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Effect of Aspirin, Other NSAIDs, and Statins on PSA and PSA Velocity

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Abstract

BACKGROUND—Aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and statins have been associated with lower risk of prostate cancer and its progression, though results have been inconsistent.

METHODS—Data from 140 men with prostate cancer enrolled in a Phase 2 clinical trial of selenium to prevent prostate cancer progression were analyzed to determine association between aspirin, other NSAIDs, or statin use with baseline serum prostate-specific antigen (PSA) levels and PSA velocity (rate of PSA change over time) using repeated measures over an average follow-up time of 3.2 years. Multiple linear regression and mixed effects models were used to model the association of medication use with PSA at baseline and with PSA velocity, respectively.

RESULTS—Baseline PSA levels were significantly lower in aspirin users compared to non-users (5.17 ng/ml vs. 7.58 ng/ml, P =0.001). This association was statistically significant in never smokers (aspirin users vs. non-users: 4.19 ng/ml vs. 8.24 ng/ml, P =0.004) but not in ever smokers (aspirin users vs. non-users: 5.52 ng/ml vs. 7.3 ng/ml, P =0.101). Statin and other NSAID use was not associated with baseline PSA. Aspirin, statin, or other NSAID use at baseline demonstrated a non-significant negative association with PSA velocity.

CONCLUSION—These findings support an effect of aspirin use on PSA, particularly among never smokers. However, they do not suggest a protective effect on the disease and support previous findings that aspirin use may mask accurate measurement of PSA warranting consideration of washout procedures prior to testing.

Keywords

PSA; PSA velocity; aspirin; NSAID; statin

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INTRODUCTION

Prostate cancer is the most common newly diagnosed non-skin cancer among men in developed countries [1]. The American Cancer Society estimates that in 2009 there were 192,280 new diagnoses and 27,360 deaths due to prostate cancer in the US [2]. Several studies have indicated a role for chronic inflammation in the pathogenesis of prostate cancer [3,4]. Sources of intraprostatic inflammation include sexually transmitted infections, other urogenital infections, as well as chemical or physical intraluminal irritants [4]. The degree to which these sources induce intraprostatic inflammation may potentially be modified by endogenous factors, such as the nature of the innate and adaptive immune response, or exogenous factors, such as use of non-steroidal anti-inflammatory drugs (NSAIDs) or statin drugs (HMG-CoA reductase inhibitors).

Currently, there are no data from large-scale randomized clinical trials examining the association between NSAID or statin use with prostate-specific antigen (PSA) and prostate cancer and the association observed in epidemiological studies has been inconsistent with some studies reporting protective effects [5–11] while others report no or increased risk with regular use [12–16]. Although most studies investigating the association of NSAIDs or statins with advanced prostate cancer report protective effects [5,8,10,12,16] the number of such studies is fewer. In a recently published article, Fowke et al. [17] describe a statistically significant negative association between aspirin use and serum levels of PSA but not with prostate volume using data from 1,277 men enrolled in The Nashville Men's Health Study. After adjusting for age and race, family history of prostate cancer, number of prior PSA tests, biopsy outcome, finasteride/dutasteride use and treatment with other medications for benign prostatic hypertrophy prostate volume was similar between aspirin users and non-users (47.6 ml vs. 46.0 ml, P =0.16). In contrast, PSA was significantly lower in aspirin users (7.3 ng/ml vs. 8.0 ng/ml, P =0.01). These authors argued that aspirin use may affect PSA level without affecting the underlying disease process and thus be of little value in the chemoprevention setting.

To further investigate the relationship between NSAID and statin use with PSA, we examined the association of self-reported use of aspirin, other NSAIDs, and statins at baseline with PSA in men diagnosed with prostate cancer and enrolled in a clinical trial examining the effect of selenium supplementation on prostate cancer progression (the Watchful Waiting (WW) study) [18]. We also investigated the association of statin and NSAID use with PSA velocity (rate of change of PSA over time) as a surrogate for progressive disease in these same men. Additionally, because of prior reports of worse outcomes among smokers, the role of smoking as a modifier of the association between medication use, PSA, and PSA velocity was also examined.

METHODS

Study Population

Detailed study design for the WW study has been published earlier [18]. Briefly, the WW study is a randomized, double-blind, placebo-controlled, multi-center, Phase 2b clinical trial designed to investigate the effects of two doses of selenized yeast compared to placebo on

the progression of clinical prostate cancer as measured by PSA velocity. All men enrolled in this trial had opted to forego active treatment in favor of WW (active surveillance) for their disease. Eligibility criteria required subjects to have biopsy-proven prostate cancer within 48 months prior to beginning the study with a Gleason score <8 and no metastatic cancer. Eligible subjects had PSA <50 ng/ml, were <85 years old, had a life expectancy of at least 3 years, and agreed not to take more than 50 μg/day of selenium supplementation from non-study sources. Subjects (n =140) were randomized to placebo (n =46), selenium 200 μg/ day (n =47), or selenium 800 μg/day (n =47) groups after a run-in period of 30 days. Subjects were followed every 3 months for up to 5 years.

