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ORIGINAL PAPER

Associations of low-dose aspirin or other NSAID use with prostate cancer risk in the Danish Diet, Cancer and Health Study

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Abstract

Purpose Epidemiologic studies suggest that use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce prostate cancer risk. We examined these associations overall and according to clinical and lifestyle parameters.

Methods We identified male participants in the Danish Diet, Cancer and Health Study ($n = 26{,}339$), holding information on anthropometric measures and lifestyle factors. From Danish nationwide registries and medical records, we retrieved complete prescription histories and prostate cancer occurrence and characteristics. Cox regression was used to estimate hazard ratios (HRs) for prostate cancer associated with low-dose aspirin or nonaspirin NSAID use, overall and by clinical characteristics, anthropometric measures, and lifestyle factors.

Results We identified 1,927 prostate cancer cases during a median follow-up of 17.0 years. Low-dose aspirin use was not associated with overall prostate cancer risk, but a reduced HR for nonaggressive prostate cancer (high use [≥ 1,825 tablets]: 0.79; 95% confidence interval (CI) 0.60–1.04) and an increased HR for aggressive disease (high use: 1.27; 95% CI 1.00–1.61) was observed with low-dose aspirin use. Long-term, high-intensity use (≥ 10 years with ≥ 0.25 defined daily doses/day) of nonaspirin NSAIDs was associated with an increased HR for prostate cancer (1.35, 95% CI 0.99–1.84), confined to localized and nonaggressive disease. No consistent variation in HRs was seen in analyses stratified by height, body mass index, smoking, and alcohol use.

Conclusion Low-dose aspirin or other NSAID use was not associated with reduced prostate cancer risk, neither overall nor according to anthropometric measures, smoking, or alcohol use. The variation according to outcome characteristics warrants further investigation.

Keywords Aspirin · Nonsteroidal anti-inflammatory drugs · Prostate neoplasms · Risk · Epidemiology · Cohort study

Introduction

Use of aspirin (acetylsalicylic acid) and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a reduced risk of colorectal cancer and other cancer

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types [1, 2]. However, epidemiologic studies of prostate cancer have provided inconsistent results [1, 2]. Recent meta-analyses of observational studies have reported a 5–15% reduction in prostate cancer risk with regular or long-term aspirin use, but with considerable heterogeneity between studies [3–7]. Results have also been mixed for nonaspirin NSAID use, with meta-analyses finding either no association or a weak inverse association with prostate cancer risk [3, 4, 6]. Differences in study design and assessment of aspirin or nonaspirin NSAID use likely contributed to these mixed results. Moreover, associations between aspirin or nonaspirin NSAID use and cancer risk may vary according to clinical characteristics, anthropometric measures, and lifestyle factors [8–10].

Some studies of aspirin use have reported stronger inverse associations for advanced or aggressive prostate cancer [3, 5–7]. Moreover, NSAID use may inhibit obesity- and smoking-induced inflammation, which is thought to be involved in the development of several cancer types [11, 12]. Epidemiologic studies of colorectal cancer have suggested that the cancer-preventive effect of aspirin may be modified by obesity and smoking [9, 10], but few studies have examined effect modification by these and other lifestyle parameters for associations between NSAID use and prostate cancer risk [13].

The aim of the current study was to examine associations of low-dose aspirin or nonaspirin NSAID use with prostate cancer risk, with particular attention to the influence of patterns of drug use, variation according to clinical characteristics, and potential effect modification by anthropometric measures and lifestyle factors.

Material and methods

Study design

We conducted a cohort study of men enrolled in the Danish "Diet, Cancer and Health" (DCH) Study, which holds information on anthropometric measures and lifestyle factors [14]. From Danish nationwide registries, we obtained data on cancer diagnoses [15], prescription drugs [16], comorbidity [17], and income [18], using the unique civil registration number assigned to all Danish residents [19]. Additional details of the DCH Study and the nationwide registries with codes used for prostate cancer, drug exposures, and covariates are provided in the Online Resource.

Study population

During 1993–1997, 27,178 men aged 50–65 years were enrolled in the DCH Study [14]. For the current study, we excluded participants who emigrated or died between enrolment and 1 January 1998 (baseline for the present study) and those who were diagnosed with cancer (except nonmelanoma skin cancer) before baseline, as recorded in the Danish Cancer Registry [15] and the Danish Civil Registration System [19] (Fig. 1).

Ascertainment of prostate cancer patients

The final study population was followed from 1 January 1998 until the date of prostate cancer or other cancer diagnosis (except nonmelanoma skin cancer), emigration, death, or end of follow-up (31 December 2014). We used the Cancer Registry [15] to identify all eligible participants with a first-time diagnosis of prostate adenocarcinoma during 1998–2014. Patients' clinical characteristics were obtained from an updated (–2013) medical record review [20], including prostate-specific antigen (PSA) level (< 10, 10–20, > 20–50, > 50 ng per ml, or unknown), Gleason score (≤ 6, 7, ≥ 8, or unknown), and clinical stage at diagnosis (see Online Resource, Table A1 for stage algorithm). For patients with missing medical record information on clinical stage, including patients diagnosed in 2014, we used information recorded in the Cancer Registry [15]. We categorized patients as having either aggressive or nonaggressive prostate cancer by combining information on PSA level, Gleason score, and clinical stage (see Online Resource, Table A1 for algorithm). Finally, we retrieved information on the reason for referral of patients for diagnosis of prostate cancer, i.e., clinical indication such as lower urinary tract symptoms, PSA testing without a clinical indication, or unknown reason.

