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ARTICLE

Maintenance use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk

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Abstract

Background Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) may have a preventive effect against prostate cancer. However, evidence is limited and still controversial, especially considering non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs).

Methods Swedish nationwide population-based cohort study including all long-term (≥180 days) adult male users of aspirin ($n = 419{,}931$) or NSAIDs ($n = 223{,}437$) followed from the first dispense date until the first cancer diagnosis, death or 31 December 2012, whichever occurred first. The risk of prostate cancer was measured as standardized incidence ratios (SIR) and 95% confidence intervals (CI), assessing duration of use, age and concomitant statins intake, comparing to the general male background population of the same age in Sweden.

Results The overall SIR suggests that maintenance use of aspirin decreases the risk of prostate cancer (SIR = 0.87, 95% CI 0.85–0.88), in particular if used ≥5 years (SIR = 0.31, 95% CI 0.30–0.32). The overall risk was decreased (SIR = 0.87, 95% CI 0.85–0.90) among other NSAIDs users, and again in particular among longer-term users (≥3 years) with SIR = 0.58 (95% CI 0.53–0.63). When statins users were excluded from all aspirin users, there was no remaining association with prostate cancer (SIR = 0.99, 95% CI 0.96–1.02), only if taken ≥5 years (SIR = 0.31, 95% CI 0.29–0.34). For non-aspirin NSAIDs users, the protective effect remained after exclusion of statins users (SIR = 0.92, 95% CI 0.88–0.95).

Conclusions This population-based cohort study provides evidence for a protective effect of aspirin and other NSAIDs against prostate cancer, in particular for longer durations of use, yet concomitant use of statins strongly influences the risk among aspirin users.

Key points

Question: Can aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) decrease the risk of prostate cancer?
Findings: this Swedish population based cohort study indicates a protective effect after long term maintenance use of aspirin or other NSAIDs against prostate cancer.
Meaning: long-term intake of aspirin or other NSAIDs is probably useful in the prevention of prostate cancer.

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Introduction

Chronic inflammation contributes to about 20% of all human cancers in adults [1, 2]. For prostate cancer specifically, there is evidence that chronic or recurrent inflammation plays an important role in prostate cancer initiation, development, progression, and metastasis [3]. Biopsies in several carcinogenic and non-carcinogenic prostate diseases show signs of inflammation, including prostatitis, benign prostatic hyperplasia (BPH), prostate cancer "risk lesions" (proliferative inflammatory atrophy (PIA), prostatic intraepithelial neoplasia (PIN)), and prostate cancer [4–6].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a family of drugs which can reduce pain and fever by inhibiting inflammation. Most NSAIDs can reversibly inhibit cyclooxygenase enzyme activity on both COX-1 and COX-2 receptors, yet some are selective on COX-2 [7]. Cyclooxygenase, also named prostaglandin-endoperoxide synthase (PTGS), is an enzyme family responsible for prostanoids formation. COX-1 is constitutively expressed in

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many tissues [8]. COX-2 expressed more specific in inflammation and can be induced by extracellular or intracellular stimuli and the induction is transient [9–11]. In prostate cancer, COX-2 expresses specifically in prostate inflammatory cells, especially in PIA lesions [5, 12]. Aspirin is a non-selective cyclooxygenase inhibitor, which therefore irreversibly inhibits both COX-1 and COX-2 isoenzymes [13]. The potential cancer-preventive effect of aspirin is increasingly investigated with ongoing clinical trials aiming to prevent colorectal cancer [14]. Yet, for other cancer types, the effect on carcinogenesis is less clear based on observational studies.

Recent original publications and meta-analysis which included 18 case-control and 13 cohort studies tried to assess the association between aspirin and non-aspirin NSAIDs [15, 16]. Results suggested that aspirin could decrease the risk of prostate cancer, especially after long-term use (≥4 years). In terms of non-aspirin NSAIDs, this meta-analysis found no protective effects against prostate cancer and authors claimed that the results were less consistent and need further investigation. The major problems of these observational studies were (1) Insufficient power because of limited sample sizes and follow-up time, in particular for non-aspirin NSAIDs which are less commonly used than aspirin; (2) different definitions of exposure which often based on e.g., questionnaires, interviews or medical notes, with a high risk of recall bias and incomplete/incorrect information on exposure in particular dose and duration. Statins are also considered promising chemo-preventive agents commonly prescribed in particular among aspirin users, although there is currently insufficient evidence supporting a protective effect against prostate cancer [17–20]. To our knowledge, no previous studies investigated the combined effect of NSAIDs and statins on the risk of prostate cancer.

