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Aspirin but not ibuprofen use is associated with reduced risk of prostate cancer: a PLCO Study

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BACKGROUND: Although most epidemiological studies suggest that non-steroidal anti-inflammatory drug use is inversely associated with prostate cancer risk, the magnitude and specificity of this association remain unclear.

METHODS: We examined self-reported aspirin and ibuprofen use in relation to prostate cancer risk among 29 450 men ages 55–74 who were initially screened for prostate cancer from 1993 to 2001 in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Men were followed from their first screening exam until 31 December 2009, during which 3575 cases of prostate cancer were identified.

RESULTS: After adjusting for potential confounders, the hazard ratios (HRs) of prostate cancer associated with <1 and $\geqslant 1$ pill of aspirin daily were 0.98 (95% confidence interval (CI), 0.90–1.07) and 0.92 (95% CI: 0.85–0.99), respectively, compared with never use (*P* for trend 0.04). The effect of taking at least one aspirin daily was more pronounced when restricting the analyses to men older than age 65 or men who had a history of cardiovascular-related diseases or arthritis (HR (95% CI); 0.87 (0.78–0.97), 0.89 (0.80–0.99), and 0.88 (0.78–1.00), respectively). The data did not support an association between ibuprofen use and prostate cancer risk.

CONCLUSION: Daily aspirin use, but not ibuprofen use, was associated with lower risk of prostate cancer risk.

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Prostate cancer is the most common non-skin malignancy, accounting for an estimated 29% of all newly diagnosed cancers in 2012 among US men (Siegel *et al*, 2012). Despite the large morbidity, the aetiology of prostate cancer remains unclear, with only older age, African ancestry, family history of the disease, and several loci in the 8q24 region as established risk factors (Hsing and Chokkalingam, 2006; Witte, 2007; Cheng *et al*, 2008; Chu *et al*, 2008). Several lines of evidence also point to chronic inflammation of the prostate as a potential predisposing factor, including data suggesting that non-steroidal anti-inflammatory drug (NSAID) use can inhibit prostate carcinogenesis (Stock *et al*, 2008; De Nunzio *et al*, 2011). Non-steroidal anti-inflammatory drugs block the conversion of arachidonic acid to prostaglandins, which are key mediators of the inflammatory response, by inhibiting the enzyme cyclooxygenase (COX, also called prostaglandin synthase; Smith *et al*, 2000). Both COX-1 and COX-2 isoforms are expressed in the human prostate (O'Neill and Ford-Hutchinson, 1993), with multiple reports of elevated COX-2 expression in prostate adenocarcinoma relative to benign hyperplasia or normal tissue (Gupta *et al*, 2000; Hsu *et al*, 2000; Madaan *et al*, 2000; Lee *et al*, 2001; Uotila *et al*, 2001). Some studies have further correlated COX-2 expression with severe tumour grade (Madaan *et al*, 2000; Lee *et al*, 2001), whereas others have found COX-2 overexpression restricted to regions of prostatic proliferative inflammatory atrophy (Zha *et al*, 2001). In addition, treatment of prostate cancer cell lines with selective COX-2 inhibitors has been shown to induce apoptosis (Liu *et al*, 1998, 2000; Hsu *et al*, 2000; Kamijo *et al*, 2001), reduce angiogenesis (Liu *et al*, 2000), and inhibit cellular invasion (Attiga *et al*, 2000).

Although some epidemiological studies have shown inverse relationships between NSAID use and prostate cancer risk (Friis *et al*, 2003; Sorensen *et al*, 2003; Garcia Rodriguez and Gonzalez-Perez, 2004; Mahmud *et al*, 2004, 2006, 2011; Jacobs *et al*, 2005, 2007, 2011; Bosetti *et al*, 2006; Dasgupta *et al*, 2006; Liu *et al*, 2006; Cheng *et al*, 2007; Salinas *et al*, 2010; Dhillon *et al*, 2011), the risk reductions have been modest and only some, not all, have yielded statistically significant results (Nelson and Harris, 2000; Habel *et al*, 2002; Roberts *et al*, 2002; Perron *et al*, 2003; Garcia Rodriguez

