Annals of Internal Medicine ORIGINAL RESEARCH

Use of Low-Dose Aspirin and Mortality After Prostate Cancer Diagnosis

A Nationwide Cohort Study

Charlotte Skriver, MSc; Christian Dehlendorff, MSc, PhD; Michael Borre, MD, PhD, DMSc; Klaus Brasso, MD, PhD; Signe Benzon Larsen, MSc, PhD; Susanne Oksbjerg Dalton, MD, PhD; Mette Nørgaard, MD, PhD; Anton Pottegård, MSc, PhD; Jesper Hallas, MD, DMSc; Henrik Toft Sørensen, MD, PhD, DMSc; and Søren Friis, MD

Background: Recent studies suggest that aspirin use may improve survival in patients with prostate cancer.

Objective: To assess the association between postdiagnosis use of low-dose aspirin and prostate cancer mortality.

Design: Nationwide cohort study.

Setting: Denmark.

Patients: Men with incident prostate adenocarcinoma between 2000 and 2011.

Measurements: Nationwide registry data on tumor characteristics, drug use, primary prostate cancer therapy, comorbidity, and socioeconomic parameters. Postdiagnosis use of low-dose aspirin (75 to 150 mg) was defined as 2 or more prescriptions filled within 1 year after prostate cancer diagnosis. Follow-up started 1 year after prostate cancer diagnosis. In secondary analyses, low-dose aspirin use was assessed within exposure periods of 5 or 7.5 years after prostate cancer diagnosis.

Results: Of 29 136 patients (median age, 70 years), 7633 died of prostate cancer and 5575 died of other causes during a median follow-up of 4.9 years (interquartile range, 3.1 to 7.2 years), through 2015. Postdiagnosis low-dose aspirin use was associated with adjusted hazard ratios (HRs) of 0.95 (95% CI, 0.89 to 1.01) for prostate cancer–specific mortality and 1.12 (CI, 1.05 to 1.20) for other-cause mortality. The secondary analyses showed that prostate cancer mortality was slightly reduced with low-dose aspirin use after the 5-year (HR, 0.91 [CI, 0.83 to 1.01]) and 7.5-year (HR, 0.84 [CI, 0.72 to 0.97]) postdiagnosis exposure periods, notably among patients filling prescriptions for a large quantity of low-dose aspirin tablets during the 7.5-year period.

Limitations: Data on over-the-counter aspirin use were unavailable. Some residual confounding was possible as a result of incomplete data on some prognostic factors.

Conclusion: The study did not support an overall effect of postdiagnosis low-dose aspirin use on prostate cancer mortality. However, results for extended exposure periods suggest that low-dose aspirin use might be inversely associated with prostate cancer mortality after 5 years from cancer diagnosis

Primary Funding Source: Danish Cancer Society.

Ann Intern Med. doi:10.7326/M17-3085 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 5 March 2019.

Regular aspirin use has been suggested to improve prostate cancer survival, but study results are inconclusive (1, 2). Pooled analyses of cardiovascular disease prevention trials have shown reduced overall cancer incidence, metastasis, and mortality (3–6) among persons assigned to aspirin use. However, these pooled analyses did not specifically evaluate the effect of aspirin use after cancer diagnosis. Thus, whether postdiagnosis aspirin use has a beneficial effect on the prognosis of prostate cancer, or other cancer types, remains unclear (1).

Results of observational studies of postdiagnosis aspirin use and prostate cancer mortality are inconsistent (7–15). A recent meta-analysis reported a 16% reduction in prostate cancer mortality associated with postdiagnosis aspirin use (1); however, the individual studies examined had mixed results and methodological heterogeneity.

Aspirin has been shown to induce apoptosis (16) and reduce growth (16, 17) and cell invasion (18, 19) in prostate tumors. The specific antineoplastic mechanisms of aspirin remain unclear; however, inhibition of cyclooxygenase (COX) enzymes seems to play an important role (20, 21). Overexpression of COX-2 has been found in prostate tumors (22) and is associated with impaired prognosis (23). At low doses, aspirin inhibits mainly COX-1 and platelet function (20, 21), but increasing evidence indicates that its antiplatelet effect influences COX-2 activity (20, 21) and is involved in cancer cell dissemination and metastasis (24).

In a nationwide cohort study in Denmark, we examined the association between postdiagnosis use of low-dose aspirin and mortality among patients with prostate cancer.

Methods

Setting and Data Sources

Using the unique civil registration numbers assigned to all residents of Denmark (25), we retrieved information from the nationwide cancer (26), pathology (27), prescription (28), patient (29), and demographic registries (25, 30–32). The **Appendix** (available at Annals.org) provides a detailed description of the registries, with codes for prostate cancer characteristics, drug exposure, and covariates.

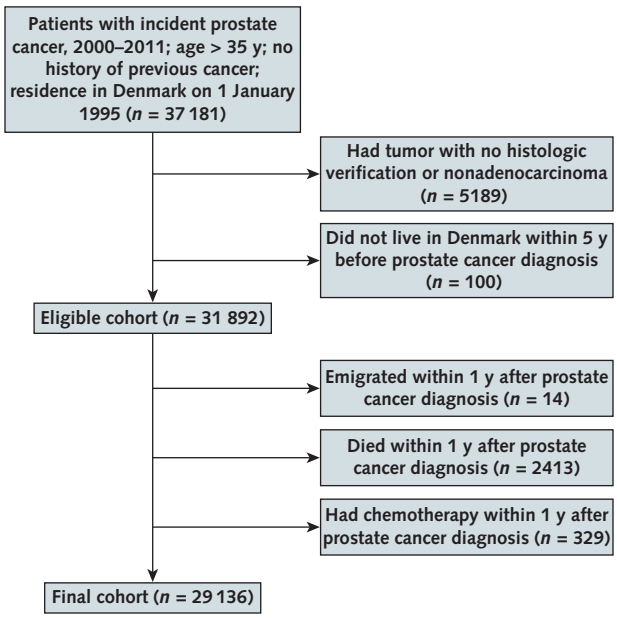
Study Population

From the Danish Cancer Registry (26), we identified all men in Denmark with a first diagnosis of prostate cancer during 2000 to 2011. Inclusion criteria were histologically verified prostate adenocarcinoma, patient age greater than 35 years, no history of cancer (except

See also:

Editorial comment 1

Figure 1. Flow chart of the cohort selection.



nonmelanoma skin cancer), and residence in Denmark on 1 January 1995, when the Danish National Prescription Registry was initiated (28, 33). In addition, patients had to have resided in Denmark for 5 years before their prostate cancer diagnosis, as recorded in the Danish Civil Registration System (25) (Figure 1).

Study Outcomes and Follow-up

Study outcomes were prostate cancer–specific and other-cause mortality based on data retrieved from the Danish Registry of Causes of Death (30). Patients were followed from 1 year after their prostate cancer diagnosis (baseline) to the date of death, emigration, or end of follow-up (31 December 2015). We excluded patients who died, emigrated, or received chemotherapy (indicating severe prostate cancer [34]) within 1 year after their diagnosis (Figure 1).

Clinical Measures

Patients with prostate cancer were categorized by clinical stage at diagnosis (localized, nonlocalized, or unknown [Appendix Table 1, available at Annals.org]) on the basis of Danish Cancer Registry data (26). We retrieved Gleason scores from the Danish Pathology Registry (27); if Gleason codes were missing from the registry, we manually reviewed pathology reports. Prostate cancer aggressiveness was based on the highest recorded Gleason score preceding diagnosis or within 6 months after diagnosis; scores were categorized into 4 groups: 6 or lower, 7, 8 or higher, and unknown.

Data on primary prostate cancer therapy received within 1 year after diagnosis were retrieved from the Danish National Patient Registry (29). Intended curative therapies (brachytherapy, radical prostatectomy) were ranked first, and radiotherapy or endocrine therapy was ranked second (Appendix Figure, available at Annals.org). No clear distinction was feasible among intended curative, salvage, and symptomatic radiotherapy. However, Danish national guidelines recommend that intended curative radiotherapy be delivered as 78 Gy in 39 fractions (35); consequently, we regarded radiotherapy with curative intent as more than 30 rounds within 1 year after prostate cancer diagnosis (assuming that the intended curative radiotherapy continued beyond this period).

Assessment of Low-Dose Aspirin Use

We identified prescriptions for low-dose aspirin (75, 100, or 150 mg per tablet) from the Danish National Prescription Registry (28). In Denmark, aspirin is available over the counter; however, most low-dose aspirin purchases (92% in 2012) are dispensed by prescription (36). In contrast, use of high-dose aspirin (500 mg per tablet) typically is sporadic, and these tablets primarily are purchased over the counter (36, 37).

We defined postdiagnosis low-dose aspirin use as 2 or more prescriptions filled after the prostate cancer diagnosis and nonuse as fewer than 2 prescriptions filled. We assessed postdiagnosis low-dose aspirin use within 1 year from prostate cancer diagnosis in the main analysis and within 5 or 7.5 years in the secondary analyses. In the secondary analyses, we further categorized postdiagnosis low-dose aspirin use according to the number of tablets dispensed (≤365, 366 to 1095, or ≥1096 tablets, equivalent to ≤1, 1 to 3, or >3 years of therapy, assuming a dosage of 1 tablet per day); tablet strength (75 to 100 mg only, 150 mg only, or mixed use); and duration of use (≤365, 366 to 1095, or ≥1096 days), defined as the time between the first and last prescription fills. Finally, we defined prediagnosis low-dose aspirin use as 2 or more prescriptions filled within 5 years before the prostate cancer diagnosis, overall and dichotomized according to the total number of tablets dispensed (1 to 999 or ≥1000 tablets) within this period.