Assessment of low-dose aspirin and nonaspirin NSAID use

We obtained complete prescription histories since 1995 for low-dose aspirin and nonaspirin NSAIDs from the Danish National Prescription Registry [16]. We defined "ever use" of low-dose aspirin or nonaspirin NSAIDs as ≥ 2 filled prescriptions and nonuse as < 2 filled prescriptions. Low-dose aspirin use was categorized according to the total number of tablets dispensed (< 1,825, 1,825–3,649, or ≥ 3,650 [corresponding to < 5, 5–9, or ≥ 10 years of use, assuming a dosing schedule of one tablet per day]), tablet strength (75–100 mg only, 150 mg only, or mixed use), and consistency of use (inconsistent, consistent [< 1,825, 1,825–3,649, or ≥ 3,650 days, equal to < 5, 5–9, or ≥ 10 years of treatment if low-dose aspirin was taken daily as prescribed]). This information was updated continuously during follow-up. Use of nonaspirin NSAIDs was categorized according to the cumulative number of defined daily doses (DDDs) [21] (< 180, 180–364, or ≥ 365) and intensity of use (< 0.25, ≥ 0.25 DDD per day) within three strata of duration

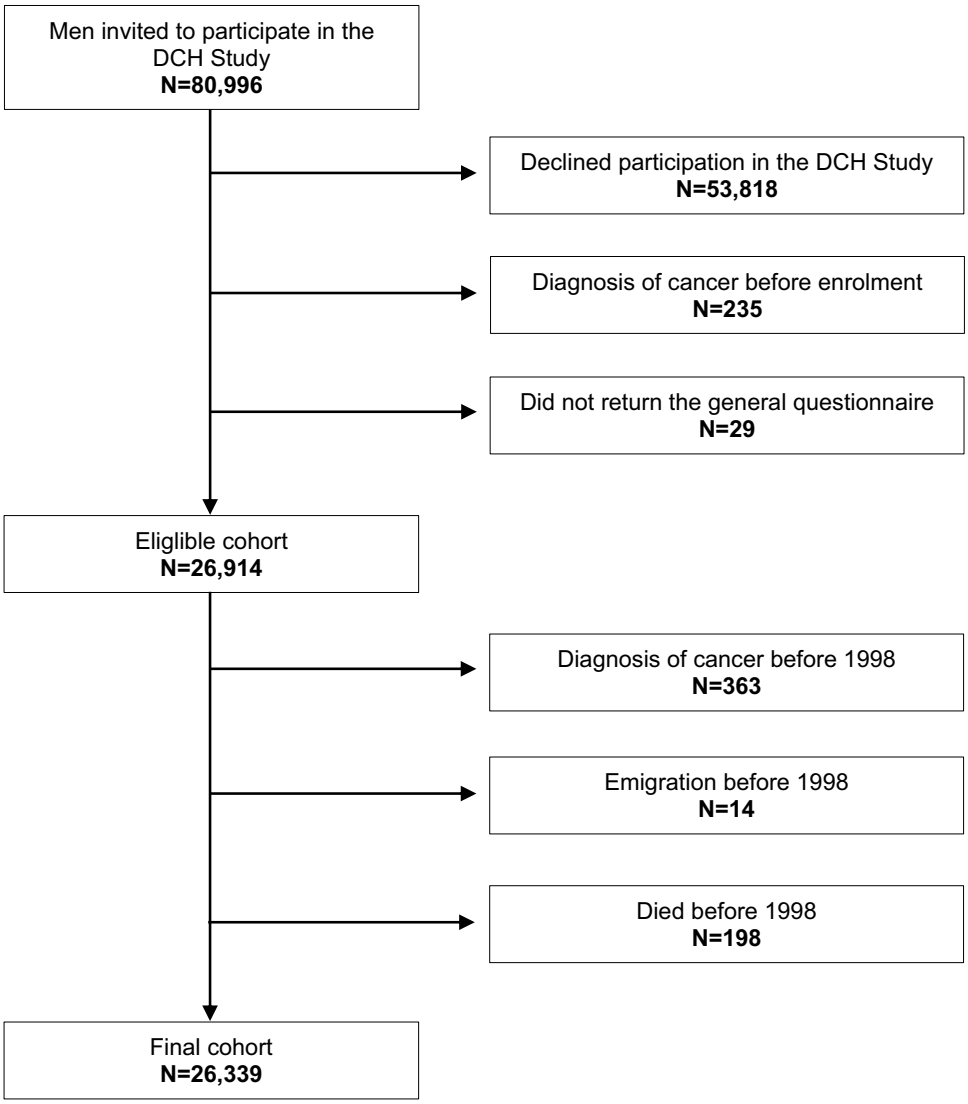

Fig. 1 Selection of the study population. Abbreviations: *DCH*, Diet, Cancer and Health

of use (< 5, 5–9, or ≥ 10 years). Further details are provided in the Online Resource.

Assessment of covariates

We selected covariates a priori based on current evidence on risk factors for prostate cancer [22, 23] and information available in the DCH Study [14] and the nationwide registries [16–18]. From the DCH Study, we obtained information on height (categorized according to approximate tertiles; ≤ 174.0, 174.5–179.5, ≥ 180.0 cm), weight (kg), body mass index (BMI; < 25, 25–30, > 30 kg per m^2), physical activity (sport practice: yes, no), smoking (never, past, current), alcohol use (0, 1–24, 25–36, > 36 g per day), education (basic or high school, short-cycle higher education, medium-cycle higher education, long-cycle higher education), and dietary intake of dairy products (g per day) and calcium (mg per day) at enrolment. From the Prescription Registry [16], we retrieved information on use (≥ 2 filled prescriptions) of high-dose aspirin, 5α-reductase inhibitors, statins, other cardiovascular drugs, insulin, metformin and other oral antidiabetic drugs. Further, we obtained information on medical history of diabetes mellitus from the Danish National Patient Registry [17] and income (disposable earnings in tertiles) at study baseline (1998) from registers administered by Statistics Denmark [18].

