Aspirin, NSAID and risk of prostate cancer: Results from the REDUCE study

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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-year largely independent of PSA, those men taking either aspirin and/or NSAID at baseline had a lower risk of prostate cancer including high-grade prostate cancer. While these data support the hypothesis that anti-inflammatory drugs may indeed have a biological role in arresting prostate cancer development, this requires formal prospective testing in randomized trials.
Abstract

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

**Experimental Design:** We examined the association between aspirin, NSAID or both and total, low-grade (Gleason<7), or high-grade (Gleason≥7) PC vs. no PC 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, BMI, treatment arm, smoking, alcohol, statins, hypertension, diabetes and cardiovascular disease.

**Results:** Overall, 3,169 men (50%) were non-users, 1,368 (21%) used aspirin, 1,176 (18%) used NSAID, and 677 (11%) used both. In unadjusted models, aspirin was associated with reduced PC risk (OR=0.85, p=0.036). In multivariable analyses, aspirin was associated with reduced total PC risk (OR=0.81, p=0.015). Use of NSAID or NSAIDs and aspirin was not associated with total, low- or high-grade PC, though all ORs were <1 (all p>0.08). Therefore, we created a dichotomous variable of aspirin and/or NSAID user vs. not. On multivariable analysis, the use of aspirin and/or NSAID 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 PC 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 PC risk. Additional studies are warranted.
Introduction

Aspirin and non-steroidal anti-inflammatory drugs (NSAID) have been associated with reduced risk of several cancers, including melanoma (1), breast (2), and lung cancers (3). However, the association with prostate cancer (PC) risk is less clear (4, 5).

A recent meta-analysis of prospective and case-control cohort studies including over 100,000 PC cases worldwide found aspirin was associated with a reduced risk of total PC and PC-specific mortality; however the effect of any NSAID on PC 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 PC (7-9) whereas North American studies found a decreased risk of total PC among any NSAID users (10-13).

Given that anti-inflammatory medications can alter PSA levels (14), which is the primary means used for PC detection, whether the findings of reduced PC risk among NSAID users in North America reflect reduced PC detection or truly a biological link with lower PC 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 NSAID 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 PC 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 PC risk is unclear.

Our goal was to test the association between anti-inflammatory medication use and PC risk while minimizing reverse causation and PSA screening bias. To accomplish this,
we examined the association between aspirin and non-aspirin NSAID on PC diagnosis among men with an elevated PSA and negative pre-study biopsy in the REDUCE study, a 4-year randomized trial of dutasteride vs. placebo on PC risk (15), where all men received biopsies at 2- and 4-years regardless of PSA levels. Given nearly 83% of men had at least one biopsy 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 NSAID and PC risk largely independent of PSA. We hypothesized a priori that aspirin and/or NSAID would be associated with lower PC risk after controlling for clinical covariates, and this association would be independent of geographic region in this population where all had undergone PSA screening prior to the study.

Material and Methods

Study population

The design of the REDUCE study has been reported (15). Eligible men were aged 50-75 years, with a serum PSA of 2.5-10 ng/mL if aged 50-60 years, or 3-10 ng/mL if >60 years, and a single, negative prostate biopsy (6-12 cores) within 6 months prior to 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 19-24 and 43-48 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 pre-study biopsy.

**Statistical analysis**

Use of either aspirin, NSAID or both, was self-reported. The association between use of aspirin, NSAID or both and baseline parameters was tested using Kruskal-Wallis for continuous variables and chi-squared for categorical variables. The association between aspirin, NSAID 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 odds ratio (OR) associated with use of aspirin, NSAID or both at baseline and risk of total, low-grade (Gleason <7) or high-grade (Gleason >7) PC 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 PC 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, NSAID or both at baseline and PC 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 to 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 vs. 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 to non-users (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 non-users, while the other 50% was comprised of 1,368 (21%) aspirin users, 1,176 (18%) NSAID users, and 677 (11%) users of both aspirin and NSAID. Aspirin users were slightly older (64 yr.) compared to non-users (63 yr.) and NSAID users (61 yr.) (p<0.001). Use of both aspirin and NSAID was more common among North American compared to European men (p<0.001). Aspirin and NSAID users were slightly but significantly heavier than non-users (p<0.001) and PSA values were lower in aspirin, NSAID and/or both users compared to non-users (p=0.007). However, more suspicious DREs were observed in aspirin and NSAID users compared to non-users (p<0.001) (Table 1). After adjusting for age, race, and DRE, relative to non-users, the use of aspirin or the use of both aspirin and NSAID were both significantly related to lower PSA (β= -0.18; -0.22, respectively, p≤0.006). The use of NSAID alone was not related to significantly lower PSA values, though the direction was for lower PSA values (β= -0.09, p=0.16).