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and Gonzalez-Perez, 2004; Jacobs *et al*, 2005, 2007, 2011; Dasgupta *et al*, 2006; Liu *et al*, 2006; Mahmud *et al*, 2006, 2011; Cheng *et al*, 2007; Dhillon *et al*, 2011). In addition, one study reported a significant elevated risk of prostate cancer in association with NSAID non-aspirin use (Murad *et al*, 2011). However, in a recent meta-analysis (Mahmud *et al*, 2010), the summary odds ratios for prostate cancer associated with aspirin use were 0.83 (95% confidence interval (CI): 0.77–0.89) for all studies and 0.81 (95% CI: 0.72–0.92) for advanced prostate cancer. The ORs associated with non-aspirin NSAID for all studies or advanced prostate cancer were 0.89 (95% CI: 0.78–1.08) and 0.98 (95% CI: 0.59–1.65), respectively. The lack of clear consistency across studies of NSAID use and prostate cancer risk may be explained by factors related to study design, including choice of study population, exposure definition and assessment, length of follow-up, prostate cancer detection, and confounding. The observed differences in cancer risk associated with aspirin relative to other NSAIDs may also be attributed in part to pharmacological differences between individual NSAIDs.

Therefore, to overcome the shortcoming of previous studies, we examined the relationship of aspirin and ibuprofen use with subsequent risk of prostate cancer in a cohort of 29 450 men participating in the screening arm of Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The use of this cohort provided us with prospective data on a wide range of topics, including medical history, allowing for adjustment for several putative confounders. In addition, men in the intervention arm of the trial were uniformly screened for prostate cancer, therefore minimising misclassification of the outcome. Previous studies may have included occult cancers, which could cause participants to increase their NSAID use, thereby masking the protective effect of NSAID use due to reverse causality. The PLCO Cancer Screening Trial, on the other hand, included few prevalent cancers owing to its nature as a screening trial. Also, given the large number and diversity of participants from 10 screening centres across the United States, the PLCO Trial presented an opportunity to further assess the relationship between NSAID use and prostate cancer risk within a more broadly representative sample of the US population than most previous studies. In addition, PLCO's use of active and passive surveillance and cause of death review process allowed the most comprehensive ascertainment of study endpoints including prostate cancer and death (Prorok *et al*, 2000).

METHODS

The PLCO Cohort detailed information on the PLCO Trial has been published elsewhere (Gohagan *et al*, 2000; Prorok *et al*, 2000). Approval of the trial protocol and procedures was granted by the Institutional Review Boards of the National Cancer Institute and the 10 screening centres (Birmingham, AL, USA; Denver, CO, USA; Detroit, MI, USA; Honolulu, HI, USA; Marshfield, WI, USA; Minneapolis, MN, USA; Pittsburgh, PA, USA; Salt Lake City, UT, USA; St Louis, MO, USA; and Washington, DC, USA). All participants provided written informed consent. Study eligibility for men was restricted to those ages 55–74 who were not under current treatment for any cancer (except basal and squamous cell skin cancer); had no prior history of prostate, lung, or colorectal cancer; had not undergone surgical removal of a lung or the prostate or colon; had not taken Proscar (Finasteride) in the past 6 months; and were not already enrolled in another cancer screening or prevention trial. This study was further limited to men randomised to the screening arm.

At study entry, men were screened for prostate cancer by digital rectal examination (DRE) and prostate-specific antigen (PSA) testing. They also completed a brief, structured questionnaire on risk factors for cancer and a 137-item food frequency questionnaire on diet and nutrient supplement use in the last 12 months. Screening for prostate cancer occurred annually for 5 years after the initial visit. Digital rectal examination was performed in the first 3 years, while serum PSA levels were tested for 5 consecutive years. Men with suspicious findings for prostate cancer (i.e., PSA $>4\,\mathrm{ng\,ml^{-1}}$ or DRE with nodularity, indurations, or asymmetry of the prostate gland) were referred for further diagnostic evaluation. Medical record review was conducted by trained abstractors to capture data on relevant diagnostic and therapeutic procedures that occurred up to 1 year after cancer detection. Also as part of the follow-up process, participants were mailed annual surveys that were used to ascertain cancer incidence and death, and loss to follow-up was established based upon failure to receive these completed surveys. For completeness of follow-up, where available, prostate cancer data were retrieved from the population-based cancer registries serving the relevant study centre. Additional ascertainment of vital status was conducted using the National Death Index. Underlying cause of death was determined for all participants by unbiased death review panels that were blinded to the study arm and not affiliated with the study centre. The death review process entails reviewing the death certificates, medical reports, and autopsy reports. Pathological grade was assessed using the biopsy/resection Gleason score (range 2–10). Clinical staging of patients were determined using the TNM staging system (Fleming *et al*, 1997). An aggressive cancer was defined as a Gleason score of 7 or higher, or a stage III or IV case.