Statistical analyses

We used Cox proportional hazards regression analysis, with age as the underlying timescale, to estimate age-adjusted and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for prostate cancer associated with low-dose aspirin or nonaspirin NSAID use, modeled as time-dependent variables with a 1-year exposure lag. Thus, participants were considered nonusers until one year

after filling their second prescription for low-dose aspirin or nonaspirin NSAIDs, and then as users for the remainder of follow-up. The 1-year lag period provided a latency period and helped to avoid the potential bias of reverse causation (i.e., that early symptoms of a yet undiagnosed cancer trigger use of the exposure drug of interest) [24, 25]. Analyses of low-dose aspirin and nonaspirin NSAID use were performed in separate regression models, with nonuse of the respective drugs as reference. Multivariable-adjusted models included the covariates described above (excluding weight and height), calendar period, and mutual adjustment for ever use of low-dose aspirin or nonaspirin NSAIDs. Concomitant drug use (1-year exposure lag) and medical history of diabetes mellitus were included as time-dependent variables. Participants with missing information on any covariate were excluded from the analyses.

We estimated HRs for prostate cancer associated with ever use, number of tablets, tablet strength, and consistency of low-dose aspirin use. For nonaspirin NSAIDs, we estimated HRs associated with ever use, cumulative amount, and duration and intensity of use. To assess the influence of clinical characteristics, we estimated HRs with ever use and high use of low-dose aspirin or nonaspirin NSAIDs by levels of clinical stage, Gleason score, PSA level, and tumor aggressiveness. High use was defined as ≥ 1,825 tablets for low-dose aspirin and as ≥ 5 years of use with ≥ 0.25 DDD/day for nonaspirin NSAIDs. In these analyses, each specific subgroup of prostate cancer outcome in turn constituted the event of interest, and the remaining prostate cancer cases were accordingly censored at date of diagnosis. To evaluate potential effect measure modification by anthropometric measures and lifestyle factors, we performed analyses stratified by height, BMI, smoking, and alcohol use.

We performed five sensitivity analyses. First, to evaluate the potential influence of opportunistic PSA screening, we assessed associations of low-dose aspirin or nonaspirin NSAID use and prostate cancer risk by reason for referral for prostate cancer assessment, both overall and stratified by tumor aggressiveness. Second, for the overall analyses, we performed analyses accounting for competing risk from death or other cancer diagnosis, using the method proposed by Fine and Gray [26–28]. Third, we repeated the analyses using a 2-year exposure lag instead of the (default) 1-year lag. Fourth, we applied a new-user design and fifth, we evaluated the influence of cyclooxygenase (COX)-2 selectivity on the association between nonaspirin NSAID use and overall prostate cancer risk. Further details and results of the latter two sensitivity analyses are provided in the Online Resource.

The proportional hazards assumption was evaluated using scaled Schoenfeld residuals and no violations were found. All analyses were performed using the statistical software R, version 3.5.0 [29].

Results

The study population comprised 26,339 men (Fig. 1). During a median follow-up of 17.0 years (interquartile range: 12.6–17.0 years), 1,927 men were diagnosed with prostate cancer. At baseline, 4.4% of participants had ever used low-dose aspirin. Compared with nonusers, ever users were on average older, heavier, of shorter height, more likely to be past smokers, had lower education and income levels, higher concomitant drug use, and higher prevalence of diabetes mellitus (Table 1). At baseline, 21.0% were ever users of nonaspirin NSAIDs. Compared with nonusers, these participants were on average slightly older, heavier, more often current smokers, had higher alcohol use, slightly lower education and income levels, and slightly higher concomitant drug use.

Ever use of low-dose aspirin or nonaspirin NSAIDs was associated with adjusted HRs for prostate cancer of 1.02 (95% CI 0.90–1.15) and 1.02 (95% CI 0.93–1.12), respectively (Table 2). The HRs were close to unity in all analyses of different patterns of low-dose aspirin or nonaspirin NSAID use, except for an increased HR with nonaspirin NSAID use of ≥ 10 years' duration with ≥ 0.25 DDD/day (1.35, 95% CI 0.99–1.84).

Influence of clinical characteristics of prostate cancer

Use of low-dose aspirin was associated with a reduced HR for nonaggressive prostate cancer (high use: 0.79, 95% CI 0.60–1.04; Table 3) and an increased HR for aggressive prostate cancer (high use: 1.27, 95% CI 1.00–1.61). A similar pattern in HRs was seen for clinical stage, Gleason score, and PSA level, with HRs below one for localized stage, Gleason score ≤ 6, and PSA ≤ 20 ng/ml, and above one for nonlocalized stage, Gleason score ≥ 7, and PSA > 20. For nonaspirin NSAIDs, high use was associated with an increased HR for nonaggressive prostate cancer (1.49, 95% CI 1.05–2.09), but not for aggressive prostate cancer (0.99, 95% CI 0.70–1.41). Increased HRs with high nonaspirin NSAID use were also seen for prostate cancer of localized stage, Gleason score 7, and PSA ≤ 20 ng/ml.

Influence of anthropometric measures and lifestyle factors

For low-dose aspirin use, HRs for prostate cancer were close to unity in all strata of height, BMI, and smoking (Table 4). High use of low-dose aspirin was associated with an increased HR for prostate cancer among participants with highest level of alcohol use (> 36 g/day; 1.22, 95% CI 0.93–1.60), but not

Table 1 Characteristics of the study population by use of low-dose aspirin and nonaspirin NSAIDs at baseline (1 January 1998)