We assume that the risk of prostate cancer is decreased in adults exposed to maintenance use of aspirin and other NSAIDs comparing to the background population. The aim of our study was therefore to evaluate the potential chemo-preventive effect of maintenance use of aspirin or other NSAIDs against prostate cancer in a Swedish population-based cohort study taking into account concomitant statins use.

Methods

Design

This nationwide population-based cohort study was designed to evaluate prostate cancer risk in adult (≥18 years) male aspirin users ($N = 419{,}931$) and non-aspirin NSAIDs users ($N = 223{,}437$) compared to the general Swedish male background population of the same age. All individuals with at least 180 days of aspirin or other NSAIDs between 1 July 2005 (the start date of the Swedish Prescribed Drug Registry) and 31 December 2012, were selected from the Swedish Prescribed Drug Registry. Individuals were followed up from the first dispense date until the first cancer diagnosis, death or 31 December 2012, whichever occurred first. Individuals who were diagnosed with any cancer (except non-melanoma skin cancer) before or within 1 year after the first prescription were excluded, as well as those who use both ≥180-day aspirin and ≥180-day of other NSAIDs.

Data collection

This study is approved by the Regional Ethical Review Board (2014/1291-31/4) and informed consent was not required. The 10-digit personal identity number was used to link all individuals with the Swedish Cancer Registry and Swedish Causes of Death Registry. The completeness of prostate cancer diagnoses in the Swedish Cancer Registry is more than 95% when compared to records of death certificates and it was used to identify cancer cases among the exposed cohort and background population [21]. Person years for the background population are obtained from Statistics Sweden (SCB), and cancer occurrence from the Cancer Registry.

Exposures

Maintenance use of aspirin or NSAIDs was defined as at least 180 days during the study period before any cancer diagnosis. This cumulative exposure was based on the defined daily dosage (DDD) per prescribed package, which is an estimation of the number of days of use for the standard indication for an average individual (as defined by the World Health Organization). In Sweden, people can also buy high-dose aspirin and some of the other NSAIDs over-the-counter without prescription, but prescribed drugs are less expensive, and therefore expected to be the major source of NSAID intake among chronic users [22]. Exposure data were collected by corresponding anatomical therapeutic chemical classification codes (ATC): Aspirin (B01AC06; N02BA) and non-aspirin NSAIDs (M01A). Individuals with ≥180 days of use of both aspirin and non-aspirin NSAIDs were excluded.

Outcomes

The outcome was a first diagnosis of prostate cancer recorded in the Swedish Cancer Registry using the International Classification of Diseases (ICD) 10th codes (C61.9) during the study period. Prostatic adenocarcinoma (diagnostic code is 096) was the single most common histological type of prostate cancer in this cohort (98.7%), and was

Table 1 Descriptive characteristics of aspirin users and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) users

	Aspirin Number (%)	Non-aspirin NSAIDs Number (%)
Total	419,931	223,437
Age		
18–49 years	26,604 (6.3)	96,598 (43.2)
50–59 years	73,732 (17.6)	61,045 (27.3)
60–69 years	126,030 (30.0)	44,296 (19.8)
70–79 years	111,182 (26.5)	16,578 (7.4)
≥80 years	82,383 (19.6)	4920 (2.2)
Statins users		
Yes	264,275 (62.9)	32,839 (14.7)
No	155,656 (37.1)	190,598 (85.3)
Prostate cancer		
All	11,291 (2.7)	3578 (1.6)
Adenocarcinoma	11,128 (2.6)	3562 (1.6)
Follow-up (person-years)		
Total	2,053,932	1,305,848

therefore not analyzed separately. Cancer which occurred within 1 year after the first prescription was excluded.

