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Chronic use of NSAIDs and/or Statins does not Impact Longitudinal PSA or PSA velocity in Men at High Risk for Prostate Cancer

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Abstract

Background—Prostate specific antigen (PSA) and PSA velocity (PSAV, rate of PSA change over time) are biomarkers for diagnosis and prognosis of prostate cancer (PCa). Men who are at high risk for PCa also have associated co-morbidities for which they are taking NSAIDs and statins for long periods; therefore it is important to understand the effect of these medications on markers used to assess PCa risk.

Methods—Using a population of 699 men, multiple linear regressions were used to investigate the associations between PSA and concomitant medications; and mixed effects models were used to investigate these associations with PSAV.

Results—After adjusting for selenium use, age, race, body mass index, and pack-years of smoking; aspirin, other NSAIDs, or statins did not demonstrate statistically significant associations with PSA ($p = 0.79, 0.68,$ and 0.79 respectively) or PSAV ($p = 0.23, 0.43,$ and 0.84 respectively). Results were not altered upon stratifying the sample between men who developed PCa during the course of the study and those who did not.

Conclusions—Results from this study indicate that chronic use of aspirin, other NSAIDs, or statins did not impact PSA levels or PSAV in men at high risk for PCa. Larger prospective studies designed to investigate these relationships are needed to confirm this result.

Impact—Long-term use of NSAIDs or statins in men at high risk for PCa may not interfere with the diagnosis or prognosis of this disease, and supports appropriate use of these medications with regard to PCa risk.

Keywords

Aspirin; NSAID; Statin; PSA; PSA-velocity

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) and statins are of interest in cancer prevention. However, data thus far have been conflicting and inconclusive [1]. The 2003

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Conflicts of Interest: None.

positive study on celecoxib showing an effect in Familial Adenomatous Polyposis (28% (p=0.003) polyp reduction in 88 patients) and the subsequent FDA-approval of celecoxib for chemoprevention in this high-risk population [2] intensified the focus for examining the effects of NSAIDs in cancer chemoprevention, including prostate cancer (PCa). However, the positive effects have not translated into other diseases. Similarly, there are compelling data regarding chemopreventive effects of statins; however, these results are controversial [3, 4].

Many men at high risk for PCa have associated comorbidities requiring long-term use of NSAIDs and statins which presents a challenge in studying these agents in a randomized trial. Furthermore, an independent effect of these drugs on PSA (prostate specific antigen) and PSA velocity (rate of PSA change over time) in those at high-risk could interfere with appropriate diagnosis and monitoring of patients with a positive prostate biopsy. Thus, our goal was to determine whether these medications elicited an independent effect of PSA in high-risk men.

MATERIALS AND METHODS

Data were obtained from the Negative Biopsy Trial (NBT); a randomized, double-blind, placebo-controlled, Phase 3 chemoprevention trial designed to investigate the effect of selenium supplementation on prevention of PCa in high-risk men, details of which are available in our earlier publication [5]. In the current study, medication use data were obtained by questionnaire at baseline and at twice-yearly follow-up visits. Baseline association was investigated using multiple linear regression analysis. PSA values were transformed via the logarithmic function to correct for skewed distribution. Statistical significance of an interaction term between medication use and time-on-study was used to assess the impact of the association between medication use and change in PSA levels over time through mixed-effects regression models. We project to have 96% power using a two sample t-test to detect a difference between PSA levels at an alpha of 0.05. Using PSA velocity of 0.51 and 0.95 ng/ml/year for aspirin users and non-users respectively [6] and assuming an average of 5 repeated measures per subject, we project power of 99% for PSA velocity for the sample size.

RESULTS

Table 1 displays the means and standard deviations for subjects using aspirin, other NSAID and statins at baseline. Using multiple linear regression analysis, the coefficient of association between baseline PSA and aspirin, other NSAID, or statins are: -0.17, 0.66, and -0.24, with respective p-values as 0.75, 0.36, and 0.62. Table 2 shows the PSA values and standard deviation of participants for each visit number, with N denoting the number of subjects in each group at each visit. Results of mixed effect regression models indicate that medication use is not associated with statistically significant change in PSA velocity (p-values 0.76, 0.40 and 0.98 respectively).