Characteristics	Low-dose aspirin		Nonaspirin NSAIDs	
	Ever use[a], *n* (%)	Nonuse[b], *n* (%)	Ever use[a], *n* (%)	Nonuse[b], *n* (%)
Total cohort	1,172 (4.4)	25,167 (95.6)	5,523 (21.0)	20,816 (79.0)
Median age [IQR], years	61.7 [57.9, 64.8]	57.7 [54.5, 61.8]	58.3 [54.8, 62.4]	57.7 [54.5, 61.9]
Concomitant prescription use[a]				
Low-dose aspirin	–	–	319 (5.8)	853 (4.1)
Nonaspirin NSAIDs	319 (27.2)	5,204 (20.7)	–	–
High-dose aspirin	13 (1.1)	56 (0.2)	35 (0.6)	34 (0.2)
5α-reductase inhibitors	28 (2.4)	260 (1.0)	85 (1.5)	203 (1.0)
Statins	280 (23.9)	397 (1.6)	177 (3.2)	500 (2.4)
Other cardiovascular drugs	848 (72.4)	3,497 (13.9)	1,157 (20.9)	3,188 (15.3)
Insulin	20 (1.7)	182 (0.7)	47 (0.9)	155 (0.7)
Metformin	22 (1.9)	86 (0.3)	34 (0.6)	74 (0.4)
Other oral antidiabetic drugs	69 (5.9)	295 (1.2)	95 (1.7)	269 (1.3)
Self-reported use[c]				
Aspirin	576 (49.1)	5,962 (23.7)	1,620 (29.3)	4,918 (23.6)
Nonaspirin NSAIDs	113 (9.6)	1,828 (7.3)	1,147 (20.8)	794 (3.8)
Missing	13 (1.1)	230 (0.9)	93 (1.7)	150 (0.7)
Comorbidity[d]				
Diabetes mellitus	103 (8.8)	511 (2.0)	154 (2.8)	460 (2.2)
BMI, kg/m^2				
< 25	293 (25.0)	8,926 (35.5)	1,575 (28.5)	7,644 (36.7)
25–30	588 (50.2)	12,541 (49.8)	2,812 (50.9)	10,317 (49.6)
> 30	287 (24.5)	3,687 (14.7)	1,130 (20.5)	2,844 (13.7)
Missing	4 (0.3)	13 (0.1)	6 (0.1)	11 (0.1)
Height[e], cm				
≤ 174.0	552 (47.1)	8,967 (35.6)	2,012 (36.4)	7,507 (36.1)
174.5–179.5	348 (29.7)	8,013 (31.8)	1,806 (32.7)	6,555 (31.5)
≥ 180.0	268 (22.9)	8,174 (32.5)	1,699 (30.8)	6,743 (32.4)
Missing	4 (0.3)	13 (0.1)	6 (0.1)	11 (0.1)
Median weight [IQR], kg	83.1 [75.4, 93.0]	81.8 [74.7, 89.8]	83.7 [75.8, 92.5]	81.5 [74.4, 89.3]
Missing	4 (0.3)	12 (< 0.1)	6 (0.1)	10 (< 0.1)
Physical activity[f]	434 (37.0)	12,372 (49.2)	2,561 (46.4)	10,245 (49.2)
Missing	69 (5.9)	197 (0.8)	19 (0.3)	247 (1.2)
Smoking				
Never	198 (16.9)	6,597 (26.2)	1,257 (22.8)	5,538 (26.6)
Past	509 (43.4)	8,651 (34.4)	1,950 (35.3)	7,210 (34.6)
Current	464 (39.6)	9,906 (39.4)	2,311 (41.8)	8,059 (38.7)
Missing	1 (0.1)	13 (0.1)	5 (0.1)	9 (< 0.1)
Alcohol use[g], g/day				
0	28 (2.4)	441 (1.8)	115 (2.1)	354 (1.7)
1–24	667 (56.9)	14,048 (55.8)	2,943 (53.3)	11,772 (56.6)
25–36	125 (10.7)	3,063 (12.2)	671 (12.1)	2,517 (12.1)
> 36	350 (29.9)	7,588 (30.2)	1,786 (32.3)	6,152 (29.6)
Missing	2 (0.2)	27 (0.1)	8 (0.1)	21 (0.1)
Median intake of dairy products [IQR], g/day	290 [149, 562]	291 [149, 570]	287 [145, 575]	292 [151, 568]
Missing	2 (0.2)	27 (0.1)	8 (0.1)	21 (0.1)
Median intake of calcium [IQR], mg/day	1,027 [781, 1,354]	1,047 [782, 1,376]	1,036 [767, 1,386]	1,048 [786, 1,372]
Missing	2 (0.2)	27 (0.1)	8 (0.1)	21 (0.1)

Table 1 (continued)

Characteristics	Low-dose aspirin		Nonaspirin NSAIDs	
	Ever use[a], *n* (%)	Nonuse[b], *n* (%)	Ever use[a], *n* (%)	Nonuse[b], *n* (%)
Educational level				
Basic or high school	192 (16.4)	2,421 (9.6)	630 (11.4)	1,983 (9.5)
Short-cycle higher education	173 (14.8)	3,425 (13.6)	808 (14.6)	2,790 (13.4)
Medium-cycle higher education	484 (41.3)	10,572 (42.0)	2,325 (42.1)	8,731 (41.9)
Long-cycle higher education	318 (27.1)	8,668 (34.4)	1,737 (31.5)	7,249 (34.8)
Missing	5 (0.4)	81 (0.3)	23 (0.4)	63 (0.3)
Income[h]				
Low	620 (52.9)	8,075 (32.1)	2,128 (38.5)	6,567 (31.5)
Medium	330 (28.2)	8,623 (34.3)	1,910 (34.6)	7,043 (33.8)
High	222 (18.9)	8,469 (33.7)	1,485 (26.9)	7,206 (34.6)

BMI body mass index, *IQR* interquartile range, *NSAID* nonsteroidal anti-inflammatory drug

[a] ≥ 2 prescriptions, modeled as a time-dependent covariate with a 1-year lag period

[b] < 2 prescriptions

[c] ≥ 2 tablets per month, at enrolment into the Diet, Cancer and Health Study

[d]Hospital-based diagnosis prior to baseline (1 Jan 1998)

[e]Categorized according to tertiles of the height of men in the study population

[f]Sport practice (yes)

[g]In Denmark, a standard drink is defined as 12 g pure alcohol [49]. The low-risk consumption threshold for men is 14 standard drinks per week and the high-risk consumption threshold is 21 standard drinks per week

[h]Categorized according to approximate tertiles of disposable earnings of men in the study population at baseline (1 Jan 1998)

among participants with lower levels of use. For nonaspirin NSAID use, we observed no consistent trends in prostate risk for height, BMI, or alcohol use, although elevated HRs occurred in some strata. High use of nonaspirin NSAIDs was associated with increased HRs among current (1.23, 95% CI 0.83–1.83) and past smokers (1.35, 95% CI 0.94–1.95).

