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Statin use in relation to prostate cancer outcomes in a population-based patient cohort study

Milan S. Geybels, MSc, Jonathan L. Wright, MD, Sarah K. Holt, PhD, Suzanne Kolb, MSc, Ziding Feng, PhD, and Janet L. Stanford, PhD

Department of Epidemiology, GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands (Milan S. Geybels); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, US (Jonathan L. Wright, Sarah K. Holt, Suzanne Kolb, Janet L. Stanford); Department of Urology, School of Medicine, University of Washington, Seattle, WA, US (Jonathan L. Wright); Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, US (Ziding Feng). Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, US (Janet L. Stanford).

Abstract

Background—We investigated associations between statin use begun before PCa diagnosis and prostate cancer (PCa) recurrence/progression and PCa-specific mortality (PCSM) in a prospective, population-based cohort study.

Methods—The analysis included 1,001 PCa patients diagnosed in 2002–2005 in King County, Washington. Statin use was assessed at baseline using a detailed in-person interview. Prostate cancer recurrence/progression events and cause-specific survival were ascertained from a follow-up survey and the SEER registry. Multivariable competing risk and Cox proportional hazards regression models were used to assess the risk of PCa outcomes according to categories of statin use.

Results—Of the 1,001 PCa patients in our study, 289 men were ever users of statin drugs. During follow-up, we identified 151 PCa recurrence/progression events and 123 total deaths, including 39 PCa-specific deaths. In unadjusted analysis, the risk of PCa-specific mortality (PCSM) was significantly lower for statin users compared to non-users (1% versus 5% at 10 years; $P < 0.01$). In multivariable analysis, the adjusted hazard ratio of PCSM for statin users versus non-users was 0.19 (95% CI: 0.06, 0.56). Statin use was not associated with overall PCa recurrence/progression and other-cause mortality.

Conclusions—Statin use begun before PCa diagnosis was unrelated to PCa recurrence/progression but was associated with a decrease in risk of PCSM.

Introduction

Statins are commonly used cholesterol-lowering drugs that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the enzyme that controls conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, an essential precursor of cholesterol (1). Statin drugs may have anticancer activities (2, 3), and statin use has been associated with a reduced risk of prostate cancer (PCa), with evidence being particularly strong for advanced and more

aggressive PCa (4–7). Potential anticarcinogenic effects of statins may be related to both cholesterol and non-cholesterol-mediated mechanisms (2, 8).

There is considerable interest in the potential ability of statin drugs to improve PCa outcomes. A number of observational studies investigated the association between statin use and biochemical recurrence and progression of PCa after definitive local therapy (9). These studies all had a retrospective design and most of them were based on radical prostatectomy or radiation therapy series. Data of these studies were summarized in a recent meta-analysis, which showed no association of statin use and PCa recurrence/progression (9). Besides PCa recurrence/progression, it has been hypothesized that statin use is associated with a decreased risk of PCa-specific mortality (PCSM). A recent nationwide study from Denmark showed that statin use was associated with a decline in cancer-related mortality (10). In a secondary analysis, the authors showed that statin use was associated with lower mortality from a number of specific cancer types including PCa (10). Very few other observational studies have examined the association of statin use and PCSM (9).

The objective of the current study was to investigate associations between statin use begun before PCa diagnosis and both PCa recurrence/progression and PCSM in a prospective, population-based patient cohort. Our study included 1,001 men who were diagnosed with PCa in 2002–2005 and these men were followed for PCa outcomes for more than five years.

Materials and Methods

Study participants and data collection

The study population consisted of PCa patients from a population-based, case-control study of PCa. These men were aged 35 to 74 at diagnosis from January 1, 2002, through December 31, 2005 (11). Patients were identified via the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) Program cancer registry. This registry provided information on Gleason score, tumor stage, and serum prostate-specific antigen (PSA) level at diagnosis, as well as primary therapy. Of the 1,327 eligible patients ascertained, 1,001 men (75%) were interviewed at diagnosis. The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and written informed consent was obtained from all participants.

Use of statin medications

Information about statin use was obtained during a detailed baseline in-person interview that inquired about any statin use, the type of statin drug used (medication show cards were used), dates of first and last use, and total duration of use for each episode. Users were defined as men who reported having taken a statin at least once a week for three months or longer. Current use of statins was defined as use within the year prior to PCa diagnosis, but current statin use was not evaluated separately since 94% of all users were current users.