**Aspirin, NSAID, and PC 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 PC (OR=0.85, p=0.036). After adjusting for multiple potential confounding factors, aspirin remained significantly associated with lower risk of total PC (OR=0.81, p=0.015). While aspirin use was not significantly related to low- or high-grade PC on multivariable analysis (OR=0.83, p=0.06; OR=0.77, p=0.06, respectively), both ORs were <1. While use of either NSAID or use of both aspirin and NSAID were not significantly related to total, low- or high-grade PC (all p≥0.08) in either univariable or multivariable analyses, again all ORs were <1 (Table 2).

Given all univariable and multivariable analysis suggested the use of aspirin, NSAID, or both were associated with a reduced risk of total prostate cancer, low-, 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 NSAID use vs. not to increase statistical power. When this was done, on crude analysis the use of aspirin and/or NSAID was linked with lower risk of total PC (OR=0.86, p=0.014). When broken down by disease grade, there was a suggestion that use of aspirin and/or NSAID was linked with lower risk of both low-grade (OR=0.88, p=0.06) and high-grade PC (OR=0.83, p=0.06), though neither reached statistical significance. After adjusting for potential confounders, the use of aspirin and/or NSAID remained associated with decreased risk of total PC (OR=0.87, p=0.030) and high-grade PC (OR=0.80, p=0.040), but not with low-grade PC (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 PC (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 PC were not significant (data not shown).

**Discussion**

Despite a protective effect of NSAID on PC development observed in animal studies (16), the epidemiologic evidence for aspirin and other NSAID use against PC is suggestive but not yet conclusive (4). Indeed a recent meta-analysis found that while aspirin use was associated with a modest reduction in PC incidence and mortality (6), use of any NSAID was associated with an increased risk of total PC in Europe (7-9), but a decreased risk of total PC in North America (10-13). One potential explanation is detection bias due to PSA screening as aspirin and NSAID lower PSA levels. To address this, we tested the association between aspirin and non-aspirin NSAID and PC 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 pre-study biopsy and an elevated PSA, we found that use of aspirin and/or NSAID was associated with reduced risk of total PC and high-grade PC risk. These data are consistent with the hypothesis that anti-inflammatory drugs reduce PC risk supporting future clinical trials of anti-inflammatory drugs for PC prevention.

Three meta-analyses (4, 6, 17) and one systemic review (18) on anti-inflammatory drugs and PC risk, which were all published in the past four years, found a 10-18% reduced risk of total PC among aspirin users. The most recent meta-analysis on aspirin and PC risk, by Huang et al. (2014) (17), which included 24 observational studies -13 case-control and 9
cohort studies (>40,000 PC cases) conducted mainly in North American and European
countries, found that protection against total PC incidence was stronger for long-term
aspirin use, defined as ≥4 years, as observed by others (6). Indeed, RR from pooled
analysis was 0.82 (95%CI 0.72-0.93) similar to the OR for the association between total PC
and aspirin use (0.81, 95%CI 0.68-0.96) found in our REDUCE study. Huang et al. (17)
also found that aspirin use was associated with a 17% reduced risk of high-grade PC, but
no benefits were detected for low-grade PC. Although we observed a trend for reduced risk
of low- and high-grade PC 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 associated
with reduced risk of high-grade PC, consistent with the Huang et al. meta-analysis.

Although these recent data and our present study support the hypothesis that aspirin
use may help reduce the risk of PC, the effects of other NSAID on PC risk is not so clear.
Indeed, a meta-analysis including over 100,000 PC cases worldwide found that use of any
NSAID had either a null effect on PC, or was associated with an increased risk of PC in
studies from Europe and with reduced PC risk in studies from North America (6).
Furthermore, use of non-aspirin NSAID was not significantly associated with PC incidence
nor with low- or high-grade PC (6). These latter findings are in agreement with our present
results showing no significant associations between non-aspirin NSAID and PC risk.
However, as the ORs for NSAIDs was <1, we cannot rule out a modest effect on PC risk.
Thus, further studies are needed to better assess the role of NSAIDs on PC risk. Of note,
when NSAID use was combined with aspirin use, the risk of PC was significantly lower
suggesting that NSAIDs may indeed be associated with lower PC risk.
Furthermore, our present findings on the protective effect of aspirin and/or NSAID 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 PC 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 NSAID may have continued to grow and detected at a later stage, explaining in part the positive associations.