Of the 38 340 men randomised to the screening arm, we focused our study on the 37 448 who had NSAID use data and who were first screened for prostate cancer between November 1993 and July 2001. Men were excluded from the analysis if they (1) reported a prior history of cancer at baseline, except non-melanoma skin cancer ($n=1726$); (2) failed to complete the baseline risk factor ($n=892$) and dietary ($n=6586$) questionnaires; (3) had no further contact (i.e., no follow-up) after the baseline screening exam ($n=4107$); and (4) had an insufficient dietary assessment (7452) or 5) did not have adequate baseline PSA ($n=4115$). Men who refrained from answering any question pertaining to NSAID use ($n=913$) were additionally excluded (counts are not mutually inclusive), resulting in a final study cohort of 29 450 men, with 3575 cases of prostate cancer identified in subsequent follow-up. There were 546 cancers diagnosed within the first year of follow-up and 3029 cancers diagnosed after the first year of follow-up.

Assessment of NSAID use

The baseline questionnaire included four questions that pertained to aspirin and ibuprofen use: (1) During the last 12 months, have you regularly used aspirin or aspirin-containing products, such as Bayer, Bufferin, or Anacin? (Specific instruction was provided to not count aspirin-free products, such as Tylenol or Panadol). (2) During the last 12 months, how many pills of aspirin or aspirin-containing products did you usually take per day, per week, or per month? (3) During the last 12 months, have you regularly used ibuprofen-containing products, such as Advil, Nuprin, or Motrin? and (4) During the last 12 months, how many pills of ibuprofen-containing products did you usually take per day, per week, or per month? Possible responses for frequency of use of aspirin or ibuprofen included none, <2 per month, 2–3 per month, 1 per week, 2 per week, 3–4 per week, 1 per day, and 2 or more per day.

Statistical analysis

In our analysis, men were categorised separately for each NSAID according to their reported frequency of use at baseline: never use, 1–29 pills per month (<1 pill per day), 1 pill per day, and $\geqslant 2$ pills per day. We also considered whether aspirin and ibuprofen were used jointly or separately by creating another variable with categories of neither, only regular aspirin use, only regular ibuprofen use, and regular use of both NSAIDs.

Hazard ratios (HRs) and 95% CIs for prostate cancer related to the frequency of aspirin and ibuprofen use were estimated by Cox regression with the HR modelled as a function of age (Korn *et al*, 1997). The follow-up period for each individual began from the individual age at the baseline screening until the individual age at the prostate cancer diagnosis, death, loss to follow-up, or the administrative censor date (31 December 2009), whichever occurred first. To examine dose response effects associated with increasing frequency of use, trend tests were performed on a continuous scale, where each category was assigned the value of 0, 1, …, and so on, and included in the model as a continuous variable. Multivariate analyses were conducted to evaluate potential confounding by age (modelled as the underlying metric/time, that is, not as a covariate in the model); race (White, Black, Asian/Pacific Islander, other); study centre; family history of prostate cancer (yes, no); the number of screening exams in the follow-up period; education (less than high school, high school graduate, some college, college graduate, or higher); smoking status (never, former cigarette use, current cigarette use, pipe, or cigar use); baseline body mass index (BMI, <25.0, 25.0–29.9, $\geqslant 30\,kg\,m^{-2}$); physical activity (none, <1, 1, 2+ hours per week); total energy (kcal per day, in quintiles); various dietary factors (grams per day, in quintiles, adjusted for energy using the residual method (Willett and Stampfer, 1986)), including total β-carotene, vitamin C, vitamin A, vitamin D, vitamin E, calcium, fat, red meat, and lycopene; and self-reported history of various medical conditions (yes or no), including hypertension, heart attack, stroke, diabetes, arthritis, and colon polyps. Final multivariate models were adjusted for age, race, study centre, family history of prostate cancer, the number of screening exams, aspirin use (for ibuprofen), and ibuprofen use (for aspirin). A variable remained in the final model if it resulted in $>10\%$ change in the HR estimate of NSAID. Calculated *P*-values were two-sided, with $P<0.05$ considered statistically significant.