Statistical Analysis

In the main analysis, we assessed postdiagnosis low-dose aspirin use and covariates until 1 year after prostate cancer diagnosis (Figure 2, *top*). We used Cox proportional hazards regression analysis, with time since baseline as the underlying axis, to estimate minimally adjusted (age and calendar period) and multivariable-adjusted hazard ratios (HRs) with 95% CIs for prostate cancer–specific or other-cause mortality associated with postdiagnosis low-dose aspirin use compared with nonuse. The multivariable-adjusted models also included clinical stage; Gleason score; primary prostate cancer therapy; postdiagnosis use (≥2 prescriptions) of nonaspirin nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors, α-adrenoreceptor antagonists, statins, nonaspirin antithrombotic agents, antihypertensives, other cardiovascular drugs, insulin, metformin, other oral antidiabetic drugs, psychotropic drugs, proton-pump inhibitors, or antihistamines; medical history of ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation or atrial flut-

ter, diabetes mellitus, chronic obstructive pulmonary disease, or moderate to severe kidney disease; education level; income; marital status; and residence (Appendix).

We estimated adjusted HRs for prostate cancer and other-cause mortality associated with postdiagnosis use of low-dose aspirin, overall and stratified by clinical stage, Gleason score, primary prostate cancer therapy, age at diagnosis, calendar period of diagnosis, and postdiagnosis statin use (≥2 prescriptions). Potential effect measure modification was evaluated by likelihood ratio tests.

In the secondary analyses, we calculated adjusted HRs for prostate cancer and other-cause mortality associated with postdiagnosis use of low-dose aspirin (≥2 prescriptions) within exposure periods of 5 or 7.5 years after prostate cancer diagnosis. Follow-up started at the end of the 2 exposure periods. Concomitant drug use and comorbidity were assessed up to 5 or 7.5 years after the diagnosis, and the remaining covariates were handled as described for the main analysis (Figure 2, *bottom*). In these analyses, postdiagnosis low-dose aspirin use also was stratified by duration of use, total number of tablets dispensed, and tablet strength used during the exposure periods.

We conducted 3 preplanned sensitivity analyses and a post hoc analysis. First, we estimated the HR for prostate cancer mortality associated with postdiagnosis low-dose aspirin use, defined as at least 1 prescription filled within 1 year after prostate cancer diagnosis, compared with nonuse, defined as no prescriptions filled. Second, for the main analysis, we performed analyses using an exposure matrix combining pre- and postdiagnosis low-dose aspirin use, including a new-user analysis (postdiagnosis use only), prediagnosis use only, both pre- and postdiagnosis use, and no pre- or postdiagnosis use (reference). Third, for the main analysis, including the analysis stratified by Gleason score, and the secondary analyses, we accounted for competing risk for death from causes other than prostate cancer by using the subdistribution hazards model proposed by Fine and Gray (38). Finally, in a post hoc analysis, we examined the influence of missing values for education level, clinical stage, Gleason score, and primary prostate cancer therapy in the main and secondary analyses by using multiple imputation (39).

We tested the proportional hazards assumption with scaled Schoenfeld residuals and found no violations. All statistical analyses were performed with statistics software R, version 3.5.0 (R Foundation for Statistical Computing) (40). The study was approved by the Danish Data Protection Agency. According to Danish law, ethics committee approval was not required (41).

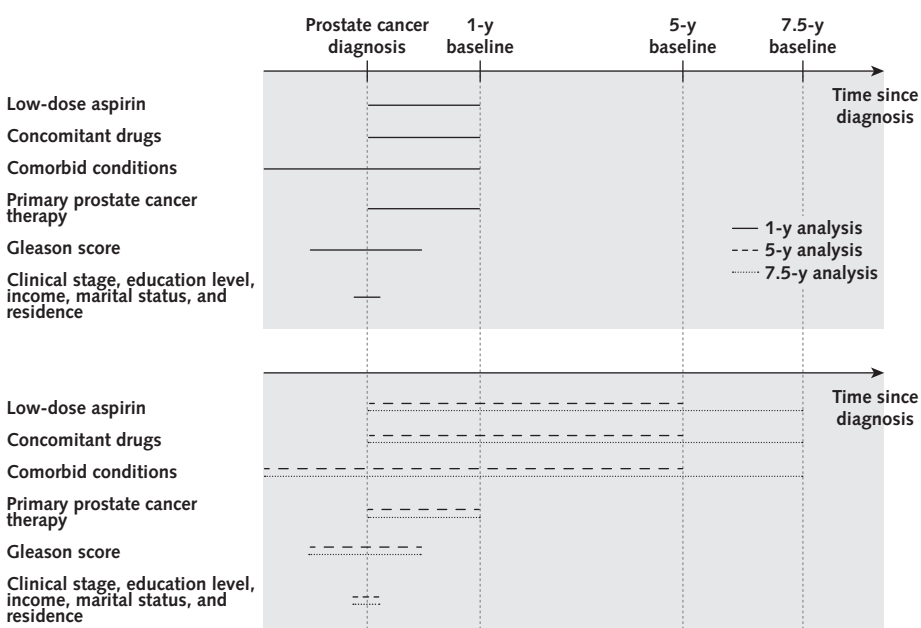
Role of the Funding Source

The funding source had no role in the design of the study; the collection, analysis, or interpretation of the data; or the decision to approve publication of the final manuscript.

RESULTS

Figure 1 shows the derivation of the final cohort of 29 136 patients with prostate cancer. During a median follow-up of 4.9 years (interquartile range, 3.1 to 7.2 years) from the 1-year baseline, 7633 patients died of prostate cancer and 5575 died of other causes. The median age at diagnosis was 70 years (interquartile

Figure 2. Overview of the assessment of postdiagnosis low-dose aspirin use and covariates.



Top. Main analysis with a fixed 1-y exposure period. **Bottom.** Secondary analyses with fixed 5- or 7.5-y exposure periods.

Table 1. Characteristics of Patients With Prostate Cancer, by Use of Low-Dose Aspirin Within 1 Year After Diagnosis, Denmark, 2000 to 2011

Characteristic	Low-Dose Aspirin Within 1 Year After Prostate Cancer Diagnosis	
	Use (*n* = 7163; 24.6%)*	Nonuse (*n* = 21 973; 75.4%)†
Mean follow-up (SD), *y*	4.7 (3.0)	5.4 (3.2)
Age at diagnosis, *n (%)*		
36–54 y	39 (0.5)	720 (3.3)
55–64 y	941 (13.1)	5641 (25.7)
65–74 y	3056 (42.7)	9477 (43.1)
75–84 y	2585 (36.1)	5264 (24.0)
≥85 y	542 (7.6)	871 (4.0)
Calendar period of diagnosis, *n (%)*		
2000–2003	1349 (18.8)	4750 (21.6)
2004–2007	2454 (34.3)	7179 (32.7)
2008–2011	3360 (46.9)	10 044 (45.7)
Clinical stage at diagnosis, *n (%)*		
Localized	3888 (54.3)	12 753 (58.0)
Nonlocalized	1122 (15.7)	3621 (16.5)
Unknown	2153 (30.1)	5599 (25.5)
Gleason score at diagnosis, *n (%)*‡		
≤6	1769 (24.7)	5731 (26.1)
7	2340 (32.7)	7479 (34.0)
≥8	2296 (32.1)	6365 (29.0)
Unknown	758 (10.6)	2398 (10.9)
Primary prostate cancer therapy, *n (%)*§		
Brachytherapy	316 (4.4)	1125 (5.1)
Radical prostatectomy	754 (10.5)	4548 (20.7)
Radiotherapy, <30 rounds	572 (8.0)	1724 (7.8)
Radiotherapy, ≥30 rounds	522 (7.3)	1629 (7.4)
Endocrine therapy	1646 (23.0)	3966 (18.0)
No therapy	3353 (46.8)	8981 (40.9)
Prediagnosis low-dose aspirin use, *n (%)*‖	6212 (86.7)	1708 (7.8)
Concomitant drug use, *n (%)**		
High-dose aspirin	<5 (<0.1)	9 (<0.1)
Nonaspirin NSAIDs	1178 (16.4)	3203 (14.6)
5α-Reductase inhibitors	264 (3.7)	578 (2.6)
α-Adrenoreceptor antagonists	1248 (17.4)	2847 (13.0)
Statins	3659 (51.1)	2967 (13.5)
Nonaspirin antithrombotic agents	1488 (20.8)	1922 (8.7)
Antihypertensives	5825 (81.3)	8842 (40.2)
Other cardiovascular drugs	1154 (16.1)	919 (4.2)
Insulin	301 (4.2)	280 (1.3)
Metformin	615 (8.6)	719 (3.3)
Other oral antidiabetic drugs	520 (7.3)	602 (2.7)
Psychotropic drugs	1964 (27.4)	4230 (19.3)
Proton-pump inhibitors	1158 (16.2)	2204 (10.0)
Antihistamines	199 (2.8)	443 (2.0)
Comorbid conditions, *n (%)*¶		
Ischemic heart disease	3207 (44.8)	1865 (8.5)
Congestive heart failure	850 (11.9)	595 (2.7)
Cerebrovascular disease	1717 (24.0)	1402 (6.4)
Atrial fibrillation or atrial flutter	1039 (14.5)	1414 (6.4)
Diabetes mellitus	939 (13.1)	1003 (4.6)
Chronic obstructive pulmonary disease	680 (9.5)	1154 (5.3)
Moderate to severe kidney disease	349 (4.9)	548 (2.5)
Moderate to severe liver disease	10 (0.1)	48 (0.2)