Prostate cancer outcomes

Cause-specific deaths were ascertained from the SEER registry, which links quarterly with the Washington State Vital Statistics Database and annually with the National Death Index. The completeness of survival follow-up through linkage with these registries is estimated to be close to 100%. Underlying cause of death obtained from these registries was verified by a review of death certificates, with over 99% agreement. The date of last follow-up for survival was November 1, 2011.

Prostate cancer recurrence/progression events were ascertained using a PCa-specific follow-up survey in 2011 that included questions on physician diagnoses of PCa recurrence/

progression, use of secondary therapies, and PSA test results. All patients who were alive at the time of the follow-up survey, consented to future contact, and were diagnosed with non-metastatic disease were used for analysis of PCa recurrence/progression (n = 900). Of these men, 661 completed the follow-up survey (73%). Prostate cancer recurrence/progression definitions on the basis of PSA level varied by primary treatment: a post-treatment PSA value of 0.2 ng/mL or greater in men who underwent radical prostatectomy; nadir PSA level + 2 ng/mL (Phoenix criteria) (12), for men treated with radiation therapy; or any PSA increase in men treated with primary androgen deprivation therapy. We coded a patient as being on active surveillance/watchful waiting if they did not undergo any form of primary therapy within one year after diagnosis date. If the patient was treated later (12+ months post diagnosis date), but we did not find evidence from a repeat biopsy showing Gleason score upgrading or a physician's statement that the patient had recurred based on PSA testing, we did not consider them as having a progression event. The date of recurrence/progression was determined for patients who died from PCa prior to the follow-up survey (n = 23) using multiple imputations (13), and for one PCa recurrence/progression case from his medical records. The censoring date for non-events was the date that the follow-up questionnaire was returned and the date of last follow-up for recurrence/progression was July 24, 2011. Data on PCa recurrence/progression were available for 685 cohort members.

Statistical analyses

Statin use was tabulated according to a number of selected characteristics. The Kaplan-Meier estimator was used to plot the crude survival curves, and the log-rank test was used to compare the curves of statin users versus non-users. Cox proportional hazards regression was used to obtain hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the associations between categories of statin use and risk of PCa outcomes. Because many PCa patients have comorbid conditions that may influence PCa-specific survival, competing risk regression was used for the analysis of PCSM (Fine & Gray; death from other causes as a competing risk). We completed age-adjusted models and multivariable models adjusted for age (years), Gleason score (2–6, 7(3+4), 7(4+3), 8–10), stage at diagnosis (local (T1, T2), regional (T3), distant (T4)), diagnostic PSA level (<10, 10–19, 20), primary treatment approach (radical prostatectomy, radiation with or without androgen deprivation therapy (ADT), ADT only, active surveillance/watchful waiting, other treatment), race (Caucasian, African-American), first-degree family history of prostate cancer (no, yes), body mass index (BMI, kg/m²; <25, 25–<30, 30), smoking status (never, former, current), lifetime alcohol consumption (drinks/week; <1, 1–7, 8–14, 15), regular aspirin use (no, yes), regular non-aspirin NSAID use (no, yes), history of diabetes mellitus (no, yes), and history of PCa screening (none, digital rectal exam only, PSA testing). The association with PCSM was studied in the full cohort and in a secondary analysis after exclusion of men with distant stage PCa at diagnosis. With regard to primary treatment, patients who received radiation with or without ADT were combined (n = 359). Of these men, 96 received radiation with ADT and 263 received radiation alone. Adjustment for a primary therapy covariate that considered these two groups separately did not alter study results. We additionally considered diagnostic PSA level as a continuous log-transformed covariate, but it did not change the hazard ratios. Including the year of diagnosis in the statistical models did not change the point estimates. The proportional hazards assumption was tested using the scaled Schoenfeld residuals (14). All tests were two-sided, with a P value less than 0.05 considered being statistically significant. Analyses were performed using STATA software (release 12, STATA Corporation, College Station, TX).