To address the probability of reverse causality (i.e., individuals with occult cancer might experience pain that lead to the use of NSAID), which may lead to variation in the risk associated with NSAID use in cancers diagnosed within the first year of follow-up and cancers diagnosed after the first year of follow-up, analyses were performed to estimate the risk of cancers diagnosed within the first year of follow-up and cancers diagnosed after the first year of follow-up in association with aspirin and ibuprofen use. The significance of the difference in risk by time of cancer diagnosis was tested by including an interaction term as cross product between aspirin/ibuprofen and time of cancer diagnosis (as a dummy variable of first year *vs* later years). Hazard ratios for non-aggressive and aggressive prostate cancers were also estimated, such that for aggressive cancer, analysis was restricted to cases with aggressive cancer compared with the controls. Similarly for non-aggressive cancers analysis was restricted to cases with non-aggressive cancers and the controls. Prostatic tumours classified as stage III or IV or designated Gleason scores of 7 or higher were defined as aggressive ($n=1560$), whereas all other tumours were defined as non-aggressive ($n=2015$). To address the possibility that death may act as a competing risk, we conducted sensitivity analysis where death was considered as a competing risk instead of being a censoring variable (Andersen, 1993). Stratified analyses were conducted to determine whether HRs associated with NSAID use varied by age (<65, $\geqslant 65$ years) and by history of selected medical conditions (yes and no). Risk differences by race could not be examined as 92.4% of the study population was White. Individuals with missing data on any variable were excluded in the analysis.

RESULTS

In this cohort, the mean age at entry was 62.8 (s.d. = 5.3) years, with a median (interquartile range) follow-up time of 11.7 (9.5,12.9) years. Most men ($>90\%$) were Caucasian and college educated. The cohort included 25 875 controls and 3575 prostate cancer cases. During the study follow-up, 105 prostate cancer-related deaths and 4708 other causes deaths were observed, with a median (interquartile range) follow-up time of 5.0 (2.0–8.5) in cases and 12.2 (10.3, 12.9) in controls. The age and race of men who did not respond to the NSAID questions were not significantly different from responders. In the following analyses, the use of aspirin or ibuprofen was assessed at the study entry. For simplicity, in the remaining of the manuscript, we will refer to these exposures as aspirin and ibuprofen use. On a daily basis, aspirin was used more than ibuprofen, with only 1.2% of men taking both drugs. For aspirin, 46% reported never use and 30.7% reported use of $\geqslant 1$ pill per day, whereas for ibuprofen, 75.2% reported never use and 7.6% reported use of $\geqslant 1$ pill per day.

As shown in Table 1, daily use of aspirin was greater with age: 26.6% for <60 years and 36.3% for $\geqslant 70$ years. Although daily use of ibuprofen was fairly consistent across age groups, the oldest men used ibuprofen least often. Daily use of either aspirin or ibuprofen was much less common among Asian/Pacific Islander men than other racial groups. Frequency of NSAID use, however, did not differ substantially by education or family history of prostate cancer. There was also minimal variation in NSAID use by smoking status, although use was most prevalent among current cigarette smokers. Use of both aspirin and ibuprofen was greatest among men with a baseline BMI of $\geqslant 30\,kg\,m^{-2}$. The prevalence of daily aspirin use was slightly higher with greater physical activity, whereas the prevalence of daily ibuprofen use was lower. Daily aspirin use was greatest among men with a history of cardiovascular-related conditions, including heart attack (72.5%), stroke (60.2%), and hypertension (41.4%), and with a history of diabetes (43.4%), whereas daily ibuprofen use was greatest among men with a history of arthritis (14.9%).

The daily use of aspirin only was significantly associated with lower risk of cancer HR (95% CI) of 0.91 (0.84–0.99). Although the daily use of ibuprofen only showed similar trend, however, it was not statistically significant 0.88 (0.65–1.20). Interestingly, the daily use of aspirin plus ibuprofen was associated with excess risk of prostate cancer 1.55 (1.13–2.13).

In multivariable analysis, the risks for prostate cancer associated with taking $<$one pill and $\geqslant 1$ pill of aspirin per day, relative to never use, were 0.98 (95% CI, 0.90–1.07) and 0.92 (95% CI, 0.85–0.99), after adjusting for race, study centre, family history of prostate cancer, number of screening exams, and ibuprofen use (Table 2). We observed a significant negative trend with the frequency of aspirin use (*P* for trend = 0.04). As expected, in the competing risk model, use of $\geqslant 1$ pill of aspirin was associated with excess risk of death, but with lower risk of prostate cancer (HR (95% CI); 1.30 (1.21–1.39) and 0.92 (0.85–0.99), respectively). Risks associated with daily aspirin use were similar but slightly lower for aggressive than non-aggressive cancers. Although the magnitude and strength of the association were slightly attenuated when we excluded cancers diagnosed within the first year of follow-up (HR (95% CI); $<$one pill 0.99 (0.90–1.09), and $\geqslant 1$ pill 0.92 (0.84–1.0)), the HRs calculated for cancer diagnosed in the first year of follow-up and in the remaining years of follow-up did not differ significantly (*P* for interaction = 0.56). There was no evidence of an association between ibuprofen use and prostate cancer risk.

