 | 0.91 (0.83–1.00) | 1518 | 0.94 (0.87–1.03) | 1043 | 1.08 (0.98–1.20) | 324 | 0.97 (0.83–1.14) | 605 | 1.00 (0.88–1.11) | 5951 | 0.98 (0.95–1.02) | 1020 | 1.03 (0.95–1.12) |
| | *p* = 0.4 for heterogeneity between risk categories [f] | | | | | | | | | | | | | |
| Lifetime smoking pack-years (per 10 pack-years) [e] | 1403 | 0.89 (0.85–0.94) | 1518 | 0.99 (0.95–1.03) | 1043 | 1.03 (0.99–1.08) | 324 | 0.96 (0.89–1.04) | 605 | 1.00 (0.95–1.06) | 5951 | 0.99 (0.97–1.01) | 1020 | 1.03 (0.99–1.07) |
| | *p* = 0.01 for heterogeneity between risk categories [f] | | | | | | | | | | | | | |
| Smoking cessation (per 10 yr of cessation) [e] | 1421 | 1.05 (0.98–1.13) | 1589 | 1.02 (0.95–1.08) | 1136 | 1.04 (0.97–1.11) | 263 | 0.96 (0.83–1.12) | 596 | 0.94 (0.85–1.03) | 5994 | 1.00 (0.97–1.03) | 1037 | 0.94 (0.88–1.01) |
| | *p* = 0.8 for heterogeneity between risk categories [f] | | | | | | | | | | | | | |

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.

[a] Localised low-risk: T1–2, Gleason score 2–6, and PSA <10 ng/ml; localised intermediate-risk: T1–2, Gleason score 7, and/or PSA 10 to <20 ng/ml; localised high-risk: T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml; regionally metastatic: T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases; distant metastases: M1 and/or PSA ≥100 ng/ml.

[b] Includes an additional 2805 prostate cancer cases not classified into a prostate cancer risk category.

[c] HRs with 95% CI were calculated via Cox regression with attained age as time scale, stratified by cohort and birth year (<1935, 1935–1939, 1940–1944, 1945–1949, ≥1950) and adjusted for age at study entry (continuous), geographical region (North, Uppsala-Örebro, Stockholm, West, South-East, South), country of birth (born in Sweden with both parents born in Sweden, born in Sweden with one parent born in Sweden, born in Sweden with both parents born abroad, born abroad), education (pre-upper secondary school <9yr, pre-upper secondary school 9yr, max 2 yr upper secondary school, 3 yr upper secondary school, post-upper secondary school <3 yr, post-upper secondary school ≥3yr including university, missing), and marital status (unmarried, married, divorced, widower, missing). Never-smokers were included in the continuous smoking-related variables and were assigned a value of 0 (continuous analyses also included an indicator of smoking status and smoking-related variables were centred). Former smokers were excluded in the analyses of smoking intensity, duration, and pack-years.

[d] Analyses for all prostate cancer and prostate cancer death were conducted for the full cohort, while analyses for prostate cancer risk categories were based on noncensored men by January 1, 1998.

[e] The total number of men (*n*) for all prostate cancer/prostate cancer risk categories was 351 448/319 926 for smoking status, 262 743/231 221 for smoking intensity, 256 664/225 142 for smoking duration and pack-years, and 225 564/194 042 for smoking cessation.

[f] The *p* values for the heterogeneity in HRs for the highest categories between prostate cancer risk categories were calculated using the Lunn and McNeil duplication method.

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**Table 4 – Hazard ratios for incident prostate cancer and prostate cancer death in the full cohort according to smoking status and BMI combined**