Sensitivity analyses

In the analysis according to reason for referral for prostate cancer diagnosis, we found no major variation in HRs for overall prostate cancer (Online Resource, Table A2), although the HR for prostate cancer with clinical indication was increased among participants with high use of nonaspirin NSAIDs (1.36, 95% CI 1.00–1.85). Additional stratification by tumor aggressiveness revealed a decreased HR for nonaggressive prostate cancer and an increased HR for aggressive prostate cancer with low-dose aspirin use only for prostate cancer with clinical indication, whereas no major variation in HRs was seen for nonaspirin NSAIDs (Online Resource, Table A3). In analyses accounting for competing risk from death or diagnosis of other cancers, associations were similar to those observed in the main analyses for both low-dose aspirin and nonaspirin NSAIDs (results not shown). Similar results were also observed when changing the exposure lag period to 2 years (results not shown). Finally, the results for the new-user design, and for COX-2 selective nonaspirin NSAIDs, were similar to those of the main analyses (for details, see the Online Resource).

Discussion

In this study, we did not find evidence of an inverse association between use of low-dose aspirin or nonaspirin NSAIDs and prostate cancer risk, neither overall nor within subgroups defined by anthropometric measures, smoking, or alcohol use. Some risk variation was seen according to clinical characteristics of prostate cancer, with low-dose aspirin users being less likely to be diagnosed with nonaggressive prostate cancer and more likely to be diagnosed with aggressive disease. Moreover, we observed an increased risk of localized and less aggressive prostate cancer with long duration and high intensity of nonaspirin NSAID use.

Although our finding of a null association between low-dose aspirin use and overall prostate cancer risk is in line with the results of some previous studies [30–35], recent meta-analyses have reported modest prostate cancer risk reductions with aspirin use, notably with long-term use [3–7]. In a previous nationwide register-based study of NSAID use and prostate cancer risk, with a partly overlapping population [36], we found a 6% reduction in risk of prostate cancer with ever use of low-dose aspirin and a 14% reduction with consistent use for at least 10 years. In the

Table 2 Use of low-dose aspirin or nonaspirin NSAIDs and prostate cancer risk, overall and by amount, tablet strength, consistency, and duration and intensity of use

	PY	Cases, *n*	Age-adjusted HR (95% CI)	Fully adjusted[a] HR (95% CI)
Low-dose aspirin[b]				
Nonuse[c]	298,176	1,388	Reference	Reference
Ever use[d]	73,614	510	1.01 (0.91–1.12)	1.02 (0.90–1.15)
Number of tablets				
< 1,825	46,057	300	1.01 (0.89–1.15)	1.01 (0.87–1.16)
1,825–3,649	19,782	154	1.05 (0.88–1.24)	1.07 (0.89–1.29)
≥ 3,650	7,775	56	0.90 (0.69–1.18)	0.94 (0.71–1.25)
Tablet strength				
75–100 mg only	37,224	286	1.07 (0.94–1.22)	1.05 (0.91–1.22)
150 mg only	16,830	109	1.10 (0.91–1.34)	1.15 (0.94–1.41)
Mixed use	19,560	115	0.83 (0.68–1.00)	0.83 (0.67–1.02)
Consistency				
Inconsistent use[e]	43,615	304	0.99 (0.87–1.12)	0.99 (0.86–1.15)
Consistent use[f]	29,999	206	1.04 (0.90–1.21)	1.06 (0.90–1.25)
< 5 years	21,492	146	1.07 (0.91–1.28)	1.07 (0.89–1.29)
5–9 years	6,116	44	1.01 (0.75–1.36)	1.06 (0.77–1.44)
≥ 10 years	2,391	16	0.87 (0.53–1.42)	0.92 (0.56–1.52)
Nonaspirin NSAID[b]				
Nonuse[c]	191,912	824	Reference	Reference
Ever use[d]	179,878	1,074	1.05 (0.96–1.16)	1.02 (0.93–1.12)
Cumulative amount				
< 180 DDDs	135,580	763	1.03 (0.93–1.14)	0.99 (0.90–1.10)
180–364 DDDs	18,352	127	1.14 (0.94–1.37)	1.11 (0.92–1.34)
≥ 365 DDDs	25,946	184	1.12 (0.95–1.32)	1.10 (0.93–1.30)
Duration and intensity of use				
< 5 years				
< 0.25 DDD/day	64,687	321	1.00 (0.88–1.14)	0.99 (0.87–1.13)
≥ 0.25 DDD/day	39,149	186	0.97 (0.83–1.14)	0.97 (0.82–1.13)
5–9 years				
< 0.25 DDD/day	40,951	285	1.12 (0.98–1.29)	1.04 (0.91–1.20)
≥ 0.25 DDD/day	5,423	32	1.03 (0.72–1.47)	1.03 (0.72–1.47)
≥ 10 years				
< 0.25 DDD/day	25,285	205	1.10 (0.94–1.28)	1.05 (0.89–1.24)
≥ 0.25 DDD/day	4,384	45	1.40 (1.04–1.90)	1.35 (0.99–1.84)

Excluding 382 men (29 cases) with missing information on at least one covariate

BMI body mass index, *CI* confidence interval, *DDD* defined daily dose, *HR* hazard ratio, *NSAID* nonsteroidal anti-inflammatory drug, *PY* person-years

[a]Adjusted for age [by design]; calendar period; use (≥ 2 prescriptions) of high-dose aspirin, 5α-reductase inhibitors, statins, other cardiovascular drugs, insulin, metformin and other oral antidiabetic drugs; medical history of diabetes mellitus; educational level; income; BMI; physical activity; smoking; alcohol use; intake of dairy products and calcium; and mutual adjustment for ever use (≥ 2 prescriptions) of low-dose aspirin or nonaspirin NSAIDs