Data Processing

During enrollment, questionnaires on demographic characteristics, medical history, medication history, selenium toxicity information, and urological symptoms were filled out. Subjects were categorized as aspirin users if they reported taking any form of aspirin at enrollment in the WW study. Otherwise they were categorized as non-users for aspirin. Similar principles were followed while classifying subjects as users or non-users for other NSAIDs and statins.

Blood was drawn to assess PSA at randomization and at every subsequent quarterly follow-up visit. Serum PSA levels were measured using an Abbott tumor markers assay module on the IMX Analyzer (Abbott Diagnostics, Abbott Park, IL). In March 2005, Abbot Diagnostics replaced the AxSYM-PSA assay with the Total AxSYM-PSA assay, a combined assay for free and bound PSA. Both assays are approved by the Food and Drug Administration in the US. A variable capturing change in the PSA assay was included in analytic models to account for any effects this might have on PSA velocity.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters square (kg/m^2). Pack-years of smoking were calculated as number of packs of cigarettes smoked per day multiplied by the number of years the subject had been smoking at or prior to enrollment. In order to investigate interactions between smoking and medication use at baseline, subjects were categorized as never smokers if they did not report any pack-years of smoking and ever smoker if they reported any pack-years of smoking. Race was dichotomized as Caucasian versus non-Caucasian since there were very few non-Caucasian subjects (12%).

Statistical Analysis

Frequencies and mean values were calculated for all variables and differences between medication groups were compared using *t*-tests (continuous variables) and chi-square tests (categorical variables). PSA values were transformed using ln(PSA +1) in order to normalize their distribution, compensate for non-linearity over time, and stabilize their variance. Multiple linear regression models were used to test association between baseline PSA and medication use at baseline. Separate models were run for aspirin, other NSAIDS, and statins. Each medication use variable was coded as 0 for non-use and 1 for current use at baseline. Models were adjusted for the potential confounders of race, age, BMI, pack-years of smoking at baseline, and Gleason score based on previous literature.

Mixed effects models with patient level random effects were used to assess the effect of medication use on PSA velocity [19]. These models allowed random intercept and slope for each subject in the study and also accounted for correlations due to repeated measures. Separate models were run for aspirin, other NSAIDS, and statins. An interaction term between aspirin use and time on study was included to allow PSA velocity to differ for aspirin users versus non-users. Significance of this interaction term is indicative if the PSA velocity is statistically significantly different between the aspirin users and non-users. Similar principles were applied while modeling other NSAIDs and statins. Models were adjusted for baseline PSA, race, age, BMI, pack-years of smoking at baseline, type of assay used to estimate PSA, and Gleason score. Previous analysis indicated no statistically significant effect of selenium supplementation on PSA velocity in men enrolled in the WW Trial [20] and hence statistical models used in this article were not adjusted for effect of selenium supplementation. Statistical significance was assessed at $P < 0.05$. All analyses were conducted using Stata10 statistical software (StataCorp IC, College Station, TX).

RESULTS

Fifty (35.7%) men identified themselves as being aspirin users at the time of enrollment (Table I). Unadjusted *t*-tests demonstrated that aspirin users had lower mean serum PSA levels than non-users although the difference was not statistically significant (6.7 ng/ml vs. 8.7 ng/ml: $P = 0.07$). Mean pack-years of smoking were statistically significantly higher among aspirin users compared to non-users (34.1 pack-years vs. 18.0 pack-years: $P = 0.006$). Age, BMI, Gleason score, and racial distribution did not differ significantly between aspirin users and non-user. Twenty-seven (19.3%) and 20 (14.3%) subjects identified themselves as taking statins and NSAIDs other than aspirin, respectively. Baseline serum PSA, age, BMI, pack-years of smoking, Gleason score, and racial distribution did not differ significantly between users and non-users of statins and other NSAIDs.

After adjusting for other variables such as age, BMI, Gleason score, and race, linear regression models demonstrated that aspirin users had statistically significant lower serum PSA values at baseline as compared to non-aspirin users (Table II). Statin and NSAID use was not statistically significantly associated with baseline PSA. Next, stratified models were used to test whether association between medication use and PSA deferred by smoking status. Subjects were classified as ever or never smokers based on their reported smoking status at baseline. Although aspirin use was associated with lower PSA levels in ever smokers as well as never smokers, the effect was statistically significant in never smokers ($P = 0.004$) but not in ever smokers ($P = 0.101$) (Table II). Among never smokers, baseline PSA values were 49% lower in aspirin users as compared to non-users (predicted PSA values 4.19 and 8.24 ng/ml, respectively), while in ever smokers the reduction was 24% (predicted PSA values 5.5 and 7.3 ng/ml, respectively). Stratified analysis by smoking status showed no differences between users and non-users for statins or other NSAIDs.

