Published OnlineFirst August 14, 2018; DOI: 10.1158/1055-9965.EPI-18-0510

Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

A Prospective Study of Aspirin Use and Prostate Cancer Risk by *TMPRSS2:ERG* Status

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Abstract

Background: In a case–control study, aspirin use was associated with a lower risk of a common prostate cancer molecular subtype, the *TMPRSS2:ERG* gene fusion. We sought to validate this finding in a prospective cohort.

Methods: In the Health Professionals Follow-up Study, 49,395 men reported on aspirin use on biennial questionnaires and were followed for prostate cancer incidence over 23 years. *TMPRSS2:ERG* status was assessed by IHC for presence of ERG on archival tumor specimens for 912 patients with prostate cancer, of whom 48% were ERG-positive.

Results: In multivariable models, we found no association between regular use of aspirin and risk of *ERG*-positive prostate cancer (HR, 1.02; 95% confidence interval, 0.85–1.23), nor any association with duration or frequency of aspirin use. In restricting to cases with either high Gleason grade or advanced stage disease, there remained no association with aspirin use.

Conclusions: Data from this prospective study with repeated assessments of aspirin use do not support the hypothesis that aspirin use is associated with a lower risk of *ERG*-positive prostate cancer.

Impact: Aspirin use is unlikely to lower the risk of this common molecular subtype of prostate cancer. However, there is emerging data supporting the role of other lifestyle and genetic factors underlying the development of the *TMPRSS2:ERG* fusion. *Cancer Epidemiol Biomarkers Prev; 27(10); 1231–3. ©2018 AACR.*

Introduction

The *TMPRSS2:ERG* gene fusion is the most common somatic event in primary prostate cancer, with an estimated 100,000 U.S. patients diagnosed with *TMPRSS2:ERG*-positive cancer annually. Our group and others have reported on associations between lifestyle and inherited genetic factors specifically associated with *TMPRSS2:ERG*-defined disease (1–4). In a retrospective case–control study, current aspirin use was associated with a lower risk of *TMPRSS2:ERG*-positive cancer [OR, 0.63; 95% confidence interval (CI), 0.43–0.93], whereas there was no association with cancers that lacked *TMPRSS2:ERG* (OR, 0.99; 95% CI, 0.69–1.42; ref. 5). The authors speculated that aspirin may protect against *TMPRSS2:ERG*-positive cancer through reduction in cellular stress, inflammation, and DNA damage. We sought to validate this association in a prospective cohort of men with longitudinal measures of aspirin use and 23 years of follow-up for prostate cancer incidence.

Materials and Methods

This study was nested in the Health Professionals Follow-up Study (HPFS), a cohort of 51,529 male health professionals age 40 to 75 years at baseline in 1986 (6). For this study, we excluded men with cancer diagnoses other than nonmelanoma skin cancer before 1986 ($n = 2,076$), missing age or diagnosis date ($n = 42$), and implausible diagnosis or death dates ($n = 16$). Participants responded to biennial questionnaires on lifestyle, diet (every 4 years), diagnoses, and medication use. Biennial follow-up rates exceeded 93%. Patients with incident prostate cancer were followed with specific questionnaires. Clinical data were abstracted from medical records and pathology reports.

On biennial questionnaires, participants reported current regular aspirin use (with example brand names provided). If participants did not return a specific questionnaire, their prior response was carried forward. Starting in 1992, men reported categories of frequency of use, and we defined regular use as ≥2 days/week.

We characterized *TMPRSS2:ERG* status on tumor tissue microarrays from men who underwent radical prostatectomy ($n = 912$)

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doi: 10.1158/1055-9965.EPI-18-0510

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Table 1. Characteristics of participants of the HPFS by aspirin use at baseline, standardized to the age distribution of the study population