DISCUSSION

This is the first study to use a longitudinal study design and mixed model analysis to determine the effect of medication use on PSA and PSA velocity. These results indicated that aspirin, other NSAIDs and statins may not interfere with the diagnosis and prognosis of PCa and hence may be safely used in men at high risk for PCa. The Irish Tumor Registry showed that aspirin did not significantly affect PCa risk (HR = 0.88, 95% CI 0.67–1.15); and a modest survival effect was observed (HR = 0.61, 95% CI 0.37–0.99) in the group defined as high-dose (75 mg daily) [7]. Although other studies suggest that there is an effect [8]. Similarly, the data thus far on statins on PCa risk are compelling but inconclusive. A meta-analysis of clinical data by Zhang et al. suggest a protective effect (OR 1.195, 95% CI 1.018–1.403, $p = 0.029$) [4]; however, study limitations including lack of prospective trials confound conclusions. Another review by Moon et al. discussed the weaknesses in current data [3] which further demonstrates that more information is needed.

Strengths of the study includes longitudinal study design which uses PSA data measured at multiple time points to increase the power of the study to provide a more reliable estimate of the patient's PSA velocity. Limitations include recall bias that may occur due to the medication data being obtained through questionnaires. However, attempts were made to minimize this bias by standardized administration of these questionnaires by trained study personnel. Additionally, if recall bias does play a role, its effect would be reduced due to it affecting the medication users and non-users equally. Average duration of time subjects were on the study was 3.5 years. This may not have been enough time for medication use to affect PSA. Role of medication compliance and dosage could not be addressed in this study due to small numbers.

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Table 1

Baseline Characteristics by Medication Use

Variable	Aspirin use at baseline			Other NSAID use at baseline			Statin use at baseline		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Number of subjects	163	528		74	617		171	520	
PSA, mean (SD)	6.9 (4.9)	6.8 (5.6)	0.79	7.3 (5.1)	6.8 (5.5)	0.49	6.9 (6.2)	6.9 (5.2)	0.72
Age, mean (SD)	67 (6.6)	65 (7.9)	0.00010	67 (7.3)	65 (7.7)	0.10	66 (6.7)	65 (8.0)	0.72
BMI, mean (SD)	28 (5.1)	28 (4.3)	0.83	29 (4.5)	27 (4.5)	0.0026	28 (4.2)	27 (4.6)	0.20
Pack years of smoking, mean (SD)	22 (26)	15 (21)	0.0010	22 (24)	16 (22)	0.028	18 (24)	16 (22)	0.20
Caucasian, N (%)	148 (91%)	429 (81%)	0.002	65 (85%)	512 (83%)	0.61	148 (86%)	429 (82%)	0.22

Note: Data presented as the mean $\pm$ SD or as the number of subjects in each group, with percentages in parentheses.

Table 2

PSA values (ng/ml) by visit number

Visit number	Aspirin use at baseline		Other NSAID use at baseline		Statin use at baseline	
	Yes	No	Yes	No	Yes	No
1 N	6.7(4.7)	6.7(4.8)	7.4(5.0)	6.6(4.8)	6.2(3.9)	6.9(5.0)
	141	457	70	528	138	460
2 N	6.7(5.2)	6.4(4.7)	7.7(6.2)	6.4(4.7)	6.4(5.2)	6.5(4.7)
	128	430	57	501	130	428
3 N	6.7(5.2)	6.4(4.6)	6.9(6.1)	6.4(4.5)	6.3(4.9)	6.5(4.7)
	123	407	57	473	125	405
4 N	6.7(5.0)	6.6(5.4)	6.4(4.9)	6.6(5.4)	6.1(4.3)	6.8(5.6)
	99	377	51	425	109	367
5 N	6.6(4.6)	6.8(8.5)	6.6(5.2)	6.7(8.0)	6.1(4.1)	6.9(8.5)
	102	337	47	392	100	339
6 N	6.0(3.8)	6.1(4.2)	5.5(2.7)	6.2(4.3)	5.9(4.3)	6.2(4.1)
	85	292	43	334	89	288
7 N	6.0(3.6)	5.9(4.1)	5.5(3.7)	6.0(4.0)	5.6(3.3)	6.0(4.1)
	74	272	34	312	73	273
8 N	6.0(4.4)	5.5(3.7)	4.6(3.1)	5.8(4.0)	6.0(3.9)	5.5(3.9)
	65	192	30	227	68	189
9 N	5.8(3.8)	5.6(3.8)	5.3(4.0)	5.7(3.8)	5.6(3.7)	5.6(3.9)
	59	172	26	205	55	176
10 N	5.9(4.8)	5.6(3.8)	5.8(4.1)	5.6(4.1)	5.2(3.1)	5.8(4.4)
	63	147	26	184	48	162
11 N	5.5(3.5)	5.3(3.8)	6.3(4.4)	5.3(3.7)	5.1(3.1)	5.5(3.9)
	57	129	19	167	42	144
p-value unadjusted model	0.97		0.08		0.52	
p-value adjusted model	0.76		0.40		0.98	

Note: Model adjusted for pack-years of smoking, race, BMI, age and diagnosis of prostate cancer