Continued on following page

Table 1–Continued

Characteristic	Low-Dose Aspirin Within 1 Year After Prostate Cancer Diagnosis	
	Use (*n* = 7163; 24.6%)*	Nonuse (*n* = 21 973; 75.4%)†
Education level at diagnosis, *n* (%)		
Basic/high school	2707 (37.8)	7346 (33.4)
Vocational	2696 (37.6)	8278 (37.7)
Higher education	1228 (17.1)	5145 (23.4)
Unknown	532 (7.4)	1204 (5.5)
Income at diagnosis, *n* (%)		
Low	3060 (42.7)	6564 (29.9)
Medium	2463 (34.4)	7447 (33.9)
High	1640 (22.9)	7962 (36.2)
Marital status at diagnosis, *n* (%)		
Married	5141 (71.8)	16 327 (74.3)
Widowed	1031 (14.4)	2243 (10.2)
Divorced	650 (9.1)	2103 (9.6)
Unknown	341 (4.8)	1300 (5.9)
Residence at diagnosis, *n* (%)		
Capital Region of Denmark	1943 (27.1)	6794 (30.9)
Central Denmark Region	1640 (22.9)	4315 (19.6)
North Denmark Region	788 (11.0)	2329 (10.6)
Region Zealand	1161 (16.2)	3767 (17.1)
Region of Southern Denmark	1631 (22.8)	4768 (21.7)

NSAID = nonsteroidal anti-inflammatory drug.
* ≥2 prescriptions filled within 1 y after prostate cancer diagnosis.
† <2 prescriptions filled within 1 y after prostate cancer diagnosis.
‡ Highest recorded Gleason score value preceding or within 6 mo after prostate cancer diagnosis.
§ Primary prostate cancer therapy recorded within 1 y after diagnosis.
‖ ≥2 prescriptions filled within 5 y before prostate cancer diagnosis.
¶ Comorbid conditions before 1 y after prostate cancer diagnosis.

range, 64 to 76 years). In the year after prostate cancer diagnosis, 24.6% of patients used low-dose aspirin (Table 1). Of these, 86.7% had also used low-dose aspirin before their diagnosis. Compared with nonusers, postdiagnosis low-dose aspirin users on average were older at diagnosis; had lower education and income levels; had a higher prevalence of cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and moderate to severe kidney disease; and had greater concomitant drug use. Moreover, a higher proportion of postdiagnosis low-dose aspirin users had endocrine therapy or no prostate cancer therapy in the year after the diagnosis; conversely, a lower proportion had radical prostatectomy.

In the main analysis, postdiagnosis low-dose aspirin use was associated with a multivariable-adjusted HR of 0.95 (95% CI, 0.89 to 1.01) for prostate cancer mortality (Table 2). For other-cause mortality, the minimally adjusted analysis revealed an HR of 1.48 (CI, 1.40 to 1.56), decreasing to 1.12 (CI, 1.05 to 1.20) in the multivariable-adjusted analysis.

We observed no substantial variation in HRs for prostate cancer mortality according to clinical stage or primary prostate cancer therapy (Table 2), whereas a reduction in prostate cancer mortality was seen among patients with low Gleason scores (≤6) (HR, 0.82 [CI, 0.70 to 0.97]). No major effect measure modification was observed with age at prostate cancer diagnosis or with postdiagnosis statin use, except for a reduced HR among patients younger than 55 years at diagnosis, which was based on small numbers (Appendix Table 2, available at Annals.org). After stratification by calendar period, the HRs for prostate cancer mortality were slightly reduced among patients who received their diagnosis during 2000 to 2003 and 2004 to 2007, but not among those whose cancer was diagnosed during 2008 to 2011.

In the secondary analyses, postdiagnosis low-dose aspirin use was associated with slightly reduced HRs for prostate cancer mortality in the 5-year (0.91 [CI, 0.83 to 1.01]) and 7.5-year (0.84 [CI, 0.72 to 0.97]) assessments (Table 3). We observed no apparent trends in duration of low-dose aspirin use or cumulative amount used in the 5-year analysis; however, in the 7.5-year analysis, HR reductions were greatest among patients with long-term use (≥1096 days; 0.79 [CI, 0.67 to 0.93]) or a high cumulative amount (≥1096 tablets; 0.77 [CI, 0.65 to 0.91]) of low-dose aspirin. The HRs did not vary substantially with tablet strength in either analysis.

The sensitivity analysis defining postdiagnosis low-dose aspirin use as at least 1 prescription filled within 1 year after prostate cancer diagnosis yielded an HR of 0.98 (CI, 0.93 to 1.04) for prostate cancer mortality. In analyses including prediagnosis low-dose aspirin use, we observed no substantial variation in HRs for prostate cancer mortality among prediagnosis users only, postdiagnosis users only (new users), and patients using low-dose aspirin both before and after their diagnosis

Table 2. Associations Between Postdiagnosis Low-Dose Aspirin Use and Prostate Cancer or Other-Cause Mortality, Overall and by Clinical Stage, Gleason Score, and Primary Prostate Cancer Therapy

Variable	Person-Years	Prostate Cancer Mortality*			Other-Cause Mortality*		
		Events, *n*	Minimally Adjusted HR (95% CI)†	Fully Adjusted HR (95% CI)‡	Events, *n*	Minimally Adjusted HR (95% CI)†	Fully Adjusted HR (95% CI)‡
Postdiagnosis low-dose aspirin use							
Nonuse§	118 322	5699	Reference	Reference	3646	Reference	Reference
Use‖	34 021	1934	0.97 (0.92–1.02)	0.95 (0.89–1.01)	1929	1.48 (1.40–1.56)	1.12 (1.05–1.20)
Clinical stage							
Localized¶	20 874/77 271	612/1720	1.03 (0.94–1.13)	0.96 (0.87–1.06)	1016/1898	1.56 (1.44–1.68)	1.16 (1.07–1.26)
Nonlocalized¶	3700/13 104	642/2269	0.95 (0.87–1.04)	0.92 (0.83–1.01)	275/563	1.41 (1.22–1.64)	1.10 (0.95–1.28)
Unknown¶	9447/27 947	680/1710	0.99 (0.90–1.08)	0.98 (0.89–1.08)	638/1185	1.39 (1.26–1.53)	1.07 (0.97–1.19)
P value**				0.56			0.46
Gleason score††							
≤6¶	10 373/37 563	222/641	0.91 (0.78–1.07)	0.82 (0.70–0.97)	528/1003	1.50 (1.34–1.66)	1.12 (1.00–1.25)
7¶	11 356/40 827	463/1323	1.06 (0.95–1.18)	0.94 (0.84–1.05)	553/1004	1.55 (1.40–1.72)	1.15 (1.03–1.29)
≥8¶	8583/26 754	953/2743	1.00 (0.93–1.08)	0.98 (0.90–1.06)	588/1057	1.48 (1.34–1.65)	1.17 (1.05–1.31)
Unknown¶	3708/13 179	296/992	0.87 (0.76–0.99)	0.87 (0.76–0.99)	260/582	1.38 (1.19–1.60)	1.05 (0.90–1.23)
P value**				0.16			0.68
Primary prostate cancer therapy‡‡							
Brachytherapy¶	1729/6573	18/38	1.67 (0.95–2.95)	1.81 (1.02–3.20)	46/81	2.06 (1.43–2.98)	1.62 (1.11–2.35)
Radical prostatectomy¶	4842/30 787	18/115	0.93 (0.57–1.54)	1.10 (0.67–1.83)	66/262	1.53 (1.17–2.01)	1.25 (0.95–1.65)
Radiotherapy, <30 rounds¶	2250/7226	227/804	0.96 (0.83–1.12)	0.91 (0.78–1.06)	136/267	1.50 (1.21–1.86)	1.12 (0.90–1.39)
Radiotherapy, ≥30 rounds¶	2944/10 109	40/144	0.86 (0.60–1.24)	1.13 (0.79–1.63)	66/168	1.38 (1.04–1.85)	1.14 (0.85–1.52)
Endocrine therapy¶	6007/14 944	707/1942	0.91 (0.83–0.99)	0.92 (0.84–1.01)	467/834	1.27 (1.14–1.43)	1.01 (0.89–1.13)
No therapy¶	16 250/48 682	924/2656	0.97 (0.90–1.05)	0.98 (0.91–1.07)	1148/2034	1.51 (1.41–1.63)	1.16 (1.07–1.26)
P value**				0.19			0.13

HR = hazard ratio.
* Excluding deaths in the year after prostate cancer diagnosis.
† Adjusted for age at diagnosis and calendar period of diagnosis.
‡ Additional adjustments for clinical stage; Gleason score; primary prostate cancer therapy; postdiagnosis use (≥2 prescriptions) of nonaspirin nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors, α-adrenoreceptor antagonists, statins, nonaspirin antithrombotic agents, antihypertensives, other cardiovascular drugs, insulin, metformin, other oral antidiabetic drugs, psychotropic drugs, proton-pump inhibitors, or antihistamines; medical history of ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation or atrial flutter, diabetes mellitus, chronic obstructive pulmonary disease, or moderate to severe kidney disease; education level; income; marital status; and residence.
§ <2 prescriptions filled within 1 y after prostate cancer diagnosis.
‖ ≥2 prescriptions filled within 1 y after prostate cancer diagnosis.
¶ Postdiagnosis low-dose aspirin use vs. nonuse within 1 y after prostate cancer diagnosis.
** Likelihood ratio test with overall model of postdiagnosis low-dose aspirin use vs. nonuse as the alternative model.
†† Highest recorded Gleason score value preceding or within 6 mo after prostate cancer diagnosis.
‡‡ Primary prostate cancer therapy recorded within 1 y after diagnosis.