Hence, given that in REDUCE the inclusion criteria 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 accounting for this effect, use of aspirin was associated with reduced risk of total and high-grade PC. 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 PC risk, under this scenario where we may have underestimated their PC risk, our results may likewise have underestimated the magnitude of the association between aspirin/NSAID use and lower PC risk. Regardless of the implications of altered PSA levels, these data support the hypothesis that aspirin and/or
NSAIDs may indeed have a biological role in arresting PC 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 synthases (PTGS)) pathway which aspirin inhibits (19). Higher expression of COX-2 was found in prostate cancer and in prostatic intraepithelial neoplasia compared to 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 1) activation of COX-2 expression via a positive feedback loop (24); 2) increased resistance to apoptosis and enhanced proliferation (25, 26); or 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 PC 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 to non-users meaning all groups had equal opportunity to have their cancer detected. Thus, it is possible anti-inflammatory drugs influence the likelihood of PC on the first biopsy, which we could not test. Finally, the interaction between aspirin and/or NSAID with other medications was not tested since 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 PC and high-grade PC. These data provide
further support to the hypothesis that anti-inflammatory drugs may help reduce the risk of PC. Prospective clinical trials to test this hypothesis are warranted.

Disclosure of Potential Conflicts of Interest
This study was supported by GlaxoSmithKline (GSK). Dr. Andriole reports receiving consulting or advisory fees from GSK. Dr. Freedland reports receiving research funding from GSK to conduct these analyses. Dr. Castro-Santamaria is an employee of GSK.

Authors’ Contributions
Conception and design: SJF, GLA,
Development of methodology: GLA, SJF
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): GLA
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): LEH, ACV, SJF
Writing, review, and/or revision of the manuscript: ACV, SJF, DMM, RCS
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): SJF
Study supervision: SJF

Acknowledgements
The authors wish to acknowledge the dedication of the patients, investigators, data and safety monitoring committee, steering committee, and GSK in the initiation and conduct of the REDUCE study.
References

Table 1. Baseline characteristics

<table>
<thead>
<tr>
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<th>Non-users (N=3,169; 50%)</th>
<th>ASA (N=1,368; 21%)</th>
<th>NSAID (N=1,176; 18%)</th>
<th>ASA &amp; NSAID (N=677; 11%)</th>
<th>p value*</th>
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<td>Mean (SD)</td>
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<tr>
<td>Median (Q1, Q3)</td>
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<td>64.0 (60.0, 68.0)</td>
<td>61.0 (57.0, 66.0)</td>
<td>63.0 (58.0, 67.0)</td>
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<td>1266 (93%)</td>
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<td>Black</td>
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<td>22 (2%)</td>
<td>12 (2%)</td>
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<tr>
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<td>69 (5%)</td>
<td>97 (8%)</td>
<td>30 (4%)</td>
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<td>535 (39%)</td>
<td>255 (22%)</td>
<td>299 (44%)</td>
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<td>675 (49%)</td>
<td>656 (56%)</td>
<td>243 (36%)</td>
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<tr>
<td>Other</td>
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<td>158 (12%)</td>
<td>265 (23%)</td>
<td>135 (20%)</td>
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<tr>
<td><strong>BMI (kg/m²)</strong></td>
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<td>Mean (SD)</td>
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<td>27.7 (3.9)</td>
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<td>28.4 (4.2)</td>
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<tr>
<td>Median (Q1, Q3)</td>
<td>26.5 (24.5, 28.9)</td>
<td>27.3 (25.1, 29.5)</td>
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<td><strong>Suspicious DRE</strong></td>
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<td>89 (3%)</td>
<td>59 (4%)</td>
<td>53 (5%)</td>
<td>40 (6%)</td>
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<tr>
<td><strong>Prostate volume (cc)</strong></td>
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<tr>
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<td>45.4 (17.5)</td>
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<td>44.6 (17.7)</td>
<td>45.1 (17.2)</td>
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<td>45.3 (34.6, 58.3)</td>
<td>42.3 (32.0, 55.4)</td>
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<td>Median (Q1, Q3)</td>
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<td>5.6 (4.3, 7.2)</td>
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Table 1. (Cont’d.)

