Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Chronic Use of NSAIDs and/or Statins Does Not Affect PSA or PSA Velocity in Men at High Risk for Prostate Cancer

Amit M. Algotar, Roxanna Behnejad, M. Suzanne Stratton, and Steven P. Stratton

Abstract

Background: PSA and PSA velocity (PSAV, rate of PSA change over time) are biomarkers for diagnosis and prognosis of prostate cancer. Men who are at high risk for prostate cancer also have associated comorbidities 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 prostate cancer 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 prostate cancer 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 affect PSA levels or PSAV in men at high risk for prostate cancer. 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 prostate cancer may not interfere with the diagnosis or prognosis of this disease, and supports appropriate use of these medications with regard to prostate cancer risk. *Cancer Epidemiol Biomarkers Prev; 23(10); 2196–8. ©2014 AACR.*

Introduction

NSAIDs and statins are of interest in cancer prevention. However, data thus far have been conflicting and inconclusive (1). The 2003 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. However, the positive effects have not translated into other diseases. Similarly, there are compelling data about chemopreventive effects of statins; however, these results are controversial (3, 4).

Many men at high risk for prostate cancer 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 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, a randomized, double-blind, placebo-controlled, phase III chemoprevention trial designed to investigate the effect of selenium supplementation on prevention of prostate cancer 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

Division of Cancer Prevention and Control, University of Arizona Cancer Center, Tucson, Arizona.

Corresponding Author: Amit M. Algotar, University of Arizona, 1515 N. Campbell Ave., Tucson, AZ 85724. Phone: 520-321-7794; Fax: 520-321-7774; E-mail: algotar@email.arizona.edu

doi: 10.1158/1055-9965.EPI-14-0605

Table 1. Baseline characteristics by medication use

	Aspirin use at baseline			Other NSAIDs use at baseline			Statin use at baseline		
Variable	**Yes**	**No**	***P***	**Yes**	**No**	***P***	**Yes**	**No**	***P***
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 ± SD or as the number of subjects in each group, with percentages in parentheses.
Abbreviation: BMI, body mass index.

have 96% power using a two-sample *t* test to detect a difference between PSA levels at an α of 0.05. Using PSA velocity of 0.51 and 0.95 ng/mL/year for aspirin users and nonusers, 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 mean and SDs for subjects using aspirin, other NSAIDs, and statins at baseline. Using multiple linear regression analysis, the coefficient of association between baseline PSA and aspirin, other NSAID, or statins is −0.17, 0.66, and −0.24, with respective *P* values as 0.75, 0.36, and 0.62. Table 2 shows the PSA

Table 2. PSA values (ng/mL) by visit number

	Aspirin use at baseline		Other NSAIDs use at baseline		Statin use at baseline	
Visit number	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1	6.7 (4.7)	6.7 (4.8)	7.4 (5.0)	6.6 (4.8)	6.2 (3.9)	6.9 (5.0)
N	141	457	70	528	138	460
2	6.7 (5.2)	6.4 (4.7)	7.7 (6.2)	6.4 (4.7)	6.4 (5.2)	6.5 (4.7)
N	128	430	57	501	130	428
3	6.7 (5.2)	6.4 (4.6)	6.9 (6.1)	6.4 (4.5)	6.3 (4.9)	6.5 (4.7)
N	123	407	57	473	125	405
4	6.7 (5.0)	6.6 (5.4)	6.4 (4.9)	6.6 (5.4)	6.1 (4.3)	6.8 (5.6)
N	99	377	51	425	109	367
5	6.6 (4.6)	6.8 (8.5)	6.6 (5.2)	6.7 (80)	6.1 (4.1)	6.9 (8.5)
N	102	337	47	392	100	339
6	6.0 (3.8)	6.1 (4.2)	5.5 (2.7)	6.2 (4.3)	5.9 (4.3)	6.2 (4.1)
N	85	292	43	334	89	288
7	6.0 (3.6)	5.9 (4.1)	5.5 (3.7)	6.0 (4.0)	5.6 (3.3)	6.0 (4.1)
N	74	272	34	312	73	273
8	6.0 (4.4)	5.5 (3.7)	4.6 (3.1)	5.8 (4.0)	6.0 (3.9)	5.5 (3.9)
N	65	192	30	227	68	189
9	5.8 (3.8)	5.6 (3.8)	5.3 (4.0)	5.7 (3.8)	5.6 (3.7)	5.6 (3.9)
N	59	172	26	205	55	176
10	5.9 (4.8)	5.6 (3.8)	5.8 (4.1)	5.6 (4.1)	5.2 (3.1)	5.8 (4.4)
N	63	147	26	184	48	162
11	5.5 (3.5)	5.3 (3.8)	6.3 (4.4)	5.3 (3.7)	5.1 (3.1)	5.5 (3.9)
N	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, body mass index, age, and diagnosis of prostate cancer.