Baseline characteristics, 1986	Nonusers of aspirin	Current users of aspirin
N	34,848	14,547
Frequency of aspirin use, mean (SD; d/mo)	0.0	8.6 (0.0)[a]
Age, mean (SD; y)[b]	53.7 (9.7)	56.5 (9.7)
BMI, mean (SD; kg/m^2)	25.5 (3.3)	25.7 (3.5)
Family history of prostate cancer	12.0%	11.8%
Smoking status		
Never smoker	45.7%	41.8%
Past smoker	39.6%	47.3%
Current smoker	9.3%	10.4%
Missing	5.4%	0.5%
Total physical activity, mean (SD; METS-h/wk)	18.8 (26.5)	18.6 (26.1)
Diabetes diagnosis	3.0%	3.6%
Cumulative incidence, by 2009		
Prostate cancer diagnosis	12.5%	12.7%
Prostate cancer death	1.3%	1.1%
Overall mortality	27.7%	30.8%

Abbreviations: BMI, body mass index; METS, metabolic equivalent tasks.
[a]This increased to 26.3 days/month (mean; SD, 4.6) among current aspirin users in 2010.
[b]Not adjusted for age.

using a genomically validated immunohistochemistry method for the ERG protein (7). A case was scored ERG-positive if at least one core had positive ERG staining within cancer cells.

Cox proportional hazards models, adjusted for predefined covariates, were used to estimate HRs and two-sided 95% CIs for total, advanced (stage, ≥T3b/N1, or M1 at any time), and high-grade (Gleason grade, ≥4 + 3) cancers, each according to ERG status.

Results

Among 49,395 men, 14,547 (29.4%) were current aspirin users at baseline in 1986. In 2008, 47.2% and 36.3% of the remaining 28,355 participants were current and past aspirin users, respectively. A total of 6,189 participants (12.5%) were diagnosed with incident prostate cancer (Table 1). From 2,332 patients treated with prostatectomy, ERG status was available for 912 tumors.

There was no statistically significant association between current regular aspirin use and the risk of ERG-positive (HR, 1.02; 95% CI, 0.85–1.23) or ERG-negative prostate cancer (HR, 1.09; 95% CI, 0.91–1.30; $P_{\text{heterogeneity}} = 0.69$ by ERG status), nor for total prostate cancer including all cases (HR, 1.05; 95% CI, 0.99–1.10) in fully adjusted models. Dose–response analyses according

Table 2. ERG-positive and ERG-negative incident prostate cancer by aspirin use (fully adjusted model[a])

	No. of cases		HR (95% CI)	
	ERG-positive	ERG-negative		
Total	**439**	**473**	**ERG-positive**	**ERG-negative**
Categories of use				
Never user	147	138	1 (ref)	1 (ref)
Past user	107	114	1.02 (0.79–1.31)	1.04 (0.82–1.33)
Current user	185	221	1.03 (0.83–1.28)	1.11 (0.89–1.37)
			$P_{\text{heterogeneity}} = 0.88$	
Current use				
Never/past user	254	252	1 (ref)	1 (ref)
Current user	185	221	1.02 (0.85–1.23)	1.09 (0.91–1.30)
			$P_{\text{heterogeneity}} = 0.63$	
Ever use				
Never user	147	138	1 (ref)	1 (ref)
Ever user	292	335	1.03 (0.84–1.25)	1.08 (0.89–1.33)
			$P_{\text{heterogeneity}} = 0.69$	
Duration of use since baseline				
Non-aspirin user	147	138	1 (ref)	1 (ref)
Aspirin use <5 years	134	149	1.00 (0.79–1.26)	1.17 (0.94–1.46)
Aspirin use 5–<10 years	90	92	1.11 (0.85–1.44)	0.98 (0.76–1.28)
Aspirin use 10 years+	68	94	0.96 (0.71–1.30)	1.03 (0.77–1.37)
			$P_{\text{heterogeneity}} = 0.48$	
Per year of use	439	473	1.00 (1.00–1.00)	1.00 (1.00–1.00)
			$P_{\text{heterogeneity}} = 0.62$	
Frequency of use				
Aspirin use <2 d/wk (never/past user)	254	252	1 (ref)	1 (ref)
Aspirin use 2–<6 d/wk	72	81	0.94 (0.73–1.21)	1.05 (0.83–1.33)
Aspirin use 6+ d/wk	113	140	1.09 (0.87–1.37)	1.12 (0.90–1.39)
			$P_{\text{heterogeneity}} = 0.82$	
Per d/wk of use	439	473	1.02 (0.98–1.05)	1.01 (0.98–1.05)
			$P_{\text{heterogeneity}} = 0.93$	