[b]Analyses of low-dose aspirin and nonaspirin NSAID use were performed in separate regression models

[c] < 2 prescriptions

[d] ≥ 2 prescriptions, modeled as a time-dependent covariate with a 1-year lag period

[e] ≥ 2 prescriptions overall, with days between consecutive prescriptions exceeding the number of tablets in the preceding prescription (assuming 1 tablet/day) plus a grace period of 60 days

[f] ≥ 2 prescriptions overall, with days between consecutive prescriptions not exceeding the number of tablets in the preceding prescription (assuming 1 tablet/day) plus a grace period of 60 days

Table 3 Use of low-dose aspirin or nonaspirin NSAIDs and prostate cancer risk by clinical stage, Gleason score, PSA level, and tumor aggressiveness at time of diagnosis

	Low-dose aspirin					Nonaspirin NSAIDs				
	Nonuse[a]	Ever use[b]		High use[c]		Nonuse[a]	Ever use[b]		High use[d]	
	Cases	Cases	HR (95% CI)[e]	Cases	HR (95% CI)[e]	Cases	Cases	HR (95% CI)[e]	Cases	HR (95% CI)[e]
Clinical stage										
Localized stage	968	314	0.94 (0.81–1.10)	121	0.93 (0.74–1.15)	546	736	1.09 (0.97–1.22)	52	1.33 (1.00–1.78)
Nonlocalized stage	275	99	1.15 (0.86–1.54)	38	1.13 (0.76–1.68)	185	189	0.86 (0.69–1.06)	10	0.69 (0.36–1.31)
Unknown	145	97	1.21 (0.87–1.66)	51	1.35 (0.91–1.99)	93	149	0.93 (0.71–1.21)	15	1.29 (0.74–2.26)
Gleason score										
≤6	429	116	0.87 (0.67–1.11)	38	0.74 (0.51–1.07)	256	289	0.94 (0.79–1.12)	18	1.00 (0.62–1.63)
7	404	144	0.96 (0.76–1.21)	64	1.08 (0.79–1.47)	225	323	1.07 (0.90–1.28)	33	1.76 (1.21–2.57)
≥8	303	149	1.32 (1.03–1.69)	59	1.24 (0.89–1.73)	195	257	0.95 (0.78–1.15)	19	1.07 (0.66–1.73)
Unknown	252	101	0.99 (0.74–1.32)	49	1.10 (0.76–1.60)	148	205	1.17 (0.93–1.46)	7	0.67 (0.31–1.45)
PSA level, ng/ml										
<10	510	163	0.96 (0.77–1.19)	59	0.89 (0.65–1.21)	280	393	1.11 (0.95–1.31)	29	1.39 (0.94–2.05)
10–20	315	104	0.88 (0.67–1.16)	41	0.88 (0.60–1.28)	183	236	1.03 (0.84–1.26)	20	1.47 (0.91–2.35)
>20–50	190	84	1.34 (0.97–1.85)	30	1.21 (0.77–1.90)	126	148	0.93 (0.73–1.19)	9	0.86 (0.43–1.72)
>50	219	76	1.14 (0.82–1.58)	32	1.24 (0.79–1.92)	158	137	0.74 (0.58–0.94)	10	0.86 (0.45–1.66)
Unknown	154	83	0.98 (0.71–1.37)	48	1.21 (0.81–1.79)	77	160	1.30 (0.98–1.73)	9	1.14 (0.56–2.32)
Tumor aggressiveness										
Nonaggressive[f]	656	193	0.83 (0.68–1.00)	74	0.79 (0.60–1.04)	339	510	1.15 (1.00–1.33)	38	1.49 (1.05–2.09)
Aggressive[g]	651	279	1.23 (1.03–1.46)	116	1.27 (1.00–1.61)	436	494	0.89 (0.78–1.02)	35	0.99 (0.70–1.41)
Unknown	81	38	0.96 (0.59–1.57)	20	1.10 (0.60–2.02)	49	70	1.17 (0.79–1.72)	<5	1.00 (0.35–2.84)

Excluding 382 men (29 cases) with missing information on at least one covariate

BMI body mass index, *CI* confidence interval, *DDD* defined daily dose, *HR* hazard ratio, *NSAID* nonsteroidal anti-inflammatory drug, *PSA* prostate-specific antigen, *TNM* tumor node metastasis

[a] <2 prescriptions

[b] ≥2 prescriptions, modeled as a time-dependent covariate with a 1-year lag period

[c] ≥1,825 low-dose aspirin tablets

[d] ≥5 years duration of nonaspirin NSAID use with ≥0.25 DDD/day

[e] Adjusted for age [by design]; calendar period; use (≥2 prescriptions) of high-dose aspirin, 5α-reductase inhibitors, statins, other cardiovascular drugs, insulin, metformin and other oral antidiabetic drugs; medical history of diabetes mellitus; educational level; income; BMI; physical activity; smoking; alcohol use; intake of dairy products and calcium; and mutual adjustment for ever use (≥2 prescriptions) of low-dose aspirin or nonaspirin NSAIDs, respectively. Analyses of low-dose aspirin and nonaspirin NSAID use were performed in separate regression models

[f] Not fulfilling the criteria for "aggressive" disease and with either clinical tumor stage ≤T2 or Gleason score ≤6

[g] Clinical stage ≥T3 or N1 or M1 or "regional" extent of disease or "distant" extent of disease, or Gleason score ≥8, or PSA level >20 ng/ml

Table 4 Use of low-dose aspirin or nonaspirin NSAIDs and prostate cancer risk by height, BMI, smoking, and alcohol use

