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Aspirin, NSAIDs, and Risk of Prostate Cancer: Results from the REDUCE Study

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Abstract

Purpose: A recent meta-analysis showed that aspirin was associated with reduced prostate cancer risk. As anti-inflammatory medications lower PSA levels, whether these findings reflect reduced prostate cancer detection or lower prostate cancer risk is unknown. We tested the association between aspirin and nonaspirin NSAID use on prostate cancer diagnosis in REDUCE, where all men received biopsies at 2 and 4 years largely independent of PSA. REDUCE tested dutasteride for prostate cancer risk reduction in men with a PSA of 2.5 to 10.0 ng/mL and a negative prestudy biopsy.

Experimental Design: We examined the association between aspirin, NSAIDs, or both and total, low-grade (Gleason < 7), or high-grade (Gleason ≥ 7) prostate cancer versus no prostate cancer using multinomial logistic regression among 6,390 men who underwent ≥1 on-study biopsy. Multivariable analyses were adjusted for age, race, geographic region, PSA, prostate volume, digital rectal examination, body mass index, treatment arm, smoking, alcohol, statins, hypertension, diabetes, and cardiovascular disease.

Results: Overall, 3,169 men (50%) were nonusers, 1,368 (21%) used aspirin, 1,176 (18%) used NSAIDs, and 677 (11%) used both. In unadjusted models, aspirin was associated with reduced prostate cancer risk (OR = 0.85, P = 0.036). In multivariable analyses, aspirin was associated with reduced total prostate cancer risk (OR = 0.81, P = 0.015). Use of NSAIDs or NSAIDs and aspirin was not associated with total, low-grade, or high-grade prostate cancer, though all ORs were <1 (all $P \geq 0.08$). Therefore, we created a dichotomous variable of aspirin and/or NSAID users versus nonusers. On multivariable analysis, the use of aspirin and/or NSAIDs was significantly associated with decreased total (OR = 0.87, P = 0.030) and high-grade (OR = 0.80, P = 0.040), but not with low-grade, prostate cancer risk (OR = 0.90, P = 0.15). Results were similar in placebo and dutasteride arms.

Conclusions: Among men with a negative biopsy, aspirin and/or NSAID use was associated with decreased prostate cancer risk. Additional studies are warranted. *Clin Cancer Res; 21(4); 756–62. ©2014 AACR.*

Introduction

Aspirin and NSAIDs have been associated with reduced risk of several cancers, including melanoma (1), breast (2), and lung cancers (3). However, the association with prostate cancer risk is less clear (4, 5).

A recent meta-analysis of prospective and case–control cohort studies including over 100,000 prostate cancer cases worldwide found aspirin was associated with a reduced risk of total prostate cancer and prostate cancer–specific mortality; however, the effect of any NSAID on prostate cancer appeared to vary by geographic region (6). Indeed, studies from Europe found that the use of any NSAID was associated with an increased risk of total prostate cancer (7–9), whereas North American studies found a decreased risk of total prostate cancer among any NSAID users (10–13).

Given that anti-inflammatory medications can alter PSA levels (14), which is the primary means used for prostate cancer detection, whether the findings of reduced prostate cancer risk among NSAID users in North America reflect reduced prostate cancer detection or truly a biologic link with lower prostate cancer risk is unknown. In other words, if only men with abnormal PSAs are referred for biopsy, and if anti-inflammatory medications lower PSA, this could lead to fewer biopsies and reduced cancer detection. On the other hand, the missed cancers in men taking aspirin and/or NSAIDs would continue to grow and be detected at a later more aggressive stage. Thus, detection bias could explain the observed association between anti-inflammatory medications and increased risk of total prostate cancer in Europe, where PSA screening is not as frequently practiced as in North America. Given these issues, the true association between anti-inflammatory medications and prostate cancer risk is unclear.