Statistical analyzes

Standardized incidence ratios (SIRs) and 95% confidence intervals (CI) were calculated by comparing aspirin users and other NSAIDs users with the general Swedish background population of the corresponding age (18–49, 50–59, 60–69, 70–79, or ≥80 years) and calendar period (2005–2006, 2007–2009, and 2010–2012). Expected incidence rates were calculated based on data from the Swedish cancer registry and general Swedish population (SCB). Variance between groups were similar based on large sample size study design. Subgroup analyzes were conducted to assess the effected of duration of use (categorized as <1 year, 1–3 years, 3–5 years, and >5 years for aspirin, and <1 year, 1–3 years, and >3 years for NSAIDs), and concomitant statins use (defined as ≥180 days during the study period). To assess the interaction between NSAIDs use and statins, multivariable Poisson regression model were used adjusting for age, for aspirin users and for non-aspirin NSAIDs users separately, and expressing the risk of prostate cancer as incidence rate ratios (IRR) and 95% CI for statins users compared to non-statins users.

Code availability

The data were analyzed by StataIC 13. The code is available upon request.

Results

Participants

In this cohort, 419,931 men (65.3%) were considered aspirin maintenance users, and 223,437 (34.7%) non-aspirin NSAIDs users (Table 1). Non-aspirin NSAIDs were younger than aspirin users (respectively, 43.2% and 6.3% younger than 50-years). Concomitant maintenance use of statins was found in 62.9% of the aspirin users and 14.7% of the non-aspirin NSAIDs users.

Aspirin use

Among aspirin users, 11,291 (2.7%) developed prostate cancer (Table 1). The overall SIR indicated a protective effect of aspirin on prostate cancer (SIR = 0.87, 95% CI 0.85–0.88) (Table 2). This reduced risk was seen among all age groups except for those younger than 50 years (showing no association) (Table 2). When the duration of use was taken into account, the protective effect was only seen among long-term users of aspirin (more than 5 years) with SIR = 0.31 (95% CI 0.30–0.32) (Table 3). After exclusion of aspirin users who also used statins, no association with prostate cancer remained (SIR = 0.99, 95% CI 0.96–1.02), except for the long-term users (SIR = 0.31, 95% CI 0.29–0.34) (Tables 2, 3). When assessing concomitant statins use among aspirin users by means of Poisson regression adjusting for age, statins use was associated with a 22% reduced risk of prostate cancer (IRR = 0.78, 95% CI 0.75–0.81) compared to non-statins users (Table 4).

Non-aspirin NSAIDs use

Among all non-aspirin NSAIDs users, 3578 (1.6%) people developed prostate cancer (Table 1). An overall SIR (0.87, 95% CI 0.85–0.90) was found showing a preventive effect of NSAIDs against prostate cancer. Yet, the association was only significantly protective among those aged 50–59 and 60–69 (Table 2). When assessing the duration of use, the preventive effect was seen from a use of 1 year or more, with the strongest preventive effect among the longest-term users (more than 3 years), with SIR = 0.58 (95% CI 0.53–0.63) (Table 3). After exclusion of those also using statins, the preventive effect remained, although less pronounced (SIR = 0.92, 95% CI 0.88–0.95) (Tables 2, 3). Among other NSAIDs users, concomitant statins use showed a 20% reduced risk of prostate cancer (IRR = 0.80, 95% CI 0.73, 0.87) compared to non-statins users (Table 4).

Discussion

This study suggested an overall decreased risk of prostate cancer among non-aspirin NSAIDs users, in particular when

Table 2 The risk of prostate cancer among maintenance users of aspirin and NSAIDs stratified by statins-use, measured by standardized incidence ratios (SIRs)