	Low-dose aspirin					Nonaspirin NSAIDs				
	Nonuse[a]	Ever use[b]		High use[c]		Nonuse[a]	Ever use[b]		High use[d]	
	Cases	Cases	HR (95% CI)[e]	Cases	HR (95% CI)[e]	Cases	Cases	HR (95% CI)[e]	Cases	HR (95% CI)[e]
Height, cm										
≤ 174.0	455	208	1.10 (0.91–1.32)	87	1.05 (0.82–1.35)	298	365	0.98 (0.84–1.15)	22	0.94 (0.61–1.46)
174.5–179.5	462	163	0.99 (0.81–1.20)	72	1.10 (0.84–1.44)	251	374	1.13 (0.96–1.34)	33	1.61 (1.11–2.32)
≥ 180.0	471	139	0.96 (0.78–1.18)	51	0.95 (0.70–1.29)	275	335	0.94 (0.80–1.11)	22	1.05 (0.68–1.62)
BMI, kg/m^2										
< 25	546	142	0.95 (0.78–1.17)	52	0.92 (0.68–1.25)	341	347	0.98 (0.84–1.14)	14	1.04 (0.61–1.79)
25–30	693	281	1.04 (0.89–1.22)	119	1.09 (0.88–1.35)	392	582	1.08 (0.95–1.23)	43	1.27 (0.93–1.75)
> 30	149	87	1.07 (0.80–1.41)	39	1.06 (0.73–1.54)	91	145	0.88 (0.68–1.15)	20	1.09 (0.67–1.79)
Smoking										
Never	445	132	1.02 (0.82–1.26)	54	1.10 (0.81–1.49)	267	310	1.03 (0.87–1.22)	16	0.91 (0.55–1.51)
Past	491	192	1.05 (0.87–1.26)	78	1.00 (0.77–1.29)	290	393	1.00 (0.86–1.17)	33	1.35 (0.94–1.95)
Current	452	186	0.98 (0.81–1.19)	78	1.03 (0.79–1.34)	267	371	1.02 (0.87–1.20)	28	1.23 (0.83–1.83)
Alcohol use, g/day										
0	23	6	0.55 (0.22–1.39)	< 5	0.68 (0.20–2.33)	13	16	0.83 (0.40–1.73)	< 5	2.36 (0.76–7.32)
1–24	817	282	0.98 (0.84–1.15)	116	0.98 (0.79–1.22)	496	603	1.01 (0.89–1.14)	41	1.18 (0.85–1.63)
25–36	171	54	0.93 (0.68–1.29)	20	0.86 (0.53–1.40)	93	132	1.10 (0.84–1.44)	12	1.63 (0.89–3.00)
> 36	377	168	1.15 (0.94–1.40)	71	1.22 (0.93–1.60)	222	323	1.01 (0.85–1.21)	20	0.95 (0.60–1.51)

Excluding 382 men (29 cases) with missing information on at least one covariate

BMI body mass index, *CI* confidence interval, *DDD* defined daily dose, *HR* hazard ratio, *NSAID* nonsteroidal anti-inflammatory drug

[a] < 2 prescriptions

[b] ≥ 2 prescriptions, modelled as a time-dependent covariate with a 1-year lag period

[c] ≥ 1,825 low-dose aspirin tablets

[d] ≥ 5 years duration of nonaspirin NSAID use with ≥ 0.25 DDD/day

[e] Adjusted for age [by design]; calendar period; use (≥ 2 prescriptions) of high-dose aspirin, 5α-reductase inhibitors, statins, other cardiovascular drugs, insulin, metformin and other oral antidiabetic drugs; medical history of diabetes mellitus; educational level; income; BMI; physical activity; smoking; alcohol use; intake of dairy products and calcium; and mutual adjustment for ever use (≥ 2 prescriptions) of low-dose aspirin or nonaspirin NSAIDs, respectively. Analyses of low-dose aspirin and nonaspirin NSAID use were performed in separate regression model

present study, we did not observe an association of low-dose aspirin use with prostate cancer risk for various patterns of use; however, we had limited power to assess associations with long-term, consistent use.

Our results for low-dose aspirin use according to clinical characteristics of prostate cancer are interesting. Contrary to previous studies [3, 5–7], we found an increased risk of aggressive prostate cancer and a decreased risk of nonaggressive prostate cancer associated with low-dose aspirin use. Similar opposite trends were observed in analyses examining clinical stage, Gleason score, and PSA level; however, CIs were wide and overlapping. Although it is possible that low-dose aspirin use influences the development of prostate cancer, our findings may reflect differences in prostate cancer detection between low-dose aspirin users and nonuser. Slightly lower PSA levels have been reported among aspirin users [37], which may decrease detection of early-stage and nonaggressive disease, delaying diagnosis, and possibly explaining the increased risk of aggressive disease with low-dose aspirin use observed in our study. Our sensitivity analyses according to referral for prostate cancer diagnosis and tumor aggressiveness provided some support for this hypothesis.

Although most previous studies on nonaspirin NSAID use and prostate cancer risk have found either inverse or null associations [30, 32, 34, 38–42], the increased risk observed in the present study concurs with our previous register-based study [36] and two Finnish studies [43, 44]. While no trends with cumulative dose or duration of nonaspirin NSAID use were seen in the earlier studies [36, 43, 44], we observed an increased risk of prostate cancer specifically for high and long-term nonaspirin NSAID use. However, long-term nonaspirin NSAID users and nonusers may differ in morbidity of chronic inflammatory conditions, which may affect prostate cancer risk. Chronic prostate inflammation has been suggested to contribute to prostate carcinogenesis [45], but whether other chronic inflammatory conditions influence prostate cancer risk is unclear [46]. Unfortunately, information on indications for drug use were not available in the Danish National Prescription Registry [16].