Our goal was to test the association between anti-inflammatory medication use and prostate cancer risk while minimizing reverse causation and PSA screening bias. To accomplish this, we examined the association between aspirin and nonaspirin NSAIDs on prostate cancer diagnosis among men with an elevated PSA and negative prestudy biopsy in the REDUCE study, a 4-year randomized trial of dutasteride versus placebo on prostate cancer risk (15), where all men received biopsies at 2 and 4 years regardless of PSA levels. Given that nearly 83% of men had at least one biopsy

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Translational Relevance

We found that in an observational study of men with a negative baseline biopsy and an elevated PSA who received routine biopsies at 2 and 4 years largely independent of PSA, those men taking either aspirin and/or NSAIDs at baseline had a lower risk of prostate cancer including high-grade prostate cancer. Although these data support the hypothesis that anti-inflammatory drugs may indeed have a biologic role in arresting prostate cancer development, this requires formal prospective testing in randomized trials.

performed and >93% were per protocol (i.e., performed regardless of PSA), this study provides a unique opportunity to test the association between aspirin and/or NSAIDs and prostate cancer risk largely independent of PSA. We hypothesized *a priori* that aspirin and/or NSAIDs would be associated with lower prostate cancer risk after controlling for clinical covariates, and this association would be independent of geographic region in this population all of whom had undergone PSA screening before the study.

Materials and Methods

Study population

The design of the REDUCE study has been reported (15). Eligible men were ages 50 to 75 years, with a serum PSA of 2.5 to 10 ng/mL if ages 50 to 60 years, or 3 to 10 ng/mL if >60 years, and a single, negative prostate biopsy (6–12 cores) within 6 months before enrollment (independent of the study).

Study design

REDUCE was a 4-year, multicenter, double-blind, placebo-controlled study (15). Eligible subjects were randomized to dutasteride (0.5 mg/day) or placebo. Visits occurred every 6 months. Total serum PSA (Beckman Coulter Inc.) was assessed every 6 months, with doubled PSA values (±0.1 ng/mL in half of the subjects) reported to investigators for men receiving dutasteride. Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Subjects underwent 10-core transrectal ultrasound (TRUS)–guided biopsy at 2 and 4 years regardless of PSA levels ("protocol-dependent" biopsies); unscheduled biopsies were performed if clinically indicated ("protocol-independent" biopsies). For-cause biopsies obtained during months 19 to 24 and 43 to 48 replaced those scheduled for years 2 and 4, and were included in the definition of protocol-dependent biopsies.

At baseline, a detailed medical history was obtained including smoking history, alcohol use, medication use, and medical comorbidities. Height and weight were measured and body mass index (BMI; kg/m^2) was calculated. Race was self-reported. Digital rectal examination (DRE) findings and TRUS prostate volume were reported from the prestudy biopsy.

Statistical analysis

Use of either aspirin, NSAIDs, or both was self-reported. The association between use of aspirin, NSAIDs, or both and baseline parameters was tested using Kruskal–Wallis for continuous variables and χ^2 for categorical variables. The association between aspirin, NSAIDs or both, and PSA as a continuous variable was examined using linear regression controlling for age (continuous), race (white, black, other), and DRE findings (suspicious for cancer vs. not).

The OR associated with use of aspirin, NSAIDs, or both at baseline and risk of total, low-grade (Gleason <7), or high-grade (Gleason $\geq$7) prostate cancer relative to no cancer was examined using multinomial logistic regression. We chose to mutually adjust multivariable models for clinical characteristics and factors empirically chosen *a priori* given their associations with prostate cancer risk. Those factors included age, race, baseline PSA, prostate volume, DRE findings, BMI, treatment arm (dutasteride vs. placebo), geographic region (North America, Europe, or other), smoking (never smokers, former smokers, current smokers), cardiovascular disease (yes vs. no), diabetes (yes vs. no), alcohol use (continuous, units per week), statin medication (yes vs. no), and hypertension (yes vs. no). To test whether the association between aspirin, NSAIDs, or both at baseline and prostate cancer risk varied by geographic region (Europe vs. North America) or treatment arm, we tested for statistical interactions by including cross-product terms into the multivariable analysis. There were not enough non-white men, men with a suspicious DRE, or men with diabetes or coronary artery disease to test for interactions, and thus such analyses were not done. All analyses were conducted using SAS 9.3, and a P value <0.05 was set as the threshold for statistical significance.