Longitudinal analyses using mixed effects models were conducted for each medication separately. These indicate that medication use had negative association with PSA velocity but did not achieve statistical significance for any of the three medications (Table III).

Stratifying these models by smoking status (ever or never smokers) did not change the above results.

DISCUSSION

These results indicated that aspirin use at baseline was associated with significantly lower baseline serum PSA levels in men with prostate cancer who elected active surveillance for their disease. The aspirin effect was statistically significant in never smokers but not in ever smokers. Neither statin use nor other NSAID use was statistically significantly associated with baseline PSA. Although each of the medications demonstrated a negative association with PSA velocity, this effect was not statistically significant and did not change upon stratification by smoking. These data combined with results from previous studies by Fowke et al. [17] lead us to believe that aspirin use may affect PSA levels but not the underlying disease process.

In their study, Fowke and colleagues investigated the association between aspirin use and serum PSA levels using a cross-sectional study design [17]. After adjusting for age, race, family history of prostate cancer, number of prior PSA tests, biopsy outcome, finasteride/dutasteride use and treatment with other medications for benign prostatic hypertrophy, PSA was significantly lower in aspirin users (7.3 ng/ml vs. 8.0 ng/ml, P =0.01). They speculate that cyclo-oxygenase (COX) enzymes may be induced with conversion to cancer, perhaps providing a target for aspirin to decrease prostaglandin (PG) synthesis and the inflammatory response. Any decrease in PGs or inflammatory infiltration in the glandular epithelium due to aspirin use may be sufficient to decrease PSA. It would have been interesting to investigate if the aspirin effect on PSA varied by smoking status. But this was not carried out in the article by Fowke et al. Our analyses not only corroborate these findings but further investigate the impact of smoking on this relationship.

Fowke et al. also report no statistically significant difference between aspirin users and non-users with regard to Gleason score or prostatic volume. This combined with our results leads us to believe that aspirin use may lead to lowering of PSA without an effect on the underlying disease process. Since PSA levels are used to guide timing of prostate biopsy, our results suggest that aspirin use may mask accurate measurement of PSA and consideration of NSAID washout procedures are needed prior to PSA testing. Serum PSA level of 4 ng/ml is the most commonly used threshold for conducting a prostate biopsy for diagnosis of prostate cancer [21]. In the current study, 26 men had baseline PSA <4 ng/ml out of which 15 (57.7%) reported themselves as aspirin users. If aspirin is associated with lower PSA it could potentially lead to underestimation of PSA values, which in turn could lead to non-conduction of prostate biopsy and hence missing an underlying focus of prostate cancer.

Although studies have noted no correlation between the degree and pattern of inflammation, presence of bacteria, serum PSA, or PSA density [22], lower PSA has been associated with anti-inflammatory treatment in other studies as well. Using a retrospective study design, Bozeman et al. reviewed records of 95 men with serum PSA >4 ng/ml diagnosed with prostatitis. After 4 weeks on anti-microbial and/or anti-inflammatory treatment mean PSA

decreased 36.4% from 8.48 to 5.39 ng/ml, and in 44 subjects (46.3%) PSA decreased to levels below 4 ng/ml (mean 2.48 ng/ml) [23]. One proposed mechanism for the PSA increase observed in prostatic inflammation involves leakage of PSA into the circulation due increased to increased vascular permeability brought about by inflammation [24,25].

Negative findings for the effect of medication use on prostate cancer progression could reflect an absence of any such association or could also be due to inadequate observation time (median follow time: 3.2 years). Aspirin demonstrated a statistically significant downward effect on PSA at baseline but not during follow-up. Perhaps the effect of aspirin had already occurred by baseline and further intake of aspirin may not have bestowed additional benefit. Although drugs classified as statins or NSAIDs have the same mechanism of action (HMG-CoA reductase inhibitors or COX inhibitors, respectively), their formulations, bioavailability, and interactions with various physiological systems are different. Classification of different statins or NSAIDs into a single aggregate group may have promoted heterogeneity that attenuated the ability to detect significant effects. Subjects taking aspirin regularly could have different co-morbidities as compared to those taking aspirin on as-needed basis, which in turn could potentially affect the associations with serum PSA. It would have been interesting to investigate the presence of a dose effect for medication use but such analyses was precluded due to small numbers in individual strata. Because a number of multivariate models were investigated, the multiple comparisons made in hypothesis testing raise the possibility of chance findings. However, similarity of our results with those obtained by Fowke et al. and other authors demonstrates consistency of these findings and reduces the probability that these results could be attributed to chance.