(Appendix Table 3, available at Annals.org). No major variation in HRs was observed when continued use (before and after diagnosis) was stratified by cumulative amount used before diagnosis. In analyses accounting for competing risk from other causes of death, associations were similar to those in the main analysis, although the inverse association among patients with Gleason scores of 6 or lower was slightly attenuated. The inverse associations persisted in the 5- and 7.5-year analyses (results not shown). Analyses that used multiple imputation of missing values showed results similar to those of the original approach for both the main and secondary analyses (results not shown).

DISCUSSION

In our nationwide study of patients with prostate cancer in Denmark, we did not find convincing evidence of an overall protective effect of postdiagnosis low-dose aspirin use on prostate cancer mortality. However, an inverse association between postdiagnosis low-dose aspirin use and prostate cancer mortality was seen among patients with low Gleason scores (≤6). In contrast, we observed no substantial effect measure modification by clinical stage. Including prediagnosis use of low-dose aspirin did not substantially influence the associations. In secondary analyses with postdiagnosis exposure periods and conditioned survival of 5 and 7.5 years, we observed a slight reduction in prostate cancer mortality with postdiagnosis low-dose aspirin use in the 5-year analysis; a somewhat greater reduction was seen in the 7.5-year analysis, notably among patients with long-term or high cumulative use of low-dose aspirin. Postdiagnosis low-dose aspirin use was associated with slightly increased other-cause mortality in most analyses. However, the findings for prostate cancer mortality persisted in the analyses that accounted for competing risk from other causes of death.

Although some earlier studies supported an inverse association between postdiagnosis aspirin use and prostate cancer mortality (7, 9, 11, 15), others observed either

null results (8, 12–14) or, as in 1 study, increased mortality (10). Recently, researchers using data from the Physicians' Health Study in the United States reported that current postdiagnosis aspirin use was associated with 32% and 28% reductions in lethal prostate cancer (metastatic disease or prostate cancer death) and all-cause mortality, respectively, among 3462 patients with nonmetastatic disease (7). Likewise, another U.S. study reported that postdiagnosis aspirin use was associated with a 57% reduction in prostate cancer mortality among 5955 patients with localized disease who had radical prostatectomy or radiotherapy (15). In contrast, we did not observe an apparent reduction in prostate cancer mortality associated with postdiagnosis low-dose aspirin use during the first year after diagnosis. Although this finding is in line with several studies reporting null results (8, 12–14), our secondary analyses did reveal slightly reduced prostate cancer mortality associated with postdiagnosis low-dose aspirin use for exposure periods of 5 or 7.5 years after prostate cancer diagnosis. These results may indicate that a potential effect of low-dose aspirin use on prostate cancer mortality requires several years to appear. On the ba-

Table 3. Associations Between Postdiagnosis Low-Dose Aspirin Use and Prostate Cancer or Other-Cause Mortality, by Use Within 5 or 7.5 Years After Prostate Cancer Diagnosis

Postdiagnosis Low-Dose Aspirin Use	Patients, *n*	Person-Years	Prostate Cancer Mortality			Other-Cause Mortality		
			Events, *n*	Minimally Adjusted HR (95% CI)*	Fully Adjusted HR (95% CI)†	Events, *n*	Minimally Adjusted HR (95% CI)*	Fully Adjusted HR (95% CI)†
5-y analysis‡								
Nonuse§	11 714	60 716	1502	Reference	Reference	1264	Reference	Reference
Use‖	6311	21 045	960	0.99 (0.91–1.07)	0.91 (0.83–1.01)	1206	1.43 (1.32–1.55)	1.06 (0.96–1.16)
Duration of use								
1–365 d	622	2668	98	1.03 (0.84–1.26)	0.94 (0.76–1.16)	135	1.57 (1.31–1.87)	1.13 (0.94–1.36)
366–1095 d	1253	4566	190	0.99 (0.85–1.15)	0.89 (0.76–1.04)	237	1.39 (1.21–1.59)	1.04 (0.90–1.21)
≥1096 d	4436	13 812	672	0.98 (0.89–1.07)	0.92 (0.82–1.02)	834	1.42 (1.30–1.56)	1.05 (0.94–1.16)
P value¶					0.89			0.70
Total number of tablets								
1–365	557	2441	92	1.08 (0.88–1.34)	0.92 (0.74–1.14)	110	1.41 (1.16–1.71)	1.06 (0.87–1.30)
366–1095	1521	5488	227	0.97 (0.84–1.11)	0.92 (0.79–1.07)	292	1.43 (1.26–1.62)	1.08 (0.94–1.23)
≥1096	4233	13 117	641	0.98 (0.89–1.08)	0.91 (0.82–1.02)	804	1.44 (1.31–1.57)	1.05 (0.94–1.16)
P value¶					0.99			0.92
Tablet strength								
75–100 mg only	4807	15 307	637	0.98 (0.89–1.08)	0.90 (0.81–1.00)	803	1.37 (1.26–1.50)	1.03 (0.93–1.14)
150 mg only	794	3098	162	0.97 (0.82–1.14)	0.91 (0.77–1.08)	200	1.48 (1.28–1.72)	1.13 (0.96–1.32)
Mixed use	710	2641	161	1.03 (0.87–1.21)	0.99 (0.83–1.18)	203	1.66 (1.43–1.92)	1.09 (0.93–1.28)
P value¶					0.57			0.51
7.5-y analysis**								
Nonuse§	5440	27 961	578	Reference	Reference	542	Reference	Reference
Use‖	3523	10 307	453	0.91 (0.81–1.04)	0.84 (0.72–0.97)	615	1.43 (1.27–1.60)	1.08 (0.93–1.24)
Duration of use								
1–365 d	302	1239	49	1.26 (0.94–1.68)	1.11 (0.82–1.50)	40	1.04 (0.75–1.43)	0.82 (0.59–1.15)
366–1095 d	529	1727	71	1.07 (0.83–1.37)	0.87 (0.67–1.14)	104	1.73 (1.40–2.14)	1.30 (1.04–1.62)
≥1096 d	2692	7340	333	0.85 (0.74–0.98)	0.79 (0.67–0.93)	471	1.42 (1.25–1.60)	1.06 (0.92–1.24)
P value¶					0.10			0.04
Total number of tablets								
1–365	298	1249	44	1.15 (0.84–1.56)	0.96 (0.70–1.31)	42	1.13 (0.83–1.55)	0.92 (0.67–1.27)
366–1095	655	2132	98	1.17 (0.94–1.45)	1.03 (0.82–1.30)	118	1.53 (1.26–1.87)	1.20 (0.97–1.48)
≥1096	2570	6926	311	0.83 (0.72–0.96)	0.77 (0.65–0.91)	455	1.43 (1.26–1.63)	1.06 (0.91–1.24)
P value¶					0.03			0.30
Tablet strength								
75–100 mg only	2629	7426	291	0.89 (0.77–1.02)	0.81 (0.68–0.95)	415	1.39 (1.22–1.58)	1.06 (0.91–1.23)
150 mg only	357	1201	59	0.88 (0.67–1.15)	0.85 (0.64–1.13)	74	1.40 (1.10–1.79)	1.10 (0.85–1.43)
Mixed use	537	1680	103	1.03 (0.83–1.27)	0.92 (0.73–1.17)	126	1.57 (1.29–1.91)	1.12 (0.90–1.39)
P value¶					0.52			0.86

HR = hazard ratio.
* Adjusted for age at diagnosis and calendar period of diagnosis.
† Additional adjustments for clinical stage; Gleason score; primary prostate cancer therapy; postdiagnosis use (≥2 prescriptions) of nonaspirin nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors, α-adrenoreceptor antagonists, statins, nonaspirin antithrombotic agents, antihypertensives, other cardiovascular drugs, insulin, metformin, other oral antidiabetic drugs, psychotropic drugs, proton-pump inhibitors, or antihistamines; medical history of ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation or atrial flutter, diabetes mellitus, chronic obstructive pulmonary disease, or moderate to severe kidney disease; education level; income; marital status; and residence.
‡ Follow-up began 5 y after prostate cancer diagnosis. Postdiagnosis drug use and comorbidity were assessed up to this 5-y baseline. Deaths within 5 y after prostate cancer diagnosis were excluded.
§ <2 prescriptions filled after prostate cancer diagnosis.
‖ ≥2 prescriptions filled after prostate cancer diagnosis.
¶ Likelihood ratio test with overall model of postdiagnosis low-dose aspirin use vs. nonuse as the alternative model.
** Follow-up began 7.5 y after prostate cancer diagnosis. Postdiagnosis drug use and comorbidity were assessed up to this 7.5-y baseline. Deaths within 7.5 y after prostate cancer diagnosis were excluded.

sis of secondary analysis of cardiovascular disease prevention trials, Rothwell and colleagues (5) suggested that aspirin use may have a delayed effect on cancer mortality. If so, it might explain our finding that patients who received their diagnosis late in the study period did not have a decrease in prostate cancer mortality associated with postdiagnosis low-dose aspirin use.