Results

Study population and baseline characteristics

The characteristics of the 8,122 men included in the efficacy population who received an on-study biopsy have been reported previously (15). Men who reported use of anti-inflammatory medications were more likely to undergo at least one on-study biopsy compared with men who reported no use of anti-inflammatory medications (50% vs. 35%; $P < 0.001$). Moreover, men who did not undergo a biopsy were similar aged, and had similar baseline PSA values and DRE findings (all $P > 0.05$). There were significant racial differences between men who did and did not undergo a biopsy ($P < 0.001$). Specifically, black men were over-represented among men who did not receive a biopsy versus the whole study population (3.9 vs. 1.9%, $P < 0.001$). Anti-inflammatory medication users were equally likely to receive a second on-study biopsy when compared with nonusers ($P = 0.12$).

Among 6,729 men with at least one on-study biopsy, we excluded men with missing data for BMI ($n = 205$), PSA ($n = 14$), DRE ($n = 7$), TRUS volume ($n = 76$), smoking or alcohol use history ($n = 36$), or hypertension ($n = 1$), resulting in a study population of 6,390.

Overall, 3,169 men (50%) were nonusers, whereas the other 50% was comprised of 1,368 (21%) aspirin users, 1,176 (18%) NSAID users, and 677 (11%) users of both aspirin and NSAIDs. Aspirin users were slightly older (64 years) compared with nonusers (63 years) and NSAID users (61 years; $P < 0.001$). Use of both aspirin and NSAIDs was more common among North American compared with European men ($P < 0.001$). Aspirin and NSAID users were slightly but significantly heavier than nonusers ($P < 0.001$), and PSA values were lower in aspirin, NSAIDs, and/or both users compared with nonusers ($P = 0.007$). However, more suspicious DREs were observed in aspirin and NSAID users compared with nonusers ($P < 0.001$; Table 1). After we adjusted for age, race, and DRE, relative to nonusers, the use of aspirin and the use of

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Table 1. Baseline characteristics

	Nonusers (*N* = 3,169; 50%)	Aspirin (*N* = 1,368; 21%)	NSAIDs (*N* = 1,176; 18%)	Aspirin and NSAIDs (*N* = 677; 11%)	*P* value[a]
Age					<0.001
Mean (SD)	62.7 (6.0)	63.9 (5.8)	61.5 (6.0)	62.7 (6.1)	
Median (Q1, Q3)	63.0 (58.0, 67.0)	64.0 (60.0, 68.0)	61.0 (57.0, 66.0)	63.0 (58.0, 67.0)	
Ethnic group					0.004[b]
White	2,910 (92%)	1,266 (93%)	1,057 (90%)	635 (94%)	
Black	50 (2%)	33 (2%)	22 (2%)	12 (2%)	
Other	209 (6%)	69 (5%)	97 (8%)	30 (4%)	
Geographic region					<0.001
US/Canada	457 (14%)	535 (39%)	255 (22%)	299 (44%)	
Europe	2,195 (69%)	675 (49%)	656 (56%)	243 (36%)	
Other	517 (16%)	158 (12%)	265 (23%)	135 (20%)	
BMI (kg/m^2)					<0.001
Mean (SD)	26.9 (3.6)	27.7 (3.9)	27.5 (3.8)	28.4 (4.2)	
Median (Q1, Q3)	26.5 (24.5, 28.9)	27.3 (25.1, 29.5)	27.1 (25.1, 29.4)	27.8 (25.5, 30.6)	
Suspicious DRE	89 (3%)	59 (4%)	53 (5%)	40 (6%)	<0.001[b]
Prostate volume (cc)					<0.001
Mean (SD)	45.4 (17.5)	47.1 (17.3)	44.6 (17.7)	45.1 (17.2)	
Median (Q1, Q3)	43.3 (33.0, 56.3)	45.3 (34.6, 58.3)	42.3 (32.0, 55.4)	43.2 (33.2, 55.1)	
PSA (ng/mL)					0.007
Median (Q1, Q3)	5.8 (4.5, 7.4)	5.6 (4.3, 7.2)	5.6 (4.3, 7.4)	5.5 (4.3, 7.1)	
Biopsy Gleason score					0.742[b]
2–6	520 (69%)	197 (69%)	180 (72%)	103 (70%)	
3+4	160 (21%)	66 (23%)	49 (20%)	35 (24%)	
≥4+3	73 (10%)	23 (8%)	21 (8%)	9 (6%)	
Smoker					<0.001[b]
Yes	1,588 (50%)	590 (43%)	488 (41%)	257 (38%)	
No	469 (15%)	182 (13%)	184 (16%)	88 (13%)	
Former	1,112 (35%)	596 (44%)	504 (43%)	332 (49%)	
Alcohol (drinks/week)					0.012
Median (Q1, Q3)	3 (1, 7)	2 (0, 7)	3 (0, 10)	3 (0, 10)	
Statin user ever	534 (17%)	759 (55%)	272 (23%)	360 (53%)	<0.001[b]
Hypertension	698 (22%)	475 (35%)	225 (19%)	183 (27%)	<0.001[b]
Coronary artery disease	135 (4%)	266 (19%)	49 (4%)	97 (14%)	<0.001[b]
Diabetes	168 (5%)	110 (8%)	52 (4%)	43 (6%)	<0.001[b]
Treatment arm					0.645[b]
Placebo	1,626 (51%)	676 (49%)	598 (51%)	351 (52%)	
Dutasteride	1,543 (49%)	692 (51%)	578 (49%)	326 (48%)	