	Aspirin ($N = 419,931$)			Non-aspirin NSAIDs ($N = 223,437$)		
	Prostate cancer	SIRs (95% CI)	*P*-value	Prostate cancer	SIRs (95% CI)	*P*-value
All	11,291	0.87 (0.85, 0.88)	<0.01	3578	0.87 (0.85, 0.90)	<0.01
18–49 years	6	1.65 (0.60, 3.60)	0.33	31	1.56 (1.06, 2.21)	0.02
50–59 years	392	0.74 (0.67, 0.82)	<0.01	503	0.77 (0.70, 0.84)	<0.01
60–69 years	3328	0.83 (0.80, 0.86)	<0.01	1677	0.83 (0.79, 0.87)	<0.01
70–79 years	4423	0.87 (0.84, 0.90)	<0.01	1043	0.95 (0.90, 1.01)	0.12
≥80 years	3142	0.93 (0.90, 0.97)	<0.01	324	1.10 (0.99, 1.23)	0.08
Statins user subgroup		($N = 264,275$)			($N = 32,839$)	
All	6982	0.80 (0.79, 0.82)	<0.01	655	0.72 (0.67, 0.78)	<0.01
18–49 years	4	1.63 (0.44, 4.17)	0.51	2	1.68 (0.19, 6.05)	0.78
50–59 years	265	0.65 (0.58, 0.74)	<0.01	59	0.56 (0.43, 0.72)	<0.01
60–69 years	2329	0.75 (0.72, 0.78)	<0.01	313	0.66 (0.59, 0.73)	<0.01
70–79 years	2882	0.79 (0.77, 0.82)	<0.01	237	0.86 (0.75, 0.97)	0.02
≥80 years	1502	0.99 (0.94, 1.04)	0.63	44	0.89 (0.65, 1.19)	0.47
Non-statins user subgroup		($N = 155,656$)			($N = 190,598$)	
All	4309	0.99 (0.96–1.02)	0.63	2923	0.92 (0.88–0.95)	<0.01
18–49 years	2	1.71 (0.19–6.17)	0.76	29	1.55 (1.04–2.23)	0.02
50–59 years	127	1.03 (0.86–1.23)	0.77	444	0.81 (0.73–0.89)	<0.01
60–69 years	999	1.10 (1.03–1.17)	<0.01	1364	0.88 (0.83–0.92)	<0.01
70–79 years	1541	1.06 (1.01–1.11)	0.03	806	0.99 (0.92–1.06)	0.69
≥80 years	1640	0.89 (0.84–0.93)	<0.01	280	1.15 (1.02–1.29)	0.02

Table 3 Duration uses of Aspirin and NSAIDs stratified by statins use, measured by standardized incidence ratios (SIRs)

	Aspirin ($N = 419,931$)			Non-aspirin NSAIDs ($N = 223,437$)		
	Prostate cancer	SIRs (95% CI)	*P*-value	Prostate cancer	SIRs (95% CI)	*P*-value
All	11,291			3578		
0–1 years	533	1.06 (0.97, 1,15)	0.23	1574	1.00 (0.95, 1.05)	0.92
1–3 years	4372	2.65 (2.57, 2.73)	<0.01	1531	0.90 (0.86, 0.95)	<0.01
3–5 years	3764	1.61 (1.56, 1.66)	<0.01	473	0.58 (0.53, 0.63)	<0.01
>5 years	2622	0.31 (0.30, 0.32)	<0.01			
Statins user subgroup						
All	6982			655		
0–1 years	214	0.93 (0.81, 1,07)	0.33	259	0.82 (0.72, 0.93)	<0.01
1–3 years	2409	2.55 (2.45, 2.65)	<0.01	292	0.75 (0.67, 0.84)	<0.01
3–5 years	2545	1.63 (1.57, 1.69)	<0.01	104	0.51 (0.42, 0.62)	<0.01
>5 years	1814	0.31 (0.29, 0.32)	<0.01			
Non-statins user subgroup						
All	4309			2923		
0–1 years	319	1.16 (1.03–1.29)	0.01	1315	1.04 (0.99–1.10)	0.14
1–3 years	1963	2.79 (2.67–2.92)	<0.01	1239	0.95 (0.90–1.00)	0.06
3–5 years	1219	1.57 (1.49–1.67)	<0.01	369	0.60 (0.54–0.66)	<0.01
>5 years	808	0.31 (0.29–0.34)	<0.01			

Table 4 Incidence rate (IR) and incidence rate ration (IRR) of aspirin and non-aspirin NSAIDs against prostate cancer, adjusting for age

	Statins	Events	IR (per 1000)	IRR	*P*-value
Aspirin and Non-aspirin NSAIDs group	No	7232	3.99	1.0	—
	Yes	7637	4.54	0.81 (0.78, 0.83)	<0.01
Aspirin group	No	4309	6.57	1.0	—
	Yes	6982	4.99	0.78 (0.75, 0.81)	<0.01
Non-aspirin NSAIDs group	No	2923	2.64	1.0	—
	Yes	655	3.30	0.80 (0.73, 0.87)	<0.01

taken over a longer-period of time. Although aspirin showed some protective effect against prostate cancer, this association was clearly influenced by statins use—which is taken concomitantly by 63% of the aspirin users.