In a study based on data from the Finnish Prostate Cancer Screening Trial, postdiagnosis aspirin use was associated with a statistically nonsignificant reduction in prostate cancer mortality, and the decrease tended to be greater with longer use but not with a higher cumulative amount of aspirin (9). In contrast, no duration–response trend was observed in the Physicians' Health Study (7), and effects of cumulative aspirin doses were not evaluated in the U.S. studies (7, 15). We found a slightly larger reduction in prostate cancer mortality among patients with long-term or high cumulative low-dose aspirin use in the 7.5-year analysis. However, no apparent trends according to the duration of low-dose aspirin use or the cumulative amount used were seen in the 5-year analysis. The reason for these differing results remains elusive. Additional studies are needed to determine whether a specific timing or duration of postdiagnosis low-dose aspirin use is necessary to reduce prostate cancer mortality.

Two U.S. studies (11, 15) reported an improved prostate cancer prognosis associated with postdiagnosis aspirin use notably among patients with high-risk disease. In contrast, we observed a reduction in prostate cancer mortality among patients with low Gleason scores at diagnosis. These apparently conflicting results may be explained partly by differences in the study populations. The U.S. studies (11, 15) included only patients with nonmetastatic prostate cancer, who make up the vast majority of patients with prostate cancer in the United States because of broad implementation of prostate-specific antigen screening (42). In contrast, Denmark had no general screening program during the study period; thus, the stage distributions were markedly different between patients in the United States and those in Denmark (43). In pooled analyses of trials of daily aspirin use for cardioprotection, Rothwell and colleagues (4) observed the greatest reduction in adenocarcinoma mortality among patients without metastases at diagnosis. This finding is compatible with the hypothesis that aspirin might reduce the risk for metastatic spread by platelet inactivation (24). Thus, the influence of aspirin use may depend on the extent of disease at drug initiation, which may explain our findings regarding Gleason scores, because tumors with low Gleason scores generally have not metastasized at diagnosis. Contrary to this explanation, we observed no substantial variation based on clinical stage or primary prostate cancer therapy. The influence of therapy and clinical stage on the associations warrants additional studies with more detailed information on therapeutic measures for prostate cancer than was available in our registry-based study.

Our study had several strengths. The large study population ensured high statistical precision. The comprehensive registry data on prostate cancer diagnosis, clinical measures, drug use, comorbidity, socioeconomic factors, and cause of death allowed detailed analyses of low-dose aspirin use and prostate cancer and other-cause mortality, with complete follow-up and broad adjustment for prognostic factors. The nationwide registry approach minimized selection bias and misclassification. The histologic verification of prostate cancer provided high case validity.

Our study also had some limitations. Confounding by indication was a potential challenge, because low-dose aspirin is used almost exclusively for cardioprotection, and cardiovascular mortality thus constituted an event competing with prostate cancer death. Therefore, patients who used low-dose aspirin after their diagnosis might have been prone to a higher risk for death from cardiovascular disease than from prostate cancer. In our minimally adjusted analyses, postdiagnosis low-dose aspirin use was indeed associated with increased other-cause mortality, which was attenuated after multivariable adjustment for the available prognostic factors. When we accounted for competing risk, the results for prostate cancer mortality were consistent with those of the main, 5-year, and 7.5-year analyses, although the inverse association observed among patients with low Gleason scores was slightly attenuated.

In addition, our results might have been affected by residual confounding due to misclassified or unmeasured prognostic factors. Of note, data on lifestyle factors were not available in the Danish registries. High body mass index and smoking have been associated with an impaired prostate cancer prognosis (44, 45) and increased risk for cardiovascular disease (46). Lack of information on these factors may have confounded our results but, if so, probably attenuated the associations. Another concern was patients with cancer of unknown clinical stage (26.6%). In an earlier study, we found that unknown stage—as defined by the tumor, node, metastasis (TNM) classification system (47)—was associated with advanced age and comorbidity (48). Although we adjusted for age, Gleason score, and comorbid conditions, we cannot exclude a potential imbalance in prognostic factors due to the missing information on clinical stage. Finally, information on Gleason scores and nonsurgical prostate cancer therapy was incomplete in the first part of the study period; however, we do not believe these missing data are likely to be associated with postdiagnosis low-dose aspirin use. Furthermore, the results of the analyses using multiple imputation of missing values were similar to those of the main and secondary analyses.

Another limitation was potential exposure misclassification due to a lack of information on over-the-counter aspirin use. Most low-dose aspirin is obtained by prescription in Denmark (36), and any misclassification would most likely be nondifferential, leading to attenuation of the associations. In contrast, high-dose aspirin is primarily purchased over the counter; however, preparations of high-dose aspirin are used predominantly for short-term treatment of transient pain (36) and, as such, probably did not influence our results ma-

terially. In addition, we used prescription data to estimate low-dose aspirin use; therefore, nonadherence may have resulted in some misclassification of long-term aspirin use. However, in a Danish validation study, the correspondence between the date of general practitioner–reported use of low-dose aspirin and the timing of prescription dispensing at pharmacies (within ±90 days) was high (93%) (49). Moreover, nonadherence to low-dose aspirin prescriptions probably would have driven the associations toward unity.

Finally, potential misclassification of cause of death may have influenced our results. However, in a study including a small sample of patients with prostate cancer in Denmark (50), we compared causes of death reported in hospital records with information in the Danish Registry of Causes of Death (30) and found good correspondence (7% misclassification).

In conclusion, our study did not support an overall effect of postdiagnosis low-dose aspirin use on prostate cancer mortality. However, our results suggest that low-dose aspirin use might be inversely associated with prostate cancer mortality after 5 years from cancer diagnosis.

From Danish Cancer Society Research Center, Copenhagen, Denmark (C.S., C.D.); Aarhus University Hospital, Aarhus, Denmark (M.B., M.N., H.T.S.); Copenhagen University Hospital, Copenhagen, Denmark (K.B.); Danish Cancer Society Research Center and Copenhagen University Hospital, Copenhagen, Denmark (S.B.L.); Danish Cancer Society Research Center, Copenhagen, Denmark and Zealand University Hospital, Næstved, Denmark (S.O.D.); University of Southern Denmark, Odense, Denmark (A.P., J.H.); and Danish Cancer Society Research Center and University of Copenhagen, Copenhagen, Denmark, and Aarhus University Hospital, Aarhus, Denmark (S.F.).

Grant Support: By grant R79-A5286 from the Danish Cancer Society.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-3085.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available to interested readers by contacting Dr. Dehlendorff (e-mail, chrdehl@cancer.dk). *Data set:* Not available.

Corresponding Author: Charlotte Skriver, MSc, Danish Cancer Society Research Center, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark; e-mail, skriver@cancer.dk.

Current author addresses and author contributions are available at Annals.org.

References

1. **Elwood PC, Pickering JE, Morgan G, Galante J, Weightman AL, Morris D, et al.** Systematic review update of observational studies further supports aspirin role in cancer treatment: time to share evidence and decision-making with patients? PLoS One. 2018;13: e0203957. [PMID: 30252883] doi:10.1371/journal.pone.0203957

2. **Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al.** Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol. 2015;26:47-57. [PMID: 25096604] doi:10.1093/annonc/mdu225

3. **Algra AM, Rothwell PM.** Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol. 2012;13:518-27. [PMID: 22440112] doi:10.1016/S1470-2045(12)70112-2

4. **Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z.** Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet. 2012;379:1591-601. [PMID: 22440947] doi:10.1016/S0140-6736(12)60209-8

5. **Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW.** Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377:31-41. [PMID: 21144578] doi:10.1016/S0140-6736(10)62110-1

6. **Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DS, et al.** Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:814-25. [PMID: 27064482] doi:10.7326/M15-2117

7. **Downer MK, Allard CB, Preston MA, Gaziano JM, Stampfer MJ, Mucci LA, et al.** Regular aspirin use and the risk of lethal prostate cancer in the Physicians' Health Study. Eur Urol. 2017;72:821-827. [PMID: 28189429] doi:10.1016/j.eururo.2017.01.044

8. **Zhou CK, Daugherty SE, Liao LM, Freedman ND, Abnet CC, Pfeiffer R, et al.** Do aspirin and other NSAIDs confer a survival benefit in men diagnosed with prostate cancer? A pooled analysis of NIH-AARP and PLCO cohorts. Cancer Prev Res (Phila). 2017;10:410-420. [PMID: 28507039] doi:10.1158/1940-6207.CAPR-17-0033

9. **Veitonmäki T, Murtola TJ, Määttänen L, Taari K, Stenman UH, Tammela TL, et al.** Use of non-steroidal anti-inflammatory drugs and prostate cancer survival in the Finnish Prostate Cancer Screening Trial. Prostate. 2015;75:1394-402. [PMID: 26073992] doi:10.1002/pros.23020

10. **Assayag J, Pollak MN, Azoulay L.** The use of aspirin and the risk of mortality in patients with prostate cancer. J Urol. 2015;193:1220-5. [PMID: 25463991] doi:10.1016/j.juro.2014.11.018

11. **Jacobs EJ, Newton CC, Stevens VL, Campbell PT, Freedland SJ, Gapstur SM.** Daily aspirin use and prostate cancer-specific mortality in a large cohort of men with nonmetastatic prostate cancer. J Clin Oncol. 2014;32:3716-22. [PMID: 25332245] doi:10.1200/JCO.2013.54.8875