[a]*P* value by Kruskal–Wallis, except where noted.
[b]*P* value by χ^2.

both aspirin and NSAIDs were both significantly related to lower PSA ($\beta = -0.18$; -0.22, respectively, $P \leq 0.006$). The use of NSAIDs alone was not related to significantly lower PSA values, though the direction was for lower PSA values ($\beta = -0.09$, $P = 0.16$).

Aspirin, NSAIDs, and prostate cancer risk

Prostate cancer was detected in 1,436 men (22%), which was low grade in 1,000 (16%), and high grade in 436 (7%). In univariable analysis, aspirin use was associated with lower risk of total prostate cancer (OR = 0.85, $P = 0.036$). After adjusting for multiple potential confounding factors, aspirin remained significantly associated with lower risk of total prostate cancer (OR = 0.81, $P = 0.015$). Although aspirin use was not significantly related to low- or high-grade prostate cancer on multivariable analysis (OR = 0.83, $P = 0.06$; OR = 0.77, $P = 0.06$, respectively), both ORs were <1. Although use of either NSAIDs or use of both aspirin and NSAIDs was not significantly related to total, low-grade, or high-grade prostate cancer (all $P \geq 0.08$) in either univariable or multivariable analyses, again all ORs were <1 (Table 2).

Given all univariable and multivariable analyses suggesting the use of aspirin, NSAIDs, or both to be associated with a reduced risk of total prostate cancer, low-grade, and high-grade prostate cancer with similar magnitude, and all agents have similar mechanisms of actions that purportedly link them with prostate cancer, we created a dichotomous variable of aspirin and/or NSAIDs use versus not to increase statistical power. When this was done, on crude analysis, the use of aspirin and/or NSAIDs was linked with lower risk of total prostate cancer (OR = 0.86, $P = 0.014$). When broken down by disease grade, there was a suggestion that use of aspirin and/or NSAIDs was linked with lower risk of both low-grade (OR = 0.88, $P = 0.06$) and high-grade prostate cancer (OR = 0.83, $P = 0.06$), though neither reached statistical significance. After adjusting for potential confounders, the use of aspirin and/or NSAIDs remained associated with decreased risk of total prostate cancer (OR = 0.87, $P = 0.030$) and high-grade prostate cancer (OR = 0.80, $P = 0.040$), but not with low-grade prostate cancer (OR = 0.90, $P = 0.15$; Table 3). When analyses were restricted to using data from only the first on-study biopsy, use of aspirin and the use of either aspirin and/or NSAIDs were both linked with lower risk of overall and high-grade prostate cancer (all OR ≤ 0.85), though due to lower numbers, not all of these associations reached statistical significance.