| | Hazard ratio (95% confidence interval)[a] | | |
|---|---|---|---|
| | BMI <25 kg/m$^2$ (normal weight) | BMI 25–29.9 kg/m$^2$ (overweight) | BMI ≥30kg/m$^2$ (obese) |
| Prostate cancer risk categories [b] ($n$ = 252 970) [c] | | | |
| Localised low-risk | | | |
| Never smoker | Reference | 0.94 (0.87–1.03) | 0.66 (0.54–0.79) |
| Current smoker | 0.72 (0.67–0.78) | 0.71 (0.65–0.78) | 0.40 (0.30–0.53) |
| Localised intermediate-risk | | | |
| Never smoker | Reference | 0.95 (0.88–1.04) | 0.90 (0.76–1.07) |
| Current smoker | 0.87 (0.80–0.94) | 0.85 (0.77–0.93) | 0.63 (0.50–0.79) |
| Localised high-risk | | | |
| Never smoker | Reference | 0.93 (0.84–1.03) | 0.83 (0.68–1.01) |
| Current smoker | 0.88 (0.80–0.99) | 0.90 (0.81–1.01) | 0.97 (0.78–1.21) |
| Regionally metastatic | | | |
| Never smoker | Reference | 1.20 (1.00–1.43) | 0.95 (0.67–1.34) |
| Current smoker | 0.98 (0.82–1.18) | 1.10 (0.90–1.34) | 1.16 (0.78–1.70) |
| Distant metastases | | | |
| Never smoker | Reference | 1.25 (1.09–1.42) | 1.20 (0.94–1.53) |
| Current smoker | 1.17 (1.02–1.34) | 1.12 (0.97–1.31) | 1.18 (0.88–1.59) |
| Overall cohort ($n$ = 277 096) [c] | | | |
| All prostate cancer [d] | | | |
| Never smoker | Reference | 0.99 (0.95–1.03) | 0.88 (0.81–0.96) |
| Current smoker | 0.88 (0.84–0.91) | 0.90 (0.85–0.94) | 0.78 (0.70–0.86) |
| Prostate cancer death | | | |
| Never smoker | Reference | 1.23 (1.11–1.36) | 1.05 (0.86–1.27) |
| Current smoker | 1.13 (1.02–1.27) | 1.27 (1.13–1.42) | 1.49 (1.21–1.84) |

BMI = body mass index; PSA = prostate-specific antigen.

[a] Hazard ratios and 95% confidence interval were calculated via Cox regression with attained age as time scale, stratified by cohort and birth year and adjusted for age at study entry, geographical region, country of birth, education, and marital status. The number of prostate cancer cases for never smokers normal weight/never smokers overweight/never smokers obese/current smokers normal weight/current smokers overweight/current smokers obese were 1545/1021/117/1128/625/53 for localised low-risk prostate cancer, 1407/1038/159/1219/736/83 for localised intermediate-risk prostate cancer, 923/835/129/816/598/94 for localised high-risk prostate cancer, 255/315/38/248/208/31 for regionally metastatic cancer, 451/561/92/529/359/59 for distant metastases, 4956/4216/625/4458/2929/389 for all prostate cancer, and 614/855/120/708/590/102 for prostate cancer death.

[b] Localised low-risk: T1–2, Gleason score 2–6, and PSA <10 ng/ml; intermediate-risk: T1–2, Gleason score 7, and/or PSA 10 to <20 ng/ml; high-risk: T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml; regionally metastatic: T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases; distant metastases: M1 and/or PSA ≥100 ng/ml.

[c] The analyses for prostate cancer death were analysed in the full cohort, while the analyses for prostate cancer risk categories used data for noncensored men by January 1, 1998 and with no missing data for body mass index.

[d] Includes an additional 1901 prostate cancer cases not classified into a prostate cancer risk category.

explain the results for the full cohort, smoking status was not related to more advanced disease, as indicated by PSA level and Gleason score within the PCa risk categories in our case-only analysis. Possible explanations for poor PCa survival among smokers could be poor treatment response due to the direct effects of smoking, or residual confounding by prognostic risk factors. Smokers with PCa have had worse outcomes than nonsmokers after treatment with radiotherapy and surgery [16,45]. For example, biochemical recurrence after radical prostatectomy was more common among smokers than among nonsmokers and this difference remained after adjustment for preoperative characteristics [19]. Potential biological mechanisms proposed for the link between smoking and PCa progression include polycyclic aromatic hydrocarbons and other carcinogens in tobacco smoke [16,46] and elevated testosterone levels in smokers [23]. However, the lack of association with advanced PCa in our study speaks against a causal biological effect of smoking. Moreover, the lack of a dose-response relationship for continuous smoking variables on PCa death in the full-cohort analysis raises doubts about causality. However, this analysis combines the contrasting associations of smoking habits with total PCa risk and with survival after diagnosis [27] and does not take into consideration the clinical characteristics that were adjusted for in the case-only analysis. It is also possible that the associations of smoking status and intensity with PCa death in case-only analyses are residually confounded by sociodemographic factors for example, which are strongly related to treatment and outcome [47].