12. **Caon J, Paquette M, Hamm J, Pickles T.** Does statin or ASA affect survival when prostate cancer is treated with external beam radiation therapy? Prostate Cancer. 2014;2014:184297. [PMID: 24729876] doi:10.1155/2014/184297

13. **Cardwell CR, Flahavan EM, Hughes CM, Coleman HG, O'Sullivan JM, Powe DG, et al.** Low-dose aspirin and survival in men with prostate cancer: a study using the UK Clinical Practice Research Datalink. Cancer Causes Control. 2014;25:33-43. [PMID: 24310109] doi:10.1007/s10552-013-0306-x

14. **Dhillon PK, Kenfield SA, Stampfer MJ, Giovannucci EL, Chan JM.** Aspirin use after a prostate cancer diagnosis and cancer survival in a prospective cohort. Cancer Prev Res (Phila). 2012;5:1223-8. [PMID: 22961777] doi:10.1158/1940-6207.CAPR-12-0171

15. **Choe KS, Cowan JE, Chan JM, Carroll PR, D'Amico AV, Liauw SL.** Aspirin use and the risk of prostate cancer mortality in men treated with prostatectomy or radiotherapy. J Clin Oncol. 2012;30:3540-4. [PMID: 22927523] doi:10.1200/JCO.2011.41.0308

16. **He Y, Huang H, Farischon C, Li D, Du Z, Zhang K, et al.** Combined effects of atorvastatin and aspirin on growth and apoptosis in human prostate cancer cells. Oncol Rep. 2017;37:953-960. [PMID: 28075470] doi:10.3892/or.2017.5353

17. **Murtola TJ, Pennanen P, Syvälä H, Bläuer M, Ylikomi T, Tammela TL.** Effects of simvastatin, acetylsalicylic acid, and rosiglitazone on

proliferation of normal and cancerous prostate epithelial cells at therapeutic concentrations. Prostate. 2009;69:1017-23. [PMID: 19301305] doi:10.1002/pros.20951
18. **Shi C, Zhang N, Feng Y, Cao J, Chen X, Liu B.** Aspirin inhibits IKK-ß-mediated prostate cancer cell invasion by targeting matrix metalloproteinase-9 and urokinase-type plasminogen activator. Cell Physiol Biochem. 2017;41:1313-1324. [PMID: 28278500] doi:10.1159/000464434
19. **Lloyd FP Jr, Slivova V, Valachovicova T, Sliva D.** Aspirin inhibits highly invasive prostate cancer cells. Int J Oncol. 2003;23:1277-83. [PMID: 14532966] doi:10.3892/ijo.23.5.1277
20. **Thun MJ, Jacobs EJ, Patrono C.** The role of aspirin in cancer prevention. Nat Rev Clin Oncol. 2012;9:259-67. [PMID: 22473097] doi:10.1038/nrclinonc.2011.199
21. **Drew DA, Cao Y, Chan AT.** Aspirin and colorectal cancer: the promise of precision chemoprevention. Nat Rev Cancer. 2016;16:173-86. [PMID: 26868177] doi:10.1038/nrc.2016.4
22. **Gupta S, Srivastava M, Ahmad N, Bostwick DG, Mukhtar H.** Overexpression of cyclooxygenase-2 in human prostate adenocarcinoma. Prostate. 2000;42:73-8. [PMID: 10579801] doi:10.1002/(SICI)1097-0045(20000101)42:1<73::AID-PROS9>3.0.CO;2-G
23. **Shao N, Feng N, Wang Y, Mi Y, Li T, Hua L.** Systematic review and meta-analysis of COX-2 expression and polymorphisms in prostate cancer. Mol Biol Rep. 2012;39:10997-1004. [PMID: 23053989] doi:10.1007/s11033-012-2001-5
24. **Contursi A, Sacco A, Grande R, Dovizio M, Patrignani P.** Platelets as crucial partners for tumor metastasis: from mechanistic aspects to pharmacological targeting. Cell Mol Life Sci. 2017;74:3491-3507. [PMID: 28488110] doi:10.1007/s00018-017-2536-7
25. **Schmidt M, Pedersen L, Sørensen HT.** The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29:541-9. [PMID: 24965263] doi:10.1007/s10654-014-9930-3
26. **Gjerstorff ML.** The Danish Cancer Registry. Scand J Public Health. 2011;39:42-5. [PMID: 21775350] doi:10.1177/1403494810393562
27. **Bjerregaard B, Larsen OB.** The Danish Pathology Register. Scand J Public Health. 2011;39:72-4. [PMID: 21775357] doi:10.1177/1403494810393563
28. **Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M.** Data resource profile: the Danish National Prescription Registry. Int J Epidemiol. 2017;46:798-798f. [PMID: 27789670] doi:10.1093/ije/dyw213
29. **Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT.** The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90. [PMID: 26604824] doi:10.2147/CLEP.S91125
30. **Helweg-Larsen K.** The Danish Register of Causes of Death. Scand J Public Health. 2011;39:26-9. [PMID: 21775346] doi:10.1177/1403494811399958
31. **Jensen VM, Rasmussen AW.** Danish Education Registers. Scand J Public Health. 2011;39:91-4. [PMID: 21775362] doi:10.1177/1403494810394715
32. **Baadsgaard M, Quitzau J.** Danish registers on personal income and transfer payments. Scand J Public Health. 2011;39:103-5. [PMID: 21775365] doi:10.1177/1403494811405098
33. **Skriver C, Dehlendorff C, Borre M, Brasso K, Sørensen HT, Hallas J, et al.** Low-dose aspirin or other nonsteroidal anti-inflammatory drug use and prostate cancer risk: a nationwide study. Cancer Causes Control. 2016;27:1067-79. [PMID: 27503490] doi:10.1007/s10552-016-0785-7
34. **Nguyen-Nielsen M, Borre M.** Diagnostic and therapeutic strategies for prostate cancer. Semin Nucl Med. 2016;46:484-490. [PMID: 27825428] doi:10.1053/j.semnuclmed.2016.07.002
35. **Danish Urologic Cancer Group (DUCG).** DUCG's nationale retningslinjer for diagnostik og behandling af prostatacancer [National guidelines for diagnostic and therapeutic strategies for prostate cancer]. Accessed at http://ducg.dk/fileadmin/www.ducg.dk/Prostatacancer/Kl._retningslinjer/2017/DUCGs_nationale_retningslinjer_for_diagnostik_og_behandling_af_prostatacancer_2016.pdf on 22 November 2018.
36. **Schmidt M, Hallas J, Friis S.** Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999-2012. Clin Epidemiol. 2014;6:155-68. [PMID: 24872722] doi:10.2147/CLEP.S59156
37. **Schmidt M, Hallas J, Laursen M, Friis S.** Data resource profile: Danish online drug use statistics (MEDSTAT). Int J Epidemiol. 2016;45:1401-1402g. [PMID: 27892409] doi:10.1093/ije/dyw116
38. **Fine JP, Gray RJ.** A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509. doi:10.1080/01621459.1999.10474144
39. **Bartlett JW, Seaman SR, White IR, Carpenter JR; Alzheimer's Disease Neuroimaging Initiative.** Multiple imputation of covariates by fully conditional specification: accommodating the substantive model. Stat Methods Med Res. 2015;24:462-87. [PMID: 24525487] doi:10.1177/0962280214521348
40. **R Core Team.** R: a language and environment for statistical computing. Version 3.5.0 [software]. Accessed at http://www.R-project.org/ on 29 January 2019.
41. **Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H.** Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011;39:12-6. [PMID: 21898916] doi:10.1177/1403494811399956
42. **Brawley OW.** Trends in prostate cancer in the United States. J Natl Cancer Inst Monogr. 2012;2012:152-6. [PMID: 23271766] doi:10.1093/jncimonographs/lgs035
43. **Outzen M, Brasso K, Martinussen N, Christensen J, Tjønneland A, Friis S, et al.** Prostate cancer in Denmark 1978-2009—trends in incidence and mortality. Acta Oncol. 2013;52:831-6. [PMID: 22809166] doi:10.3109/0284186X.2012.702922
44. **Zhong S, Yan X, Wu Y, Zhang X, Chen L, Tang J, et al.** Body mass index and mortality in prostate cancer patients: a dose-response meta-analysis. Prostate Cancer Prostatic Dis. 2016;19:122-31. [PMID: 26754262] doi:10.1038/pcan.2015.64
45. **Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E.** Smoking and prostate cancer survival and recurrence. JAMA. 2011;305:2548-55. [PMID: 21693743] doi:10.1001/jama.2011.879
46. **Koene RJ, Prizment AE, Blaes A, Konety SH.** Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133:1104-14. [PMID: 26976915] doi:10.1161/CIRCULATIONAHA.115.020406
47. **Sobin LH, Gospodarowicz MK, Wittekind C, eds.** TNM Classification of Malignant Tumours. 7th ed. Hoboken, NJ: Wiley-Blackwell; 2009.
48. **Nguyen-Nielsen M, Frøslev T, Friis S, Borre M, Harving N, Søgaard M.** Completeness of prostate cancer staging in the Danish Cancer Registry, 2004-2009. Clin Epidemiol. 2012;4 Suppl 2:17-23. [PMID: 22936853] doi:10.2147/CLEP.S32004
49. **Johannesdottir SA, Mægbæk ML, Hansen JG, Lash TL, Pedersen L, Ehrenstein V.** Correspondence between general practitioner-reported medication use and timing of prescription dispensation. Clin Epidemiol. 2012;4:13-8. [PMID: 22291479] doi:10.2147/CLEP.S26958
50. **Larsen SB, Brasso K, Christensen J, Johansen C, Tjønneland A, Friis S, et al.** Socioeconomic position and mortality among patients with prostate cancer: influence of mediating factors. Acta Oncol. 2017;56:563-568. [PMID: 27911129] doi:10.1080/0284186X.2016.1260771

Current Author Addresses: Ms. Skriver and Drs. Dehlendorff, Dalton, and Friis: Danish Cancer Society Research Center, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.
Dr. Borre: Department of Urology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark.
Drs. Brasso and Larsen: Copenhagen Prostate Cancer Center, Department of Urology, Copenhagen University Hospital, Ole Maaløes Vej 24, DK-2200 Copenhagen N, Denmark.
Drs. Nørgaard and Sørensen: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43–45, DK-8200 Aarhus N, Denmark.
Drs. Pottegård and Hallas: Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, J. B. Winsløws Vej 19, DK-5000 Odense C, Denmark.