The interactions of anti-inflammatory drug use with geographic region (*P* interaction = 0.41) or with treatment arm (*P* interaction = 0.86) in predicting risk of overall prostate cancer were not significant (data not shown).

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Table 2. Association between aspirin and NSAID use and prostate cancer risk or disease grade versus nonuse

		Aspirin users		NSAID users		Aspirin and NSAID users	
Variable	**Nonusers**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Overall prostate cancer risk							
Number with cancer/total	753/3,169	286/1,368		250/1,176		147/677	
Univariable	Referent	0.85 (0.73–0.99)	**0.036**	0.87 (0.74–1.02)	0.08	0.89 (0.73–1.09)	0.25
Multivariable[a]	Referent	0.81 (0.68–0.96)	**0.015**	0.92 (0.78–1.08)	0.30	0.89 (0.72–1.10)	0.28
Low-grade disease							
Number with cancer/total[b]	520/2,936	197/1,279		180/1,106		103/633	
Univariable	Referent	0.85 (0.71–1.01)	0.07	0.90 (0.75–1.09)	0.28	0.90 (0.72–1.14)	0.39
Multivariable[a]	Referent	0.83 (0.68–1.01)	0.06	0.95 (0.79–1.15)	0.62	0.92 (0.72–1.18)	0.52
High-grade disease							
Number with cancer/total[c]	233/2,649	89/1,171		70/996		44/574	
Univariable	Referent	0.85 (0.66–1.10)	0.22	0.78 (0.56–1.04)	0.09	0.86 (0.62–1.20)	0.38
Multivariable[a]	Referent	0.77 (0.58–1.02)	0.06	0.83 (0.62–1.10)	0.19	0.81 (0.57–1.16)	0.25

[a]Adjusted for age, race, geographic region, PSA levels, prostate volume, digital rectal examination findings, BMI, treatment arm, smoking, alcohol, statin use, hypertension, diabetes, and cardiovascular disease.
[b]Numbers reflect men included in the analysis: those with low-grade disease and those without cancer.
[c]Numbers reflect men included in the analysis: those with high-grade disease and those without cancer.

Discussion

Despite a protective effect of NSAIDs on prostate cancer development observed in animal studies (16), the epidemiologic evidence for aspirin and other NSAID use against prostate cancer is suggestive but not yet conclusive (4). Indeed a recent meta-analysis found that although aspirin use was associated with a modest reduction in prostate cancer incidence and mortality (6), use of any NSAID was associated with an increased risk of total prostate cancer in Europe (7–9), but a decreased risk of total prostate cancer in North America (10–13). One potential explanation is detection bias due to PSA screening as aspirin and NSAIDs lower PSA levels. To address this, we tested the association between aspirin and nonaspirin NSAIDs and prostate cancer in the REDUCE study (14), where the vast majority of men underwent per-protocol biopsies regardless of PSA levels. In REDUCE, where all men had a negative prestudy biopsy and an elevated PSA, we found that use of aspirin and/or NSAIDs was associated with reduced risk of total prostate cancer and high-grade prostate cancer risk. These data are consistent with the hypothesis that anti-inflammatory drugs reduce prostate cancer risk, supporting future clinical trials of anti-inflammatory drugs for prostate cancer prevention.

Three meta-analyses (4, 6, 17) and one systemic review (18) on anti-inflammatory drugs and prostate cancer risk, which were all published in the past four years, found a 10% to 18% reduced risk of total prostate cancer among aspirin users. The most recent meta-analysis on aspirin and prostate cancer risk, by Huang and colleagues (17), which included 24 observational studies, 13 case–control and 9 cohort studies (>40,000 prostate cancer cases), conducted mainly in North American and European countries, found that protection against total prostate cancer incidence was stronger for long-term aspirin use, defined as $\geq$4 years, as observed by others (6). Indeed, the relative ratio from pooled analysis was 0.82 [95% confidence interval (CI), 0.72–0.93] similar to the OR for the association between total prostate cancer and aspirin use (0.81, 95% CI, 0.68–0.96) found in our REDUCE study. Huang and colleagues (17) also found that aspirin use was associated with a 17% reduced risk of high-grade prostate cancer, but no benefits were detected for low-grade prostate cancer. Although we observed a trend for reduced risk of low- and high-grade prostate cancer among aspirin users (OR = 0.83, 0.77, respectively), the associations were not statistically significant. However, in our secondary analysis, when aspirin and/or NSAID use was combined, anti-inflammatory medication use was