To the best of our knowledge, this is the only study of its kind to investigate the association between medication use and PSA velocity using a mixed effects models. These models account for correlation due to repeated measures, and allow independent random intercept and random coefficient for each subject thus using the maximum amount of information provided by the subject to derive an estimate of PSA velocity. It also avoids the instability associated with other methods such as Best Line Fit or First and Last Observation methods and provides a more reliable estimate of PSA velocity [26].

Lower PSA values in subjects taking aspirin, especially among never smokers is an interesting finding. Although these results need to be verified in a larger study, they support potential concerns that aspirin use may mask accurate measurement of PSA and act as a confounder in association studies. This warrants consideration of aspirin washout procedures prior to PSA testing.

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TABLE I

Selected Baseline Characteristics by Medication Use

Variable	Users	Non-users	*P*-value[a]
Aspirin (N, %)	50 (35.7)	90 (64.3)	
PSA (mean, SD, ng/ml)	6.7 (5.7)	8.7 (6.2)	0.07
Age (mean, SD, years)	72.3 (5.8)	73.1 (7.1)	0.45
BMI (mean, SD, kg/m^2)	27.4 (3.9)	26.5 (4.1)	0.20
Smoking (mean, SD, pack-years)	34.1 (35.0)	18.0 (24.8)	0.01
Gleason score (mean, SD)	5.7 (0.1)	5.7 (0.1)	0.77
Ever smokers (N, %)	34 (69.39)	52 (59.09)	0.23
Caucasian (N, %)	79 (87.8)	44 (88.0)	1.00
Statins	27 (19.3)	113 (80.7)	
PSA (mean, SD, ng/ml)	8.5 (6.2)	7.9 (6.1)	0.67
Age (mean, SD, years)	72.6 (6.0)	72.9 (6.8)	0.82
BMI (mean, SD, kg/m^2)	27.3 (4.9)	26.7 (3.9)	0.56
Smoking (mean, SD, pack-years)	33.3 (34.1)	21.5 (28.4)	0.11
Gleason score (mean, SD)	5.8 (1.0)	5.6 (1.0)	0.52
Ever smokers (N, %)	16 (61.54)	70 (63.06)	0.87
Caucasian (N, %)	23 (85.2)	100 (88.5)	0.74[a]
Other NSAIDs	20 (14.3)	120 (85.7)	
PSA (mean, SD, ng/ml)	8.1 (5.8)	8.0 (6.2)	0.93
Age (mean, SD, years)	72.5 (6.0)	73.0 (6.8)	0.78
BMI (mean, SD, kg/m^2)	27.5 (4.5)	26.8 (4.0)	0.52
Smoking (mean, SD, pack-years)	25.3 (30.8)	23.5 (29.7)	0.82
Gleason score (mean, SD)	5.75 (0.6)	5.7 (1.01)	0.58
Ever smokers (N, %)	12 (63.16)	74 (62.71)	0.97
Caucasian (N, %)	16 (80)	107 (89.2)	0.27[a]

[a] *t*-Test was used to derive a *P*-value for continuous variables whereas chi-square or Fischer's exact test were used for categorical variables.

TABLE II

Association Between Medication Use, Smoking, and PSA at Baseline

Main predictor variable	Mean baseline PSA[a] (never smokers) ng/ml	Mean baseline PSA[a] (ever smokers) ng/ml	Mean baseline PSA[a] (total population) ng/ml
Aspirin users	4.19	5.52	5.17
Aspirin non-users	8.24	7.30	7.58
Percentage difference	49.2	24.4	31.8
P-value	0.004	0.10	0.001
Other NSAID users	7.90	4.89	6.35
Other NSAID non-users	6.43	6.77	6.66
Percentage difference	22.9	27.8	4.7
P-value	0.51	0.28	0.89
Statin users	7.39	6.84	7.12
Statin non-users	6.43	6.57	6.51
Percentage difference	14.9	4.1	9.4
P-value	0.90	0.50	0.77

[a]Mean baseline PSA values were predicted using linear regression models adjusted for age, BMI, and Gleason score. PSA calculations were based on a Caucasian population since 87% of the study population was Caucasian.

TABLE III

Association Between Medication Use and Smoking at Baseline With PSA Velocity

Main predictor variable	Mean PSA velocity (never smokers) ng/ml/year	Mean PSA velocity (ever smokers) ng/ml/year	Mean PSA velocity (total population) ng/ml/year
Aspirin users	0.27	0.88	0.51
Aspirin non-users	0.69	0.96	0.95
P-value	0.50	0.70	0.56
Other NSAID users	0.71	0.62	0.64
Other NSAID non-users	0.45	0.98	0.73
P-value	0.95	0.74	0.90
Statin users	0.21	0.71	0.34
Statin non-users	0.59	1.00	0.84
P-value	0.26	0.43	0.25