Author Contributions: Conception and design: C. Skriver, C. Dehlendorff, M. Borre, K. Brasso, S.O. Dalton, A. Pottegård, J. Hallas, H.T. Sørensen, S. Friis.
Analysis and interpretation of the data: C. Skriver, C. Dehlendorff, M. Borre, K. Brasso, S.B. Larsen, S.O. Dalton, M. Nørgaard, A. Pottegård, J. Hallas, S. Friis.
Drafting of the article: C. Skriver, K. Brasso, S.B. Larsen, S.O. Dalton, S Friis.
Critical revision for important intellectual content: C. Dehlendorff, M. Borre, S.B. Larsen, S.O. Dalton, M. Nørgaard, A. Pottegård, J. Hallas, H.T. Sørensen, S. Friis.
Final approval of the article: C. Skriver, C. Dehlendorff, M. Borre, K. Brasso, S.B. Larsen, S.O. Dalton, M. Nørgaard, A. Pottegård, J. Hallas, H.T. Sørensen, S. Friis.
Statistical expertise: C. Dehlendorff, A. Pottegård.
Obtaining of funding: C. Skriver, S. Friis.
Collection and assembly of data: C. Dehlendorff, C. Skriver, S. Friis.

Appendix: Data Sources, Identification of Covariates, and Additional Results

Data Sources

The Danish National Health Service provides tax-supported health care to all residents, guaranteeing uniform access to general practitioners and hospitals, and partial reimbursement for prescribed medications (25). Information on demographic and health-related issues is available in registries covering the entire Danish population (41). Unambiguous linkage of individual-level data is secured by use of the unique civil registration number assigned to all Danish residents by the Danish Civil Registration System (25).

The Danish Cancer Registry (26) contains accurate and nearly complete information on incident cancer in Denmark since 1943. Cancer diagnoses are recorded according to the International Classification of Diseases, 10th Revision (ICD-10), and the International Classification of Diseases for Oncology, Third Edition, is used to code histologic details. The cancer data also include details on clinical stage, recorded as localized, regional, distant, or unknown, until 2003 and according to the TNM system from 2004 to the present (26, 47).

The Danish Pathology Registry (27) contains information on all cytologic and pathologic examinations in Denmark and became nationwide in 1999. Pathologic diagnoses are coded according to a Danish version of the Systematized Nomenclature of Medicine, including information on Gleason scores for prostate specimens.

The Danish Registry of Causes of Death (30) has recorded the dates and specific causes of death for the entire Danish population since 1875. Causes of death have been classified according to the ICD-10 since 1994.

The Danish National Prescription Registry (28) holds detailed information on all drug prescriptions dispensed at Danish pharmacies since 1995. Each prescription record includes the date of dispensing, type of drug according to the Anatomical Therapeutic Chemical classification system (51), and quantity of drug dispensed. The drug quantity is given as the number of units (for example, tablets), strength, and number of defined daily doses (average maintenance dose per day) (51). Dosing schedules and indications are not recorded, and individual-level information on drug use in the hospital setting is not available.

The Danish National Patient Registry (29) has recorded all nonpsychiatric hospital admissions since 1977 and all outpatient contacts and psychiatric admissions since 1995. Each record includes information on the date of admission, discharge, or contact; diagnoses; and associated diagnostic procedures, surgical procedures, or medical therapy. Diagnoses were recorded according to the ICD-8 until 1993 and the ICD-10 from 1994 to the present. Surgical or diagnostic procedures have been coded according to a Danish version of the Nordic Medico-Statistical Committee classification since 1996 (29).

Statistics Denmark is a governmental institution that manages registries with information on a large variety of characteristics of all Danish residents, including socioeconomic parameters (41). The Danish Population Education Registry (31) contains annually updated information on the highest education level achieved. The Danish registries on personal income and transfer payments (32) hold data on income and allowances of the Danish population since 1976.

The Danish Civil Registration System (25) has maintained continuously updated information on addresses, marital status, migration, and deaths for all Danish residents since 1968.

Data on Covariates

Covariates were selected a priori on the basis of current evidence on prognostic factors for prostate cancer (50, 52–55) and data available from the nationwide registries (25, 28, 29, 31, 32).

From the Danish National Prescription Registry (28), we retrieved all prescriptions for high-dose aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors, α-adrenoreceptor antagonists, statins, nonaspirin antithrombotic agents, antihypertensives, other cardiovascular drugs, insulin, metformin, other oral antidiabetic drugs, psychotropic drugs, proton-pump inhibitors, and antihistamines. We defined postdiagnosis use of concomitant drugs as 2 or more prescriptions to reduce the influence of potential nonadherence.

From the Danish National Patient Registry (29), we retrieved information on comorbid conditions before and after the prostate cancer diagnosis, including diagnoses of ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation or atrial flutter, diabetes mellitus, chronic obstructive pulmonary disease, moderate to severe kidney disease, and moderate to severe liver disease.

We obtained information on highest education level achieved and gross earnings at the time of the prostate cancer diagnosis from the education and income registries within Statistics Denmark (31, 32). Education level was categorized as basic/high school, vocational, higher education (short, medium, or long), or unknown; income was categorized as low, medium, or high, according to approximate tertiles of the gross earnings of all patients.

Finally, from the Danish Civil Registration System (25), we retrieved information on marital status (married, widowed, divorced, or unknown) and residence (5 regions) at the time of prostate cancer diagnosis.

Web-Only References

51. **WHO Collaborating Centre for Drug Statistics Methodology.** Guidelines for ATC classification and DDD assignment 2018. Accessed at www.whocc.no on 23 November 2018.

52. **Litwin MS, Tan HJ.** The diagnosis and treatment of prostate cancer: a review. JAMA. 2017;317:2532-2542. [PMID: 28655021] doi:10.1001/jama.2017.7248

53. **Raval AD, Thakker D, Negi H, Vyas A, Kaur H, Salkini MW.** Association between statins and clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2016;19:151-62. [PMID: 26782711] doi:10.1038/pcan.2015.58

54. **Murtola TJ, Karppa EK, Taari K, Talala K, Tammela TL, Auvinen A.** 5-Alpha reductase inhibitor use and prostate cancer survival in the Finnish Prostate Cancer Screening Trial. Int J Cancer. 2016;138:2820-8. [PMID: 26804670] doi:10.1002/ijc.30017

55. **Nguyen-Nielsen M, Nørgaard M, Jacobsen JB, Borre M, Thomsen RW, Søgaard M.** Comorbidity and survival of Danish prostate cancer patients from 2000-2011: a population-based cohort study. Clin Epidemiol. 2013;5:47-55. [PMID: 24227923] doi:10.2147/CLEP.S47153

Appendix Table 1. List of Codes for Prostate Cancer Diagnosis, Prostate Cancer Stage, Drug Use, Selected Chronic Diseases (Comorbid Conditions), and Prostate Cancer Therapy

Danish Cancer Registry

Prostate Cancer Diagnosis and Morphology	Codes
ICD-10	C61.9
ICD-O-3	M81403—adenocarcinoma
Stage	**Codes**
Localized: classification until 2003	Localized
Localized: TNM codes, after 2003	T1–4,x; N0; M0 T1–2; N0,x; M0,x
Nonlocalized: classification until 2003	Regional, distant
Nonlocalized: TNM codes, after 2003	T1–4,x; N1–3; M0,x T1–4,x; N0–3,x; M1

Danish National Prescription Registry

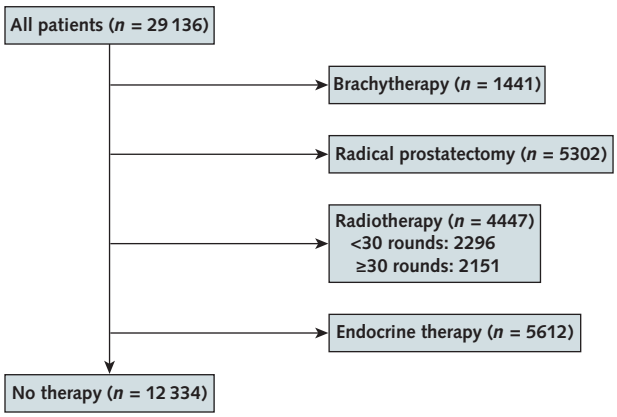
Drugs	Anatomical Therapeutic Chemical Classification Codes
Aspirin—low-dose	B01AC06 (75 mg, 100 mg, or 150 mg per tablet), N02BA01 (100 mg or 150 mg per tablet)
Other drugs (covariates)	
Aspirin—high-dose	N02BA01 (500 mg per tablet), N02BA51 (500 mg per tablet)
Nonaspirin nonsteroidal anti-inflammatory drugs	M01A, excluding M01AX
5α-Reductase inhibitors	D11AX10, G04CB01, G04CB02
α-Adrenoreceptor antagonists	G04CA (excl. G04CA52*)
Statins	C10AA, C10BA
Nonaspirin antithrombotic agents	B01AA, B01AB, B01AC04, B01AC07, B01AC22, B01AC24, B01AC30, B01AE, B01AF
Antihypertensives	C02, C03, C07, C08, C09
Other cardiovascular drugs	C01
Insulin	A10A
Metformin	A10BA02, A10BD (excl. A10BD04, A10BD09)
Other oral antidiabetic drugs	A10BB, A10BC, A10BD04, A10BD09, A10BF, A10BG, A10BH, A10BX
Psychotropic drugs	N05, N06A
Proton-pump inhibitors	A02BC
Antihistamines	R06A