Table 3. Association between aspirin and/or NSAID use and prostate cancer risk or disease grade versus nonuse

		Aspirin and/or NSAID users	
Variable	**Nonusers**	**OR (95% CI)**	***P* value**
Overall prostate cancer risk			
Number with cancer/total	753/3,169	683/3,221	
Univariable	Referent	0.86 (0.77–0.97)	**0.014**
Multivariable[a]	Referent	0.87 (0.76–0.99)	**0.030**
Low-grade disease			
Number with cancer/total[b]	520/2,953	480/3,018	
Univariable	Referent	0.88 (0.77–1.01)	0.06
Multivariable[a]	Referent	0.90 (0.77–1.04)	0.15
High-grade disease			
Number with cancer/total[c]	233/2,665	203/2,741	
Univariable	Referent	0.83 (0.68–1.01)	0.06
Multivariable[a]	Referent	0.80 (0.64–0.99)	**0.040**

[a]Adjusted for age, race, geographic region, PSA levels, prostate volume, digital rectal examination findings, BMI, treatment arm, smoking, alcohol, statin use, hypertension, diabetes, and cardiovascular disease.
[b]Numbers reflect men included in the analysis: those with low-grade disease and those without cancer.
[c]Numbers reflect men included in the analysis: those with high-grade disease and those without cancer.

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associated with reduced risk of high-grade prostate cancer, consistent with the Huang and colleagues meta-analysis.

Although these recent data and our present study support the hypothesis that aspirin use may help reduce the risk of prostate cancer, the effects of other NSAIDs on prostate cancer risk is not so clear. Indeed, a meta-analysis including over 100,000 prostate cancer cases worldwide found that use of any NSAID had either a null effect on prostate cancer, or was associated with an increased risk of prostate cancer in studies from Europe and with reduced prostate cancer risk in studies from North America (6). Furthermore, use of nonaspirin NSAIDs was significantly associated with neither prostate cancer incidence nor low- or high-grade prostate cancer (6). These latter findings are in agreement with our present results showing no significant associations between nonaspirin NSAIDs and prostate cancer risk. However, as the ORs for NSAIDs were <1, we cannot rule out a modest effect on prostate cancer risk. Thus, further studies are needed to better assess the role of NSAIDs on prostate cancer risk. Of note, when NSAID use was combined with aspirin use, the risk of prostate cancer was significantly lower, suggesting that NSAIDs may indeed be associated with lower prostate cancer risk.

Furthermore, our present findings on the protective effect of aspirin and/or NSAIDs in the REDUCE study, where the majority of men were recruited from Europe and biopsies were performed independent of PSA, seem to indicate that previous studies conducted in European countries which showed a positive association between NSAID use and prostate cancer risk may have been subjected to bias due to PSA detection. Indeed, given that anti-inflammatory drugs lower PSA levels and PSA screening is not as common in Europe as in North America, missed cancers in men taking aspirin and/or NSAIDs may have continued to grow and been detected at a later stage, explaining in part the positive associations.

Hence, given that in REDUCE the inclusion criterion was men with an elevated PSA (2.5–10 ng/mL), and biopsies were performed independent of PSA levels, detection bias by lower PSA levels due to use of anti-inflammatory drugs is unlikely. Consistent with prior studies, we found that after adjusting for key confounders, PSA levels were lower in aspirin and/or NSAID users (14). Of note, the effect in REDUCE of anti-inflammatory drugs on PSA levels was small, which may represent the narrow spectrum of PSA values mandated by the study enrollment criteria. However, even after we accounted for this effect, use of aspirin was associated with reduced risk of total and high-grade prostate cancer. Moreover, if we presume that anti-inflammatory drugs result in an "artificially lower" PSA level, then if we correct for this effect, the baseline estimated cancer risk in aspirin/NSAID users would have been even higher than modeled in our analyses. As such given that we found aspirin/NSAID use was associated with lower prostate cancer risk, under this scenario where we may have underestimated their prostate cancer risk, our results may likewise have underestimated the magnitude of the association between aspirin/NSAID use and lower prostate cancer risk. Regardless of the implications of altered PSA levels, these data support the hypothesis that aspirin and/or NSAIDs may indeed have a biologic role in arresting prostate cancer development, though this requires formal prospective testing in randomized trials.