Similar to our earlier register-based study, the increased risk observed with nonaspirin NSAID use in the current study was confined to localized and less aggressive prostate cancer. In the Finnish Prostate Cancer Screening Trial, Veitonmäki et al. also found an increased risk of localized prostate cancer with NSAID use, but a larger increase in risk of metastatic disease [44]. Reverse causation bias, i.e., use of nonaspirin NSAIDs due to symptoms of undiagnosed prostate cancer, may explain the increased risk of metastatic disease, but is unlikely to account for the increased risk of localized disease among long-term nonaspirin NSAID users observed in our study. Moreover, the sensitivity analysis applying a 2-year exposure lag yielded results similar to the main analysis. Although no general screening program for prostate cancer has been introduced in Denmark [47], long-term nonaspirin NSAID users may receive increased medical attention and thus be more likely to undergo opportunistic PSA testing. This may provide a possible explanation for the increased risk of localized prostate cancer. However, in our sensitivity analysis of reasons for referral, nonaspirin NSAID use was not associated with risk of prostate cancer detected with no clinical indication. Additional large studies with detailed information on nonaspirin NSAID use, including indications for use and PSA testing, are needed to evaluate the association between nonaspirin NSAID use and risk of localized prostate cancer.

Studies of colorectal cancer have suggested that the cancer-preventive effect of aspirin may be attenuated among obese individuals [9, 10]. In a secondary analysis of cardiovascular disease prevention trials of daily aspirin, Rothwell et al. found that the 20-year risk of colorectal cancer was reduced among low-dose aspirin users with bodyweight < 70 kg, but not among those weighing ≥ 70 kg [9]. We observed no material influence of BMI on associations between low-dose aspirin use and prostate cancer risk, which is in line with analyses from the Health Professionals Follow-Up Study, examining the interaction between high-dose aspirin and BMI on prostate cancer risk [13]. However, few participants in our study had a bodyweight below 70 kg, and additional studies are needed to further clarify whether body size influences the association between aspirin use and prostate cancer risk.

To our knowledge, no previous studies have examined the influence of smoking and alcohol use on associations between NSAID use and prostate cancer risk. However, in a meta-analysis using individual-level data from 12 observational studies, Wang et al. observed a larger decrease in colorectal cancer risk with aspirin use among nonsmokers than among smokers [10]. In contrast, we observed no reduction in prostate cancer risk with low-dose aspirin use among never, past, or current smokers. Moreover, in the study by Wang et al., the effect of nonaspirin NSAID use did not differ by smoking status, and alcohol use did not appear to modify associations with colorectal cancer for either aspirin or nonaspirin NSAID use [10]. We found a slightly increased prostate cancer risk with low-dose aspirin use among participants with high alcohol use, and with high and long-term nonaspirin NSAID use among current and past smokers; however, explanations are elusive.

Our study had several strengths. The prospectively collected, comprehensive information in the DCH Study and in Danish prescription and health registries allowed for detailed analyses of patterns of low-dose aspirin and nonaspirin NSAID use with adjustment for a range of putative prostate cancer risk factors, and for analyses of effect measure modification by anthropometric measures and lifestyle factors. Moreover, virtually complete follow-up

was achieved through linkage to Danish cancer and population registries. Histological verification of prostate cancer cases ensured high case validity. Moreover, the medical record review provided high-quality information on clinical stage, Gleason score, and PSA levels. Anthropometric measures were obtained by trained staff at DCH enrolment, eliminating misclassification due to self-reporting.

Our study also had limitations. Misclassification of participants according to anthropometric measures and lifestyle factors may have occurred over time, as we only had information on these factors at DCH enrolment. However, it may be reasonable to assume that anthropometric measures and presumably smoking and alcohol use remain relatively unchanged among men above 50 years of age.

Nondifferential misclassification of low-dose aspirin and nonaspirin NSAID use is another potential limitation. Although most (92% in 2012) low-dose aspirin is dispensed on prescription in Denmark, some low-dose aspirin (less than 10%) and most high-dose aspirin, typically used for transient pain conditions, is sold over the counter [48]. Nonaspirin NSAIDs are mostly sold on prescription (75% in 2012), with only low-dose (200 mg) ibuprofen available over the counter (and low-dose diclofenac during 2007–2008) [48]. Nonetheless, lack of information on over-the-counter NSAID use in our study may have attenuated observed associations with prostate cancer risk. It is also possible that nonadherence to prescribed NSAIDs led to misclassification of NSAID use. However, such misclassification may occur less often among participants with long-term use, and thus is unlikely to have influenced our results for high and long-term nonaspirin NSAID use.

Another limitation of our study is that we cannot rule out residual confounding from factors associated with both NSAID use and prostate cancer risk. However, we adjusted for a large number of medical and lifestyle factors, including BMI and smoking, and this did not materially influence the risk estimates. We had no information on two established prostate cancer risk factors, ethnicity and family history [22]. However, the homogeneity of the Danish population precludes confounding by ethnicity, and NSAID use is unlikely to differ by family history of prostate cancer.

Moreover, our findings may not be generalizable to other populations with different patterns of drug use, PSA testing, or lifestyle factors. Specifically, participants in the DCH Study have been shown to have higher socioeconomic status than nonparticipants and may thus have different behavior in relation to prostate cancer risk [14].

Finally, our analyses according to clinical characteristics, anthropometric measures, and lifestyle factors had limited statistical precision, especially for associations with high use of low-dose aspirin and nonaspirin NSAIDs. Additional studies with greater statistical precision and detailed assessment of low-dose aspirin and nonaspirin NSAID use are needed to confirm or refute our findings.

In conclusion, our study does not support a protective effect of low-dose aspirin or nonaspirin NSAID use on prostate cancer risk, neither overall nor within any subgroup defined by anthropometric measures, smoking, or alcohol use. However, we observed variation in estimated associations according to clinical characteristics, including an increased risk of aggressive, but a decreased risk of nonaggressive, prostate cancer with low-dose aspirin use and an increased risk of localized prostate cancer with long-term nonaspirin NSAID use. Further studies are needed to explore whether these findings result from confounding by indication or detection bias, or are indicative of true causal relationships.

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Compliance with ethical standards

Conflict of interest Professor Sørensen does not report receiving fees, honoraria, grants, or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. Authors not named here have disclosed no conflicts of interest.

Ethical approval The DCH Study was approved by relevant Scientific Committees and the Danish Data Protection Agency.

Informed consent Informed consent was obtained from all participants to retrieve information from nationwide registries [14]. Approval for medical record review was granted by the Danish National Committee on Health Research Ethics.

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