Results

Figure 1 shows a flow diagram of the patient cohort. The cohort included 1,001 PCa patients and 289 of these men were statin users (Table 1). Statin users compared to non-users were older, had a higher BMI, and were more likely to use aspirin and non-aspirin NSAIDs, and to have a history of diabetes. Statin users were more likely to have had PSA screening and less likely to be diagnosed with distant disease and to have a high PSA value (≥ 20 ng/ml) at diagnosis. The most commonly used statin drugs were atorvastatin (63.3%), simvastatin (31.5%), lovastatin (14.5%), and pravastatin (13.8%); the prevalence of use of other types of statins was low ($<5\%$). Overall, 86% of users exclusively took lipophilic statins, 5% had only used hydrophilic statins, and 9% had used both lipophilic and hydrophilic statins.

There were 685 patients with data on PCa recurrence/progression and during an average follow-up of 6.1 years, 151 PCa patients had a PCa recurrence/progression event (22%). These 151 events included 25 PCa-specific deaths, 12 metastatic cancers, 82 cases who received secondary treatment, and 32 cases with a rise in PSA only. The risk of overall PCa recurrence/progression was not different for statin users compared to non-users (22% versus 21% at 9 years; $P = 0.64$) (Figure 2). In multivariable analysis, statin use was not associated with the risk of overall PCa recurrence/progression (adjusted HR = 1.06; 95% CI: 0.74, 1.54) and there were no patterns of risk for duration of use, age at first use, and time since first use (Table 2). In an additional analysis we excluded those men for whom the only evidence of recurrence/progression was a rise in PSA ($n = 32$), and the adjusted HR (users versus non-users) was 0.94 (95% CI: 0.62, 1.41) (data not in tables). We investigated the association between statin use and PCa recurrence/progression separately for patients whose primary treatment was radical prostatectomy (52%) and those whose initial treatment was radiation therapy (33%), and we found no evidence of an association (data not in tables). We also evaluated three different subgroups based on the definition of PCa recurrence/progression. These subgroups were PCa specific deaths and metastatic cancers combined ($n = 37$), cases who received secondary treatment ($n = 82$), and cases with a rise in PSA only ($n = 32$); and adjusted HRs (95% CI) for statin users versus non-users were 0.55 (0.25, 1.24), 1.15 (0.71, 1.85), and 1.62 (0.78, 3.37), respectively (data not in tables).

All 1,001 patients had data on cause-specific mortality and during an average follow-up of 7.6 years there were 123 total deaths (12%), including 39 PCa-specific deaths (4%). Figure 3 shows the Kaplan-Meier curves for PCa-specific survival according to statin use. The risk of PCSM was significantly lower among statin users compared to non-users (1% versus 5% at 10 years; $P < 0.01$). In multivariable analysis, treating death from other causes as a competing risk (Fine and Gray model), the adjusted HR of PCSM for statin users versus non-users was 0.19 (95% CI: 0.06, 0.56) (Table 3). When other-cause deaths were treated as censored observations, the adjusted HR was 0.16 (95% CI: 0.04, 0.56) (data not in tables). Statin use was not associated with other-cause death (adjusted HR = 0.89; 95% CI: 0.54, 1.48). In an additional analysis, we evaluated the association between statin use and PCSM after excluding PCa patients who presented with distant stage disease at diagnosis ($n = 22$), and the adjusted HR for statin users versus non-users was 0.23 (95% CI: 0.06, 0.83) (data not in tables).

Discussion

In this population-based cohort of PCa patients, statin use begun before diagnosis was not associated with PCa recurrence/progression. We, however, observed a significant decrease in risk of PCSM associated with statin use. No association was observed with other-cause mortality. The hazard ratios were similar after multivariable adjustment, which implies that there was no substantial confounding by any of the additionally included covariables.

A number of studies investigated associations between statin use and patient outcomes (15–25). Those studies all followed a retrospective, hospital-based design and most of them exclusively evaluated recurrence/progression events. Our observation that statin use is unrelated to PCa recurrence/progression is supported by a recent meta-analysis (9). That meta-analysis included eight studies and showed no association with biochemical (rising PSA) recurrence of PCa (HR for statin users versus non-users = 0.91; 95% CI: 0.72, 1.13). The eight studies in the meta-analysis were five studies based on radical prostatectomy series and three studies based on radiation therapy series and the association was not different in these subgroups. The authors, however, found substantial evidence of heterogeneity across studies.