History of various medical conditions including; diabetes, hypertension, stroke, heart attack, arthritis, and colon polyp did not appreciably modify the association between the use of either NSAID and prostate cancer risk (data not in tables). However, in stratified analysis, the inverse associations appeared more pronounced among men taking at least one aspirin daily who were older than 65 years with a HR (95% CI) of 0.87 (0.78–0.97) and who reported having a history of cardiovascular-related diseases HR (95% CI) = 0.89 (0.80–0.99) or arthritis HR (95% CI) = 0.88 (0.78–1.00) despite the lack of significant interaction.

Table 1 Population characteristics by frequency of aspirin and ibuprofen use at baseline[a]

	Aspirin use in last 12 months					Ibuprofen use in last 12 months					Total
	Never	<1 per day	1 per day	⩾2 per day		Never	<1 per day	1 per day	⩾2 per day		
	n = 13 539	*n* = 6849	*n* = 7604	*n* = 1440	*P*-value	*n* = 22 113	*n* = 5064	*n* = 592	*n* = 1634	*P*-value	*n*
	%	%	%	%		%	%	%	%		
Total	46.0	23.3	25.8	4.9		75.2	17.2	2.0	5.6		29 540
Number of screening exams median (interquartile range)	6 (5, 6)	6 (5, 6)	6 (5, 6)	6 (4, 6)	0.01	6 (5, 6)	6 (5, 6)	6 (4, 6)	6 (5, 6)	<0.01	6 (5, 6)
Follow-up time median (interquartile range)	11.9 (9.7, 12.9)	12.0 (9.8, 12.9)	11.4 (9.3, 12.9)	11.5 (9.3, 12.9)	<0.0001	11.8 (9.5, 12.9)	11.5 (9.6, 12.9)	11.4 (9.2, 12.9)	11.5 (9.5, 12.9)	0.25	11.7 (9.5, 12.9)
Age at entry					<0.0001					<0.0001	
55–59	48.2	25.2	21.8	4.8		70.9	21.7	2.0	5.4		9129
60–64	47.3	23.6	24.5	4.7		75.5	16.7	2.1	5.8		9396
65–69	43.4	21.5	30.1	5.0		78.1	14.6	1.7	5.6		6959
70+	42.4	21.3	31.1	5.2		79.5	12.8	2.3	5.4		3966
Race					<0.0001					<0.0001	
White	45.3	23.3	26.4	5.0		74.8	17.4	2.0	5.8		27 200
Black	50.8	23.7	20.8	4.7		751	17.9	2.9	4.1		999
Asian/Pacific Islander	58.0	23.1	16.6	2.2		84.8	12.3	0.8	2.2		1184
Other	52.2	17.9	23.9	601		76.1	2246	0.0	1.5		67
Education					<0.0001					<0.0001	
Less than high school	46.2	20.9	26.1	6.9		75.3	14.2	2.4	8.2		2232
High school graduate	46.1	21.9	26.6	5.4		74.9	16.9	2.2	6.1		5423
Some college	45.8	23.9	25.4	4.9		74.4	17.8	2.1	5.7		9482
College graduate or higher	46.1	23.8	25.8	4.3		76.0	17.5	1.8	4.7		12 286
Family history of prostate cancer					0.80					0.24	
No	46.1	23.2	25.8	4.9		75.5	17.0	2.0	5.5		26 489
Yes	46.0	23.6	25.3	5.0		74.2	17.7	2.0	6.2		2241
Smoking history					<0.0001					<0.0001	
Never	51.1	22.5	22.	4.0		78.9	14.7	1.6	4.6		8670
Former cigarette use	46.8	25.1	21.9	6.2		74.3	18.2	1.9	5.6		3127
Current cigarette use	43.1	23.2	28.6	5.2		73.5	18.3	2.3	6.0		15 324
Pipe or cigar use only	45.2	24.5	26.0	4.4		74.0	17.8	2.0	6.2		2324
Body mass index					<0.0001					<0.0001	
<18.5–24.9	49.5	24.0	22.5	4.1		79.8	14.8	1.5	3.9		7544
25.0–29.9	45.3	23.6	26.4	4.6		74.9	17.7	2.0	5.5		14 736
30.0+	43.9	21.4	28.4	6.3		70.9	18.9	2.6	7.6		6874
Physical activity (per week)					<0.0001					<0.001	
None	48.7	21.8	23.2	6.3		74.5	16.8	2.1	6.6		4402
<1 h	47.2	23.7	23.7	5.4		73.5	18.0	2.1	6.4		5125
1 h	46.3	24.6	24.8	4.4		74.8	17.9	2.0	5.3		3387
2 or more hours	44.8	23.3	27.5	4.4		76.0	17.0	2.0	5.0		16 446
Medical history											
Hypertension	37.5	21.1	35.8	5.6	<0.0001	74.4	16.9	2.6	6.1	<0.0001	9761
Heart attack	17.2	10.4	67.2	5.3	<0.0001	78.4	14.3	2.1	5.2	<0.0001	3768
Stroke	28.5	11.2	52.7	7.5	<0.0001	80.4	11.8	1.9	5.9	<0.01	695
Diabetes	38.7	17.9	37.5	5.9	<0.0001	73.9	17.4	2.2	6.5	0.14	2452
Arthritis	42.8	22.1	27.1	8.0	<0.0001	65.9	19.3	3.6	11.3	<0.0001	8687
Colon polyps	43.6	23.1	28.8	4.5	<0.01	74.5	17.5	1.7	6.3	0.26	2486