The main strength of this study was the large sample size introduced by population-based design which included all Swedish adults during the study period. The nationwide Swedish health registries are an accurate and valid data source, in particular to define prescribed drug use—eliminating the risk of recall bias, and reducing the risk of misclassification of the exposure.

Nevertheless, some NSAIDs may have been bought over-the-counter, in particular high-dose aspirin (for pain relief) and some NSAIDs. Yet, since prescribed drugs are available at a lower price, we expect that the majority of NSAIDs use has been recorded, in particular among long-term users. Unfortunately, we do not have information on drug use before the initiation of the Prescribed Drug Registry (July 2005). One of the limitations of our study is that our design only took into account confounding by age and calendar period, and the interaction between aspirin/NSAIDs and statins could not be measured based on the design, because we standardized the incidence of prostate cancer by using the total Swedish background population for which only limited information was available. Since aspirin and NSAIDs are commonly used drugs in Sweden, this approach may have diluted our results.

Obesity is a known risk factor for prostate cancer, yet body mass index is not registered in the nationwide Swedish registries, and the diagnosis obesity is underreported; so this could not be taken into account. Another risk factor that cannot be taken into account either is diet, since men who consume large amount of meat or high-fat products may have an increased risk to develop prostate cancer. Sweden is highly developed yet relatively small country considering the number of inhabitants (~10 million) and the majority of the population is of European decent with relatively limited differences in socio-economic status, so we assume that socio-economic and ethno-geographic risk factors have a limited impact on the results. Confounding by indication may, however, be a problem, in particular for aspirin use, since aspirin use may be administered for thrombotic events related to cancer, although a 6 month duration of aspirin use before any cancer diagnosis was used to define maintenance use [23]. Unfortunately, no data on prescribed drug use before July 2005 could be collected since The Swedish Prescribed Drug Registry started from 1 July 2005. We assessed only the estimated duration of use by average DDDs per package instead of accurate daily dose and duration, which may have resulted in over or under-estimation of the real duration of use.

Overall, the current project showed that 2.6% of aspirin users developed prostate cancer, and 1.6% among other NSAIDs users. A higher proportion of aspirin users developed prostate cancer compared to the other NSAIDs users, yet this was also heavily influenced by the different age distribution where aspirin users were markedly older.

The effect of statins use is controversial in current publications and there is no conclusion if long term use of statins could decrease prostate cancer incidence [24]. In our study when statins users were removed from the analyzes, the protective effect of aspirin and non-aspirin NSAIDs was clearly less pronounced which suggests a not negligible interaction with statins especially among aspirin users who commonly use both drugs. The subgroup analysis comparing the effects of aspirin use among those who do and do not use statins are of particular interest, since both drugs are often used in parallel (i.e., individuals with a cardiovascular risk profile). Previous studies did not assess concomitant use, yet our results indicate that the shown preventive effect of aspirin may be largely attributed to the statins instead.

To better understand the role of aspirin and NSAIDs use in the development of prostate cancer, it may be useful to assess previous drug exposure in cohorts of pre-malignant or inflammatory prostate diseases for whom biopsy material is available, so local inflammatory patterns could be explored further. This may help to identify high-risk populations which could benefit most from chronic aspirin/NSAIDs intake in the prevention (or progression) of prostate cancer.

Conclusions

This Swedish population-based cohort study indicated a protective effect of aspirin and other NSAIDs against prostate cancer after long-term maintenance use, yet the combined effect of statins use should not be neglected.

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Authors' contributions Literature search: Y.M.+N.B.; design of the study: Y.M.+N.B.; data collection and preparation for analyzes: N.B.; data analysis: Y.M.+N.B.; data interpretation: Y.M.+N.B.; writing of first draft: Y.M., revised and approved by all authors.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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