Danish National Patient Registry

Chronic Diseases (Comorbid Conditions)	Codes
ICD-8 (1977–1993)	
Ischemic heart disease	410–414
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49
Cerebrovascular disease	430–438
Atrial fibrillation or atrial flutter	427.93, 427.94
Diabetes mellitus	249, 250
Chronic obstructive pulmonary disease	491–492
Moderate to severe kidney disease	403, 404, 580–583, 584, 590.09, 593.19, 753.10–753.19, 792
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09
ICD-10 (1994–present)	
Ischemic heart disease	I20–I25
Congestive heart failure	I50, I11.0, I13.0, I13.2
Cerebrovascular disease	I60–I69, G45, G46
Atrial fibrillation or atrial flutter	I48
Diabetes mellitus	E10–E14
Chronic obstructive pulmonary disease	J41–J44
Moderate to severe kidney disease	I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61
Moderate to severe liver disease	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Prostate Cancer Therapy	**SKS Codes†**
Brachytherapy	BWGE, KKEV30
Radical prostatectomy	KKEC
External radiotherapy	BWGC
Endocrine therapy	
Hormonal and antihormonal antineoplastic treatment	BWHC
Bilateral orchiectomy	KKFC10, KKFC13
Chemotherapy	BWHA

ICD = International Classification of Diseases; ICD-O = International Classification of Diseases for Oncology; TNM = tumor, node, metastasis.
* Combination of tamsulosin and dutasteride; negligible use among Danish men in the study period (37).
† Health Care Classification System codes used in the Danish National Patient Registry (29).

Appendix Figure. Categorization of patients with prostate cancer according to primary prostate cancer therapy received in the year after prostate cancer diagnosis.



Appendix Table 2. Associations Between Postdiagnosis Low-Dose Aspirin Use and Prostate Cancer or Other-Cause Mortality, by Age at Diagnosis, Calendar Period of Diagnosis, and Postdiagnosis Statin Use

Variable	Person-Years*	Prostate Cancer Mortality†			Other-Cause Mortality†		
		Events, *n**	Minimally Adjusted HR (95% CI)‡*	Fully Adjusted HR (95% CI)§*	Events, *n**	Minimally Adjusted HR (95% CI)‡*	Fully Adjusted HR (95% CI)§*
Age at diagnosis							
36–54 y	225/4233	6/128	0.87 (0.38–1.96)	0.66 (0.29–1.51)	6/26	4.30 (1.77–10.44)	2.85 (1.13–7.16)
55–64 y	5496/34 565	166/988	1.09 (0.93–1.29)	0.89 (0.75–1.06)	98/454	1.39 (1.12–1.73)	0.97 (0.77–1.21)
65–74 y	16 065/53 629	651/2127	1.07 (0.98–1.16)	0.99 (0.91–1.09)	633/1315	1.69 (1.53–1.86)	1.23 (1.11–1.37)
75–84 y	10 655/23 343	876/2008	0.91 (0.84–0.99)	0.96 (0.88–1.05)	949/1550	1.40 (1.29–1.52)	1.07 (0.98–1.16)
≥85 y	1580/2552	235/448	0.80 (0.69–0.94)	0.85 (0.73–1.00)	243/301	1.24 (1.05–1.47)	1.11 (0.94–1.32)
P value‖				0.37			0.03
Calendar period of diagnosis							
2000–2003	6957/29 578	628/2355	0.97 (0.89–1.06)	0.92 (0.83–1.01)	542/1301	1.44 (1.30–1.60)	1.05 (0.94–1.17)
2004–2007	13 604/45 039	755/2049	0.99 (0.91–1.08)	0.93 (0.85–1.02)	784/1408	1.43 (1.30–1.56)	1.11 (1.01–1.22)
2008–2011	13 461/43 705	551/1295	1.10 (0.99–1.22)	1.09 (0.98–1.21)	603/937	1.64 (1.47–1.81)	1.27 (1.14–1.42)
P value‖				0.02			0.03
Postdiagnosis statin use							
Nonuse¶	16 156/103 267	1144/5196	1.04 (0.97–1.11)	0.96 (0.90–1.03)	1133/3189	1.60 (1.49–1.71)	1.17 (1.08–1.26)
Use**	17 864/15 055	790/503	1.00 (0.89–1.12)	0.92 (0.82–1.04)	796/457	1.22 (1.09–1.37)	1.05 (0.93–1.18)
P value‖				0.57			0.12

HR = hazard ratio.
* Postdiagnosis low-dose aspirin use vs. nonuse within 1 y after prostate cancer diagnosis.
† Excluding deaths in the year after prostate cancer diagnosis.
‡ Adjusted for age at diagnosis and calendar period of diagnosis. In analyses stratified by age at diagnosis or calendar period of diagnosis, no adjustment was made for the stratifying variable.
§ Additional adjustments for clinical stage; Gleason score; primary prostate cancer therapy; postdiagnosis use (≥2 prescriptions) of nonaspirin nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors, α-adrenoreceptor antagonists, statins, nonaspirin antithrombotic agents, antihypertensives, other cardiovascular drugs, insulin, metformin, other oral antidiabetic drugs, psychotropic drugs, proton-pump inhibitors, or antihistamines; medical history of ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation or atrial flutter, diabetes mellitus, chronic obstructive pulmonary disease, or moderate to severe kidney disease; education level; income; marital status; and residence.
‖ Likelihood ratio test with overall model of postdiagnosis low-dose aspirin use vs. nonuse as the alternative model.
¶ <2 statin prescriptions filled within 1 y after prostate cancer diagnosis.
** ≥2 statin prescriptions filled within 1 y after prostate cancer diagnosis.

Appendix Table 3. Associations Between Postdiagnosis Low-Dose Aspirin Use and Prostate Cancer or Other-Cause Mortality, by Prediagnosis Low-Dose Aspirin Use

Low-Dose Aspirin Use	Person-Years	Prostate Cancer Mortality*			Other-Cause Mortality*		
		Events, *n*	Minimally Adjusted HR (95% CI)†	Fully Adjusted HR (95% CI)‡	Events, *n*	Minimally Adjusted HR (95% CI)†	Fully Adjusted HR (95% CI)‡
No prediagnosis use§ or postdiagnosis use‖	110 408	5198	Reference	Reference	3208	Reference	Reference
Prediagnosis use§ only	7914	501	1.11 (1.01–1.22)	1.08 (0.98–1.19)	438	1.49 (1.35–1.65)	1.11 (1.00–1.23)
Postdiagnosis use‖ only (new users)	4712	314	1.11 (0.99–1.24)	1.01 (0.90–1.13)	265	1.51 (1.33–1.71)	1.18 (1.03–1.34)
Prediagnosis use§ and postdiagnosis use‖	29 309	1620	0.95 (0.90–1.01)	0.95 (0.89–1.02)	1664	1.55 (1.46–1.65)	1.14 (1.06–1.23)
P value¶				0.21			0.15
Prediagnosis use§ and postdiagnosis use‖							
1–999 tablets prediagnosis**	9692	528	0.88 (0.80–0.96)	0.92 (0.84–1.02)	544	1.52 (1.39–1.67)	1.15 (1.04–1.27)
≥1000 tablets prediagnosis**	19 618	1092	1.00 (0.93–1.06)	0.97 (0.90–1.05)	1120	1.56 (1.46–1.68)	1.14 (1.05–1.23)

HR = hazard ratio.
* Excluding deaths in the year after prostate cancer diagnosis.
† Adjusted for age at diagnosis and calendar period of diagnosis.
‡ Additional adjustments for clinical stage; Gleason score; primary prostate cancer therapy; postdiagnosis use (≥2 prescriptions) of nonaspirin nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors, α-adrenoreceptor antagonists, statins, nonaspirin antithrombotic agents, antihypertensives, other cardiovascular drugs, insulin, metformin, other oral antidiabetic drugs, psychotropic drugs, proton-pump inhibitors, or antihistamines; medical history of ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation or atrial flutter, diabetes mellitus, chronic obstructive pulmonary disease, or moderate to severe kidney disease; education level; income; marital status; and residence.
§ ≥2 prescriptions filled within 5 y before prostate cancer diagnosis.
‖ ≥2 prescriptions filled within 1 y after prostate cancer diagnosis.
¶ Likelihood ratio test with overall model of postdiagnosis low-dose aspirin use vs. nonuse as the alternative model.
** Total number of tablets dispensed within 5 y before prostate cancer diagnosis, among users with pre- and postdiagnosis use.