[a]Row percentages.

DISCUSSION

Data from this prospective cohort study suggest that regular use of aspirin, but not ibuprofen, was associated with a reduced prostate cancer risk. Overall decreases in prostate cancer risk associated with regular aspirin use were modest, although there was some evidence of further risk reduction with more frequent use, particularly among men who were older than age 65 or who had a prior history of cardiovascular-related diseases or arthritis.

The lack of an association between ibuprofen use and prostate cancer risk in this analysis is likely attributed in part to the low prevalence of ibuprofen use in the PLCO cohort. Previous studies

Table 2 HRs for prostate cancer in relation to frequency of aspirin and ibuprofen use in the 12 months before study entry

		Aspirin				Ibuprofen			
	Frequency of use in last 12 months	Cases	RR[a]	95% CI	*P* for trend	Cases	RR[a]	95% CI	*P* for trend
Total prostate cancer	None	1669	1.00	Reference		2686	1.00	Reference	
	<1 per day	848	0.98	0.90–1.07		602	1.01	0.93–1.11	
	⩾1 per day	1056	0.92	0.85–0.99	*0.04**	283	1.01	0.89–1.14	*0.79*
Aggressive cancer	None	753	1.00	Reference		1182	1.00	Reference	
	<1 per day	347	0.89	0.78–1.02		248	0.98	0.85–1.13	
	⩾1 per day	459	0.88	0.78–0.99	*0.05**	128	1.04	0.86–1.25	*0.96*
Non-aggressive cancer	None	916	1.00	Reference		1504	1.00	Reference	
	<1 per day	501	1.06	0.95–1.19		354	1.03	0.92–1.17	
	⩾1 per day	597	0.94	0.85–1.04	*0.42*	155	0.98	0.83–1.15	*0.87*

Abbreviation: CI = confidence interval. [a]Adjusted for race, study centre, family history of prostate cancer, the number of screening exams, aspirin use (for ibuprofen only), and ibuprofen use (for aspirin only). *Significant at 0.05 level.

of ibuprofen have conflicting results. Although few studies reported reduced risk of prostate cancer in association with non-aspirin NSAID use (Dasgupta *et al*, 2006; Mahmud *et al*, 2011), some studies reported increased (Murad *et al*, 2011) or no risk (Platz *et al*, 2005; Brasky *et al*, 2010). Laboratory data indicate that both aspirin and ibuprofen can inhibit prostatic carcinogenesis (Attiga *et al*, 2000; Andrews *et al*, 2002; Lloyd *et al*, 2003). In a study that compared the effect of various non-prescription NSAIDs (including aspirin and ibuprofen) on prostate tumour cell survival, ibuprofen was the most effective in suppressing proliferation and inducing apoptosis, particularly at clinically prescribed doses (Andrews *et al*, 2002).