<table>
<thead>
<tr>
<th></th>
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<th>p value*</th>
</tr>
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<tbody>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
<td></td>
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<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Yes</td>
<td>1588 (50%)</td>
<td>590 (43%)</td>
<td>488 (41%)</td>
<td>257 (38%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>469 (15%)</td>
<td>182 (13%)</td>
<td>184 (16%)</td>
<td>88 (13%)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1112 (35%)</td>
<td>596 (44%)</td>
<td>504 (43%)</td>
<td>332 (49%)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol (drinks/week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>3 (1, 7)</td>
<td>2 (0, 7)</td>
<td>3 (0, 10)</td>
<td>3 (0, 10)</td>
<td></td>
</tr>
<tr>
<td><strong>Statin user ever</strong></td>
<td>534 (17%)</td>
<td>759 (55%)</td>
<td>272 (23%)</td>
<td>360 (53%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>698 (22%)</td>
<td>475 (35%)</td>
<td>225 (19%)</td>
<td>183 (27%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>168 (5%)</td>
<td>110 (8%)</td>
<td>52 (4%)</td>
<td>43 (6%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Treatment arm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.645†</td>
</tr>
<tr>
<td>Placebo</td>
<td>1626 (51%)</td>
<td>676 (49%)</td>
<td>598 (51%)</td>
<td>351 (52%)</td>
<td></td>
</tr>
<tr>
<td>Dutasteride</td>
<td>1543 (49%)</td>
<td>692 (51%)</td>
<td>578 (49%)</td>
<td>326 (48%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PSA (prostate specific antigen), SD (standard deviation), IQR (interquartile range)

*P value by Kruskal-Wallis, except where noted.
†P value by χ²
Table 2. Association between ASA and NSAID use and prostate cancer risk or disease grade vs. non-use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-users</th>
<th>ASA users</th>
<th>NSAID users</th>
<th>ASA and NSAID users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>Overall prostate cancer risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with cancer/total</td>
<td>753/3,169</td>
<td>286/1,368</td>
<td>250/1,176</td>
<td>147/677</td>
</tr>
<tr>
<td>Univariable</td>
<td>Referent</td>
<td>0.85</td>
<td>0.73-0.99</td>
<td>0.036</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>Referent</td>
<td>0.81</td>
<td>0.68-0.96</td>
<td>0.015</td>
</tr>
<tr>
<td>Disease grade, low grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with cancer/total**</td>
<td>520/2,936</td>
<td>197/1,279</td>
<td>180/1,106</td>
<td>103/633</td>
</tr>
<tr>
<td>Univariable</td>
<td>Referent</td>
<td>0.85</td>
<td>0.71-1.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>Referent</td>
<td>0.83</td>
<td>0.68-1.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Disease grade, high grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with cancer/total***</td>
<td>233/2,649</td>
<td>89/1,171</td>
<td>70/996</td>
<td>44/574</td>
</tr>
<tr>
<td>Univariable</td>
<td>Referent</td>
<td>0.85</td>
<td>0.66-1.10</td>
<td>0.22</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>Referent</td>
<td>0.77</td>
<td>0.58-1.02</td>
<td>0.06</td>
</tr>
</tbody>
</table>

OR, odds ratio
CI, confidence interval
*Adjusted for age, race, geographic region, prostate specific antigen levels, prostate volume, digital rectal examination findings, body mass index, treatment arm, smoking, alcohol, statin use, hypertension, diabetes and cardiovascular disease.
**Numbers reflect men included in the analysis: those with low-grade disease and those without cancer.
***Numbers reflect men included in the analysis: those with high-grade disease and those without cancer.
Table 3. Association between ASA and/or NSAID use and prostate cancer risk or disease grade vs. non-use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-users</th>
<th>ASA and/or NSAID users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Overall prostate cancer risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with cancer/total</td>
<td>753/3,169</td>
<td>683/3,221</td>
</tr>
<tr>
<td>Univariable</td>
<td>Referent</td>
<td>0.86</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>Referent</td>
<td>0.87</td>
</tr>
<tr>
<td>Disease grade, low grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with cancer/total**</td>
<td>520/2,953</td>
<td>480/3,018</td>
</tr>
<tr>
<td>Univariable</td>
<td>Referent</td>
<td>0.88</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>Referent</td>
<td>0.90</td>
</tr>
<tr>
<td>Disease grade, high grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with cancer/total***</td>
<td>233/2,665</td>
<td>203/2,741</td>
</tr>
<tr>
<td>Univariable</td>
<td>Referent</td>
<td>0.83</td>
</tr>
<tr>
<td>Multivariable</td>
<td>Referent</td>
<td>0.80</td>
</tr>
</tbody>
</table>

OR, odds ratio  
CI, confidence interval  
*Adjusted for age, race, geographic region, prostate specific antigen levels, prostate volume, digital rectal examination findings, body mass index, treatment arm, smoking, alcohol, statin use, hypertension, diabetes and cardiovascular disease.  
** Numbers reflect men included in the analysis: those with low-grade disease and those without cancer.  
***Numbers reflect men included in the analysis: those with high-grade disease and those without cancer.
Aspirin, NSAID and risk of prostate cancer: Results from the REDUCE study

Adriana C. Vidal, Lauren E. Howard, Daniel M Moreira, et al.

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