values and SD 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 prostate cancer and hence may be safely used in men at high risk for prostate cancer. The Irish Tumor Registry showed that aspirin did not significantly affect prostate cancer risk [HR, 0.88; 95% confidence interval, 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; ref. 7). Although other studies suggest that there is an effect (8). Similarly, the data thus far on statins on prostate cancer risk are compelling but inconclusive. A meta-analysis of clinical data by Zhang and colleagues (4) suggests a protective effect (OR, 1.195; 95% CI, 1.018–1.403, $P = 0.029$); however, study limitations including lack of prospective trials confound conclusions. Another review by Moon and colleagues discussed the weaknesses in current data (3), which further demonstrates that more information is needed.

Strengths of the study include longitudinal study design that 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. In addition, if recall bias does play a role, its effect would be reduced due to it affecting the medication users and nonusers 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A.M. Algotar, M.S. Stratton, R. Behnejad, S.P. Stratton
Development of methodology: A.M. Algotar, R. Behnejad, S.P. Stratton
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. Algotar, M.S. Stratton, R. Behnejad, S.P. Stratton
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Algotar, M.S. Stratton, R. Behnejad
Writing, review, and/or revision of the manuscript: A.M. Algotar, M.S. Stratton, R. Behnejad
Study supervision: A.M. Algotar, M.S. Stratton, S.P. Stratton

Acknowledgments

The authors thank the study participants and families for their contribution to this work.

Grant Support

This study was supported by PHS grants CA079080 and CA023074.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 2, 2014; accepted June 19, 2014; published OnlineFirst July 24, 2014.

References

1. Half E, Arber N. Colon cancer: preventive agents and the present status of chemoprevention. Expert Opin Pharmacother 2009;10:211–9.
2. Phillips RK, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP, et al. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. Gut 2002;50:857–60.
3. Moon H, Hill MM, Roberts MJ, Gardiner RA, Brown AJ. Statins: protectors or pretenders in prostate cancer? Trends Endocrinol Metab 2014;25:188–96.
4. Zhang Y, Zang T. Association between statin usage and prostate cancer prevention: a refined meta-analysis based on literature from the years 2005–2010. Urol Int 2013;90:259–62.
5. Algotar AM, Stratton MS, Ahmann FR, Ranger-Moore J, Nagle RB, Thompson PA, et al. Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer. Prostate 2013;73:328–35.
6. Algotar AM, Thompson PA, Ranger-Moore J, Stratton MS, Hsu CH, Ahmann FR, et al. Effect of aspirin, other NSAIDs, and statins on PSA and PSA velocity. Prostate 2010;70:883–8.
7. Flahavan EM, Bennett K, Sharp L, Barron TI. A cohort study investigating aspirin use and survival in men with prostate cancer. Ann Oncol 2014;25:154–9.
8. Bonovas S, Filioussi K, Sitaras NM. Statin use and the risk of prostate cancer: a metaanalysis of 6 randomized clinical trials and 13 observational studies. Int J Cancer 2008;123:899–904.