### 4.1. *Strengths and limitations*

Our study had a large sample size with access to extensive and highly valid PCa clinical data. The long follow-up allowed investigation of PCa death in the full cohort, and for cases only in relevant case categories. We adjusted for many relevant confounders, except for PCa heredity. Family history of PCa is associated with higher PCa risk, but adjusting for this in a subset of men in our population for whom this information was available had virtually no effect on the association of smoking with PCa risk. However, it remains unclear whether smoking habits were surveyed during a relevant time window. Smoking habits changed for some of the participants for whom repeat smoking information was available, but incorporation of time-dependent smoking status into the analysis did not change our findings. Nevertheless, it is likely that smoking information clo-

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**Table 5 – Hazard ratios for prostate cancer death according to smoking status among cases only**

| Smoking status | Localised low- and intermediate-risk [a] | | Localised high-risk [a] | | Regionally metastatic [a] | | Distant metastases [a] | | All prostate cancer | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Events (*n*) | HR (95% CI) [b] | Events (*n*) | HR (95% CI) [b] | Events (*n*) | HR (95% CI) [b] | Events (*n*) | HR (95% CI) [b] | Events (*n*) | HR (95% CI) [b] |
| | *n* = 21 926 | | | | | | | | *n* = 21 926 | |
| Never smoker | 181 | Reference | 329 | Reference | 190 | Reference | 573 | Reference | 1273 | Reference |
| Former smoker | 139 | 0.99 (0.79–1.24) | 281 | 1.19 (1.01–1.41) | 112 | 1.07 (0.84–1.37) | 405 | 0.99 (0.86–1.12) | 937 | 1.05 (0.96–1.15) |
| Current smoker | 142 | 1.23 (1.00–1.55) | 259 | 1.24 (1.04–1.46) | 162 | 1.15 (0.90–1.44) | 519 | 1.15 (1.02–1.32) | 1082 | 1.20 (1.11–1.31) |
| *p* for trend | 0.1 | | 0.01 | | 0.3 | | 0.04 | | | |
| | *p* = 0.8 for heterogeneity between risk categories [d] | | | | | | | | | |

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.

[a] Localised low-risk: T1–2, Gleason score 2–6, and PSA <10 ng/ml; localised intermediate-risk: T1–2, Gleason score 7, and/or PSA 10 to <20 ng/ml; localised high-risk: T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml; regionally metastatic: T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases; distant metastases: M1 and/or PSA ≥100 ng/ml.

[b] HRs and 95% CIs were calculated via Cox regression with time since diagnosis at time scale, stratified by cohort and birth year (<1935, 1935–1939, 1940–1944, 1945–1949, ≥1950) and adjusted for age at time of diagnosis (continuous), geographical region (North, Uppsala-Örebro, Stockholm, West, South-East, South), country of birth (born in Sweden with both parents born in Sweden, born in Sweden with one parent born in Sweden, born in Sweden with both parents born abroad, born abroad), education closest to diagnosis (pre-upper secondary school <9 yr, pre-upper secondary school 9 yr, max 2 yr upper secondary school, 3 yr upper secondary school, post-upper secondary school <3 yr, post-upper secondary school ≥3 yr including university, missing), marital status closest to diagnosis (unmarried, married, divorced, widower, missing), source of income closest to diagnosis (work, studies, care of child or family, sick, unemployed, early retirement, social benefits, labour market policy activity, pensioner, no income, missing), Charlson comorbidity index (none, mild, severe), and primary treatment (conservative, curative, noncurative, missing), as well as for prostate cancer risk category for all prostate cancer.

ser to PCa diagnosis is more relevant for PCa survival than our assessment several years before, which may have resulted in a weaker association in our study in comparison to the association in patient studies with smoking habits assessed around the time of diagnosis [23]. An essential question to answer in future studies is whether smoking cessation after PCa diagnosis improves the prognosis of PCa.

## 5. Conclusions

This large, prospective study showed a lower PCa risk for smokers, which is probably because of low uptake of PSA testing by these men. By contrast, smokers had a higher risk of PCa death, which further increased when smoking status was combined with overweight and obesity. Further studies are needed to clarify the causes for the poorer PCa prognosis observed for smokers and the putative effect of smoking cessation after diagnosis.

***Author contributions***: Sylvia H.J. Jochems had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Jochems, Stocks.
*Acquisition of data:* Jochems, Stocks.
*Analysis and interpretation of data:* Jochems, Fritz, Stocks.
*Drafting of the manuscript:* Jochems, Stocks.
*Critical revision of the manuscript for important intellectual content:* All authors.
Statistical analysis: Jochems, Fritz.
*Obtaining funding:* Stocks.
*Administrative, technical, or material support:* None.
*Supervision:* Stocks.
*Other:* None.

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***Data sharing statement***: Data are only available for bona fide researchers on reasonable request submitted to the authors.

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## Appendix: Peer Review Summary

Peer Review Summary and Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.eururo.2022.03.033.

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