Owing to the potential adverse effects of aspirin, such as gastrointestinal tract and renal toxicity, it is useful to identify subgroups of men for whom use of aspirin is particularly beneficial. In analyses restricted to men with a history of cardiovascular-related diseases and men with a history of arthritis, we observed inverse associations between frequency of aspirin use and prostate cancer risk. Although the questionnaire lacked data on specific dose and duration of NSAID use, our results of lower risk among men older than 65 years and among those who have history of cardiovascular diseases and arthritis suggest that the reduction in prostate cancer risk is likely conferred by aspirin taken at generally low doses (such as for cardiovascular disease) for long duration (among older men). This notion is further supported by the current common medical practice, where for the purpose of coronary artery disease prevention doctors prescribe the lower dose aspirin ($81\,mg\,day^{-1}$) for the majority of patients (about 60%) and regular dose aspirin ($325\,mg\,day^{-1}$) for about 35% (Campbell *et al*, 2007)).

Several sources of bias, including confounding and detection bias, could have affected the observed associations of aspirin and ibuprofen use with prostate cancer risk. Men who take NSAIDs daily for preventive purposes may be more health conscious and more likely to engage in positive health-related behaviours, such as maintaining a healthy diet and exercising regularly, which could influence their risk for prostate cancer. However, controlling for physical activity, dietary fat consumption, and other dietary factors suspected to decrease prostate cancer risk, including lycopene and vitamin E intake, did not materially alter the risk estimates for either NSAID. Confounding may further exist if NSAID use is related to a physical condition that directly affects prostate cancer risk (Psaty *et al*, 1999). Although adjustment for several factors, including arthritis and hypertension, did not alter the results, residual confounding by unknown factors cannot be ruled out.

The intriguing association between aspirin use and prostate cancer risk among men with cardiovascular-related diseases merits further investigation. Reasons for the inverse relation between aspirin use and prostate cancer risk observed among men with cardiovascular-related diseases are unknown, but recent studies suggest that prostate cancer and cardiovascular disease share common risk factors, such as hyperlipidemia and chronic inflammation, and that regular statin use lowers the risk of prostate cancer (Platz *et al*, 2006; Flick *et al*, 2007; Jacobs *et al*, 2007; Taylor *et al*, 2008). It should be noted that the prevalence of daily aspirin use was greater among men who reported a history of cardiovascular-related diseases or diabetes than men without these conditions. In the PLCO cohort, diabetes, a major risk factor for cardiovascular disease, had divergent relations with prostate cancer by tumour aggressiveness. In these men, diabetes was associated with a reduced risk of total prostate cancer but an increased risk of aggressive prostate cancer among men who were lean or physically active (Leitzmann *et al*, 2008). Additional adjustment for history of diabetes, however, did not materially change the association between aspirin use and prostate cancer risk in our analysis.

Surveillance bias is possible but not likely to account for the suggestive association between aspirin use and prostate cancer risk. In theory, NSAID users, being either more health conscious or more burdened with other medical problems, may be under closer medical surveillance than non-users, thereby increasing their chances for early detection of prostate cancer. Such bias, if any, is likely minimal in our study, as men participating in the screening arm of the PLCO Trial had an equal opportunity for cancer detection – a unique difference from prior studies – with screening visits scheduled annually over the first 5 years of follow-up. To account for any residual difference in adherence to annual screening between NSAID users and non-users, the total number of screening visits across the follow-up period for each individual was treated as a confounding variable (Weiss, 2003), but it yielded no substantial change in the magnitude or direction of risk associated with NSAID use.

Although recall bias was minimised by the prospective study design, exposure misclassification could have occurred if there were any changes in NSAID use related to symptoms of undiagnosed prostatic disease within the last 12 months before enrolment. This would be most likely to affect those men diagnosed with prostate cancer earlier in the follow-up period. Although excluding the 15% of cases who were diagnosed within the first year of follow-up (i.e., probably prevalent cases) from the analysis did weaken the association between daily aspirin use and prostate cancer risk, there was no meaningful difference in the HRs for cancers diagnosed within the first year of follow-up and cancers diagnosed after the first year of follow-up. Another unresolved issue is whether NSAIDs are more effective at inhibiting tumour progression than initiation. Two studies have suggested that frequent aspirin use reduces risk for advanced or

metastatic prostate cancer (Norrish *et al*, 1998; Leitzmann *et al*, 2002). In contrast, another cohort study showed about a 24% reduction in prostate cancer risk with daily aspirin use, the magnitude of which did not differ between local and regional/distant disease (Habel *et al*, 2002). Given that our male cohort originated from the screening arm of the PLCO Trial, participants were screened annually. Therefore, cancer cases were more likely to be caught early. Thus, few cases of metastatic cancer were diagnosed, with almost half of the metastatic cancer cases detected within 1 year of the initial screening visit. Under these circumstances, only regular aspirin use in relation to advanced prostate cancer could be examined. We found a slightly lower risk for aggressive compared with non-aggressive tumours, indicating that aspirin might be more influential in hindering the progression than development of prostatic tumours.