Pretreatment PSA levels and biochemical recurrence are poor predictors of PCa-specific survival (26, 27). This was also evident from our data; 22% of participants had PCa recurrence/progression (mean follow-up of 6.1 years) while only 4% of men died of PCa (mean follow-up of 7.6 years). Hence, the influence of statins on the rate of PCa recurrence/progression may differ in magnitude from their influence on the rate of PCa-specific survival. Very few studies of statin use in relation to PCa-specific survival have been conducted, probably because such analyses require much longer follow-up than analyses of biochemical recurrence. Indeed, it typically takes a long time for PCa to progress to a fatal outcome (28). Only two of the eight studies included in the meta-analysis described above also examined PCSM and both studies showed no association with this clinically relevant endpoint (15, 17). Those studies, however, had some limitations including a short follow-up period for assessing survival (15), which limited data on PCSM, and use of unadjusted statistical models only (17). Zaorsky et al. investigated the association between statin non-use and early biochemical failure (less than 18 months), which is assumed to be a strong predictor of PCSM (25). The authors showed a positive association (odds ratio = 2.47; 95% CI: 1.53, 3.97) suggesting that statin drugs may reduce PCSM.

Recently, Nielsen et al. conducted a nationwide study in Denmark to investigate the association between statin use and cancer-related mortality (10). The study included patients from the entire Danish population who were 40 years or older and who had received a diagnosis of cancer between 1995 and 2007 ($n = 295,925$), with follow-up until 2009 (median, 2.6 years; range, 0 to 15). The authors showed that statin use was associated with a reduced risk of death from cancer (adjusted HR = 0.85; 95% CI: 0.82, 0.87). In a secondary analysis, the authors studied associations with death from 27 specific cancer types and observed a reduced cancer-related mortality for 13 cancer types, including prostate cancer (adjusted HR for statin users versus non-users = 0.81; 95% CI: 0.75, 0.88). Although both our study and the Danish study observed an association with reduced PCSM, the association was much more pronounced in our study. There are a number of differences between our study and the Nielsen et al. study that may explain the difference in outcome. In particular, the frequency of statin use in our US-based study (28% of controls (11)) is much higher than in the Nielsen et al. study (8% of men (10)). It is possible that in the Danish study statins were more often prescribed to men with a particularly bad health status or unhealthy lifestyle putting them at increased risk of fatal PCa. Unfortunately, data on potentially important confounders such as smoking status, body mass index, and cancer screening history were missing in the Danish study (10).

Statin drugs have several properties that may explain the observed association with a decreased risk of PCSM. Statins reduce circulating cholesterol levels and its availability for incorporation into cell membranes (2). Cholesterol-rich domains in cell membranes play a key role in intracellular signaling and some of these pathways such as the Akt signaling pathway are related to PCa cell survival (2, 29). Statins also reduce the concentration of the cholesterol precursor mevalonate, which is a precursor for isoprenoids known as farnesyl

pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These isoprenoids attach to G-proteins permitting these proteins to be recruited to the cell membrane where they promote PCa cell survival and proliferation (2, 30). A laboratory study showed that lipophilic statins reduce the migration and colony formation of malignant prostate epithelial cells in human bone marrow stroma by inhibiting GGPP production, and that this reduces the formation and the spread of metastatic prostate colonies (31). In addition, statins can directly affect apoptosis, angiogenesis, and inflammatory processes, all of which are thought to play a role in PCa progression (2, 30).

Our study has several strengths including its population-based, prospective design and extended follow-up for cause-specific mortality. Although we had no access to pharmacy records, we used standardized interviews with trained interviewers and medication show cards to ascertain statin use. Previous work with a subset of this study population has found high agreement between self-reported medication usage and pharmacy records (11). We also had detailed information on lifestyle, medical history, and clinical and pathological parameters and were therefore able to adjust for potential confounding.