Abbreviation: ref, reference category.
[a]Adjusted for age, calendar time, race (Caucasian, other), family history of prostate cancer in father or brother (yes, no), height (≤68, >68–70, >70–72, >72 inches), body mass index (<21, 21–<25, 25–<30, 30+ kg/m^2), body mass index at age 21 years (<20, 21–<25, 25–<30, 30+ kg/m^2), physical activity (quintiles of metabolic equivalents-hours/week), smoking (never, former/quit >10 years ago, former/quit ≤10 years ago, current), history of diabetes (yes, no), time-varying current statin use (yes, no), PSA testing in the 2 years prior to the questionnaire date (yes, no; lagged by one period to avoid counting diagnostic PSA tests as screening), and PSA testing in >50% of possible time periods (yes, no; lagged by one period to avoid counting diagnostic PSA tests as screening).

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to cumulative duration or frequency of aspirin use were null (Table 2). Results for ERG-positive cancer were also null for age-adjusted models for advanced and high-grade cancer.

Discussion

In this prospective study with updated information on aspirin, we found no association between regular aspirin use and risk of *ERG*-positive prostate cancer. Similarly, we found no association between duration or frequency of aspirin use and *ERG*-positive disease, including for clinically significant high-risk cancers. Our findings are in contrast with those of Wright and colleagues' (5), who reported a strong inverse association in their case–control study, which included 346 cases (49% ERG-positive) and 942 controls.

Differences in results may partly be due to differences in study design. First, our study was nested in a prospective cohort, whereas the prior study collected data from cases after diagnosis and used random digit dialing to select controls free from prostate cancer. Second, genetic and environmental factors are associated with ERG status (1–4) and could lead to confounding if not controlled for (5). In our study population, however, adjusted and unadjusted estimates were nearly identical. Third, misclassification of aspirin exposure is expected to be nondifferential in HPFS, where medical professionals repeatedly reported on medication use before cancer diagnosis. Recall bias in the prior study cannot account for differences in risk according to ERG status, which was unknown to participants. It is unlikely that ERG assessment via IHC or FISH would have biased either study's result (7). Finally, differences in results may be due to chance. Our study had >99% power to detect an HR of 0.63, corresponding to the previously reported effect size (5).

In summary, our data do not support the hypothesis that aspirin use lowers the risk of *TMPRSS2:ERG*-positive prostate cancer. Emerging data suggest other modifiable etiologic and prognostic factors for this common molecular subtype (1–4, 8).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: M.K. Downer, S. Finn, R.E. Graff
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Finn, R.T. Lis, L.A. Mucci
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.H. Stopsack, A.G. Gonzalez-Feliciano, M.K. Downer, A. Pettersson, M. Loda, P.W. Kantoff, T.U. Ahearn, L.A. Mucci
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Acknowledgments

We would like to thank the participants and staff of the Health Professionals Follow-up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. In particular, we would like to recognize the contributions of Liza Gazeeva, Siobhan Saint-Surin, Robert Sheahan, and Betsy Frost-Hawes. The Health Professionals Follow-up Study was supported by NIH grant U01 CA167552. This research was funded in part by the Dana-Farber/Harvard Cancer Center Specialized Programs of Research Excellence program in Prostate Cancer (5P50 CA090381), the NCI (R01CA136578 to L.A. Mucci; T32CA09001 to M.K. Downer and C.H. Pernar; and R25CA112355 to R.E. Graff), and the NIH/NCI Cancer Center Support Grants P30 CA008748 and P30 CA06516. K.H. Stopsack, S. Finn, and L.A. Mucci are Prostate Cancer Foundation Young Investigators.

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Received May 10, 2018; revised May 30, 2018; accepted July 30, 2018; published first August 14, 2018.

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Published OnlineFirst August 14, 2018; DOI: 10.1158/1055-9965.EPI-18-0510

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