Even though the underlying mechanisms have yet to be precisely delineated, the potential benefit of aspirin does support the prevailing hypothesis that chronic inflammation contributes to prostate carcinogenesis. As a response in the repair of damaged or infected prostatic tissue, chronic inflammation may promote neoplastic development and growth by triggering specific cytokines and growth factors, activating COX-2 in macrophages and epithelial cells, and inducing oxidative stress (Lucia and Torkko, 2004). Accordingly, increasing attention has been devoted to the focal lesions of epithelial atrophy associated with chronic inflammation and a high proliferative index, collectively known as proliferative inflammatory atrophy. These lesions have been commonly observed in the peripheral zone of the prostate where most tumours originate, found in close proximity to both adenocarcinoma and high-grade prostatic intraepithelial neoplasia, and associated with COX-2 upregulation (Zha *et al*, 2001; Platz and De Marzo, 2004).

Despite numerous strengths, including low attrition, nearly complete histological confirmation of cancer cases, comprehensive baseline data on potential confounders, and equal access for prostate cancer screening among participants, this study had several limitations. Data on frequency of aspirin and ibuprofen use were collected at a single point in time (during the last 12 months), without record of dose (pill count), duration, or indication for use. Therefore, there might be some misclassification of NSAID use because the assessment relied only on baseline self-reports. However, although there might be an underestimation because people tend to increase the frequency or the dose of use of NSAID by age, this underestimation is expected to be non-differential because the reporting was before the development of cancer. In fact this underestimation, if it biased our results at all, would bias the results towards the null. Thus, our estimates are conservative. In addition, misclassification might have occurred because of the use of some prescription and/or over-the-counter NSAID that the respondent might overlooked. However, if there is misclassification, it would most likely be non-differential, therefore potentially attenuating our results.

The prevalence of regular aspirin use in this study (31%), nevertheless, was comparable to that noted in the other US-based cohort studies of prostate cancer, which ranged from 17% (for daily use) to 59% (for use in the past month; Paganini-Hill *et al*, 1989; Schreinemachers and Everson, 1994). In a US study on patterns of aspirin use among adults ages 45–64, the prevalence of aspirin use among white men was 31%, with increasing trends in prevalence noted both across the study period (1987 to 1989) and with older age. In addition, a recent report from the Household Component of the Medical Expenditure Panel Survey by the Agency for Health Care Research and Quality concluded that 19.3% of the adult US non-institutionalised individuals report aspirin use either daily or every other day. The use increases by age, and almost 50% of individuals older than 65 years old reported daily use (Soni, 2007). Exposure assessment was also limited by not taking into account the use of other specific NSAIDs and by not verifying self-reported data on NSAID use through medical record review. However, misclassification due to the use of COX-2 selective inhibitors, such as celecoxib and rofecoxib, was probably minimal, as these 'new generation' NSAIDs were first introduced in 1999, which was toward the end of the trial recruitment period. Although the extent and impact of exposure misclassification cannot be determined, extensive measurement error would most likely lead to risk attenuation.

In addition, as the majority of the participants are White, the results might not be generalisable to other races. Another limitation of this type of data is left truncation, such that participants who enter the cohort at a certain age have obviously not died or developed cancer before that age. Subjects who died or developed cancer before enrolment would clearly not be included in the cohort, thus resulting in left truncation. However, we used PROC PHREG in SAS/STAT software (Version 9.2, SAS Institute Inc., Cary, NC, USA), which allows late entry models. This analysis method handles the left truncated data therefore alleviates this limitation.

Another limitation that should be noted is the competing mortality due to aging or other medical conditions. However, in the competing risk sensitivity analysis, the inverse associations we observed between NSAID use and prostate cancer are unlikely to be due to an increased risk of death among men who take NSAIDs; since the results were essentially the same for the analysis with and without death included as a competing risk.

In summary, this prospective cohort study suggests that aspirin use was associated with a reduced prostate cancer risk, in particular, in certain subgroups of men. Additional studies with more detailed exposure measurement are warranted to evaluate the dose, duration, and timing of NSAID use in relation to prostate cancer risk. The association between non-selective and selective COX-2 inhibitors, as well as non-COX inhibitors, should also be investigated. Coupled with laboratory-based research, these efforts should further expand our knowledge of the mechanisms by which NSAIDs, particularly aspirin, may influence prostate carcinogenesis.

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