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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 immunohistochemistry for presence of ERG on archival tumor specimens for 912 prostate cancer patients, 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 (hazard ratio, 1.02; 95% confidence interval, 0.85 to 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.

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Conflicts of Interest: None declared.

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.

Keywords

Aspirin; prostate cancer; TMPRSS2:ERG; prospective cohort study; validation

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 (odds ratio [OR] 0.63; 95% confidence interval [CI], 0.43 to 0.93), whereas there was no association with cancers that lacked *TMPRSS2:ERG* (OR, 0.99; 95% CI, 0.69 to 1.42) (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.

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 non-melanoma 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 four years), diagnoses, and medication use. Biennial follow-up rates exceeded 93%. Patients with incident prostate cancer were followed with specific questionnaires. Clinical data was 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) 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 hazard ratios (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. 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 to 1.23) or ERG-negative prostate cancer (HR, 1.09; 95% CI, 0.91 to 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 to 1.10) in fully adjusted models. Dose-response analyses according 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 to those of Wright *et al.* (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, while 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 non-differential 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 immunohistochemistry or fluorescence in-situ hybridization 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).

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References

1. Graff RE, Meisner A, Ahearn TU, Fiorentino M, Loda M, Giovannucci EL, et al. Pre-diagnostic circulating sex hormone levels and risk of prostate cancer by ERG tumour protein expression. Br J Cancer. 2016;114:939–44. [PubMed: 26986253]
2. Egbers L, Luedeke M, Rinckleb A, Kolb S, Wright JL, Maier C, et al. Obesity and Prostate Cancer Risk According to Tumor TMPRSS2:ERG Gene Fusion Status. Am J Epidemiol. 2015;181:706–13. [PubMed: 25852077]
3. Graff RE, Pettersson A, Lis RT, Ahearn TU, Markt SC, Wilson KM, et al. Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. Am J Clin Nutr. 2016;103:851–60. [PubMed: 26817504]
4. Penney KL, Pettersson A, Shui IM, Graff RE, Kraft P, Lis RT, et al. Association of Prostate Cancer Risk Variants with TMPRSS2:ERG Status: Evidence for Distinct Molecular Subtypes. Cancer Epidemiol Biomarkers Prev. 2016;25:745–9. [PubMed: 26941365]
5. Wright JL, Chery L, Holt S, Lin DW, Luedeke M, Rinckleb AE, et al. Aspirin and NSAID use in association with molecular subtypes of prostate cancer defined by TMPRSS2:ERG fusion status. Prostate Cancer Prostatic Dis. 2016;19:53–6. [PubMed: 26503111]
6. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer. 2007;121:1571–8. [PubMed: 17450530]
7. Pettersson A, Graff RE, Bauer SR, Pitt MJ, Lis RT, Stack EC, et al. The TMPRSS2:ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012;21:1497–509. [PubMed: 22736790]
8. Pettersson A, Lis RT, Meisner A, Flavin R, Stack EC, Fiorentino M, et al. Modification of the association between obesity and lethal prostate cancer by TMPRSS2:ERG. J Natl Cancer Inst. 2013;105:1881–90. [PubMed: 24292212]

Table 1.

Characteristics of participants of the Health Professionals Follow-up Study (HPFS) by aspirin use at baseline, standardized to the age distribution of the study population.

Baseline characteristics, 1986	**Non-users of aspirin**	**Current users of aspirin**
n	34,848	14,547
Frequency of aspirin use, mean (SD) [days/month]	0.0	8.6 (0.0)[a]
Age, mean (SD) [years][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-hours/week]	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 %

[a]This increased to 26.3 days/month (mean; SD, 4.6) among current aspirin users in 2010.

[b]Not adjusted for age

Abbreviations: BMI, body mass index; SD, standard deviation; kg, kilograms; METS, metabolic equivalent tasks

Table 2.

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

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

[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); prostate-specific antigen testing in the two 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).

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; ref, reference category