Several mechanisms have been proposed to explain the potential effect of anti-inflammatory drugs on prostate carcinogenesis, mainly involving the cyclooxygenase enzymes [COX 1 and 2; also known as prostaglandin-endoperoxide synthase (PTGS)] pathway, which aspirin inhibits (19). Higher expression of COX-2 was found in prostate cancer and in prostatic intraepithelial neoplasia compared with benign human prostate tissue (20–22), which also positively correlated with tumor grade (22). Overexpression of COX-2 is associated with increased production of prostaglandins, which have been shown to be highly expressed in malignant prostate tissue (23) and to promote tumor growth through either (i) activation of COX-2 expression via a positive feedback loop (24); (ii) increased resistance to apoptosis and enhanced proliferation (25, 26); or (iii) inhibition of immune surveillance (27) and suppression of natural killer cell activity (28). Other possible mechanisms include aspirin's positive effects on the DNA mismatch-repair system and its role in decreasing DNA damage (29).

Our study was limited by the fact that data on aspirin and NSAID dose, frequency, and duration of use were not available, which precluded us from examining more specific dose–effect relationships. Although our results are similar to those that reported aspirin amount and duration of intake (9), and other studies found no evidence of aspirin dose–effect (7, 30–33) or frequency–effect (31, 34, 35) relationship, the inability to evaluate for a dose–response relationship between aspirin/NSAID use and prostate cancer is an important limitation of this study. Second, we did not have updated data available on aspirin/NSAID use during the study. As there was likely drop-in and drop-out of aspirin/NSAID users, this potential misclassification would bias our results to the null. Thus, our results may have underestimated the true association between aspirin/NSAID use and prostate cancer risk. Third, we did not have available data on markers of systemic inflammation, physical activity level, or diet which could have confounded the associations. However, our analyses were adjusted for coronary artery disease, which we previously found to be an independent predictor of prostate cancer incidence (36). Fourth, all men in the current study had an elevated PSA. Thus, though once enrolled on the study, biopsies were generally independent of PSA, enrollment on the study was not. As such, this creates another selection bias. As data were unavailable regarding the men with a negative biopsy but who did not enroll in REDUCE due to not meeting the PSA entry criteria, it is unclear how this may have affected our results. Also, our study only included men with a negative biopsy. Men who reported use of anti-inflammatory medications were more likely to receive one on-study biopsy and thus be included in our study, though how this may have influenced our results is unclear. Importantly, men who used anti-inflammatory medications were equally likely to receive a second on-study biopsy compared with nonusers, meaning all groups had equal opportunity to have their cancer detected. Thus, it is possible anti-inflammatory drugs influence the likelihood of prostate cancer on the first biopsy, which we could not test. Finally, the interaction between aspirin and/or NSAIDs with other medications was not tested because this analysis was beyond the scope of our study.

In summary, in REDUCE, where all men had a negative baseline biopsy and an elevated PSA and received biopsies regardless of PSA levels, aspirin and/or NSAID use was associated with a reduced risk of total prostate cancer and high-grade prostate cancer. These data provide further support to the hypothesis that

anti-inflammatory drugs may help reduce the risk of prostate cancer. Prospective clinical trials to test this hypothesis are warranted.

Disclosure of Potential Conflicts of Interest

R. Castro-Santamaria is employed by and holds ownership interest (including patents) in GlaxoSmithKline. G.L. Adriole reports receiving a commercial research grant and speakers bureau honoraria from GlaxoSmithKline. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.C. Vidal, G.L. Andriole, S.J. Freedland
Development of methodology: A.C. Vidal, L.E. Howard, D.M. Moreira, S.J. Freedland
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