Our study also has several limitations that need to be addressed. First, it is possible that men receiving statins had more significant comorbidities and that this competing mortality lowered the chance to observe PCSM in the group of statin users. We therefore completed competing risk regression models, and the association of statin use with PCSM was not different compared to Cox regression models. Second, our analyses used baseline data and changes in statin use after diagnosis were not considered. It is, however, unlikely that statin use dropped considerably after diagnosis in our study population because most statin users are recommended to stay on these drugs indefinitely. This pattern was also clear from a subset of our data. The follow-up survey used to collect recurrence/progression data also queried information on statin use and based on these follow-up data, less than 6% of patients who reported use on the baseline questionnaire had stopped using statins after diagnosis. A third limitation of the present study is the number of PCa-specific deaths, which did not allow us to evaluate detailed measures of statin use (e.g., duration of use, age at first use, or time since first use) or to investigate subgroups defined by primary treatment (e.g., radical prostatectomy, radiation therapy). The limited number of PCa-specific deaths is expected given the typically long time for PCa to progress to a fatal outcome. Fourth, despite the careful and stepwise selection of confounders in the present study, because of the observational nature of the study residual confounding cannot be ruled out. One potentially important confounder of the association between statin use and PCSM is aspirin and/or NSAID use (32). In a multivariable model adjusted for use of aspirin and other NSAIDs, the association between statin use and PCSM was unchanged.

Conclusions

Our data indicate that statin use begun before PCa diagnosis is associated with a substantial decrease in risk of PCSM. This finding needs to be replicated in future patient cohorts with extended follow-up for assessment of PCSM.

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Figure 1.
Flow diagram of study participants, King County, Washington, 2002-2005

Figure 2.

Proportion free from prostate cancer recurrence/progression by categories of statin use, King County, Washington, 2002–2011; statin use was defined as use at least once a week for 3 months or longer. The P value for the log rank test was 0.67.

Figure 3. Probability of prostate cancer-specific survival by categories of statin use, King County, Washington, 2002–2011; statin use was defined as use at least once a week for 3 months or longer. The P value for the log rank test was <0.01.

Table 1
Selected baseline characteristics of study participants by categories of statin use, King County, Washington, 2002–2005

Statin use				
	Yes ^a n = 289		No n = 712	
Variables	%	No. participants	%	No. participants
Mean age at diagnosis, y (SD)	63.1 (6.8)		60.9 (8.1)	
Caucasian race	87.5	253	82.9	590
First-degree family history of prostate cancer	19.7	57	23.7	169
College or graduate degree	56.7	164	56.0	399
Mean body mass index, kg/m ² (SD)	28.5 (4.5)		27.0 (4.0)	
Never smokers	39.8	115	44.0	313
High (15 drinks/week) alcohol consumption	22.1	64	19.5	139
Aspirin use ^a	68.9	199	40.0	285
Non-aspirin NSAID use ^a	25.6	74	19.4	138
History of diabetes mellitus	19.0	55	5.9	42
Prostate cancer screening history ^c				
None	6.6	19	16.0	114
Digital rectal exam only	13.8	40	16.7	119
PSA testing	79.6	230	67.3	479
Prostate cancer screening as a result of symptoms	20.1	58	24.2	172
Gleason score				
2–6 ^d	52.9	153	52.2	372
7 (3+4)	27.3	79	30.2	215
7 (4+3)	9.3	27	7.2	51
8–10	10.4	30	9.6	68
Missing	0.0	0	0.7	5
Stage of cancer				
Local	72.3	209	72.6	517
Regional	14.5	42	14.2	101

Statin use				
Variables	Yes ^a n = 289		No n = 712	
	%	No. participants	%	No. participants
Distant	3.8	11	8.1	58
Missing	9.3	27	5.1	36
Median PSA value at diagnosis, ng/ml (p25, p75)	5.7 (4.4, 8.5)		6.3 (4.7, 9.5)	
Primary treatment for prostate cancer				
Radical prostatectomy	42.9	124	48.9	348
Radiation with or without ADT ^e	41.5	120	33.6	239
ADT only	2.8	8	5.6	40
Active surveillance/watchful waiting	12.5	36	11.7	83
Other	0.3	1	0.3	2
Mean follow-up time for recurrence/progression, y (range)	7.5 (8.8)		7.6 (9.1)	
Mean follow-up time for cause-specific death, y (range)	5.9 (8.2)		6.2 (8.5)	

Abbreviations: SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

^aUse at least once a week for 3 months or longer.

^bA chi-square test (categorical variables) or t-test (continuous variables) was used.

^cProstate cancer screening within the 5-year period before prostate cancer diagnosis.

^dLess than 1% of cancers were Gleason 2-4 (1 user and 6 non-users of statin drugs).

^eOf the 359 patients who received radiation with or without ADT as primary treatment, 96 men received both radiation with ADT.

Table 2

Hazard ratio (HR) and 95% confidence interval (CI) for prostate cancer recurrence/progression according to categories of statin use, King County, Washington, 2002–2011

Prostate cancer recurrence/progression ^a n = 151				
	Person-years ^b	No.	HR ^c (95% CI ^c)	HR ^d (95% CI ^d)
Statin use				
No (reference)	2,940	104	1.00	1.00
Yes ^e	1,235	47	1.06 (0.74, 1.51)	1.06 (0.74, 1.54)
Duration of use, y				
<5	652	25	1.06 (0.68, 1.64)	1.14 (0.72, 1.81)
5	584	22	1.06 (0.67, 1.67)	0.99 (0.61, 1.60)
Age at first use, y				
<59	710	25	1.01 (0.65, 1.57)	1.02 (0.65, 1.60)
59	525	22	1.12 (0.69, 1.81)	1.12 (0.68, 1.86)
Time since first use, y				
<5	624	27	1.19 (0.78, 1.82)	1.28 (0.82, 2.01)
5	611	20	0.92 (0.57, 1.48)	0.87 (0.53, 1.43)

^aThe 151 prostate cancer recurrence/progression events included 25 PCa-specific deaths, 12 metastatic cancers, 82 cases who received secondary treatment, and 32 cases with a rise in PSA only.

^bAnalyzed by Cox proportional hazards regression.

^cAge-adjusted model.

^dMultivariable model adjusted for age at diagnosis (years), Gleason score (2–6, 7 (3+4), 7 (4+3), 8–10), stage at diagnosis (local, regional, distant), diagnostic PSA level (<10, 10–19.9, 20), primary treatment approach (radical prostatectomy, radiation with or without androgen deprivation therapy (ADT), ADT only, active surveillance/watchful waiting, other treatment), race (Caucasian, African-American), first-degree family history of prostate cancer (no, yes), body mass index (kg/m²; <25, 25–<30, 30), smoking status (never, former, current), lifetime alcohol consumption (drinks/week; <1, 1–7, 8–14, 15), aspirin use (no, yes), non-aspirin NSAID use (no, yes), history of diabetes mellitus (no, yes), and history of prostate cancer screening (none, digital rectal exam only, PSA testing).

^eUse at least once a week for 3 months or longer.

Table 3

Hazard ratio (HR) and 95% confidence interval (CI) for prostate cancer-specific and other-cause mortality according to categories of statin use, King County, Washington, 2002–2011

	Statin use	
	No	Yes^a
Participants, No.	712	289
Prostate cancer-specific deaths, No. ^b	36	3
HR (95% CI) ^c	1.00	0.19 (0.06, 0.62)
HR (95% CI) ^d	1.00	0.19 (0.06, 0.56)
Other-cause deaths, No. ^e	59	25
HR (95% CI) ^c	1.00	0.93 (0.58, 1.49)
HR (95% CI) ^d	1.00	0.89 (0.54, 1.48)

^a Use at least once a week for 3 months or longer.

^b Analyzed by competing risk regression, with death of other causes assigned the competing risk.

^c Age-adjusted model.

^d Multivariable model adjusted for age at diagnosis (years), Gleason score (2–6, 7 (3+4), 7 (4+3), 8–10), stage at diagnosis (local, regional, distant), diagnostic PSA level (<10, 10–19.9, ≥20), primary treatment approach (radical prostatectomy, radiation with or without androgen deprivation therapy (ADT), ADT only, active surveillance/watchful waiting, other treatment), race (Caucasian, African-American), first-degree family history of prostate cancer (no, yes), body mass index (kg/m²; <25, 25–<30, ≥30), smoking status (never, former, current), lifetime alcohol consumption (drinks/week; <1, 1–7, 8–14, ≥15), aspirin use (no, yes), non-aspirin NSAID use (no, yes), history of diabetes mellitus (no, yes), and history of prostate cancer screening (none, digital rectal exam only, PSA testing).

^e Analyzed by Cox proportional hazards regression. Men who died of prostate cancer were censored at the time of death.