Author Manuscript Published OnlineFirst on November 28, 2018; DOI: 10.1158/1055-9965.EPI-18-0965
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Aspirin and Non-Aspirin NSAID Use and Prostate Cancer Incidence, Mortality, and Case-Fatality in the Atherosclerosis Risk in Communities Study

Lauren M. Hurwitz[1], Corinne E. Joshu[1,2], John R. Barber[1], Anna E. Prizment[3,4], Mara Z. Vitolins[5], Miranda R. Jones[1,2], Aaron R. Folsom[3], Misop Han[6], Elizabeth A. Platz[1,2,6]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
[2]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
[3]Division of Epidemiology and Community Health, University of Minnesota School of Public Health
[4]Masonic Cancer Center, University of Minnesota
[5]Department of Epidemiology and Prevention, Wake Forest School of Medicine
[6]Department of Urology and the James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine

Running title: Aspirin and prostate cancer incidence and mortality

Keywords: aspirin, NSAIDs, prostate cancer risk, mortality

Research support: The Atherosclerosis Risk in Communities study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, and Department of Health and Human Services, under the following contract numbers: HHSN268201700001I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I, HHSN268201700002I. Studies on cancer in Atherosclerosis Risk in Communities (ARIC) are also supported by the NCI (U01 CA164975). This research was additionally supported by an NCI Cancer Center Support Grant (P30 CA006973). Lauren Hurwitz was supported by an NCI National Research Service Award (T32 CA09314). The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Corresponding author: Elizabeth A. Platz, ScD, MPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St. Baltimore, MD 21205; email: eplatz1@jhu.edu.

The authors declare no potential conflicts of interest.

Word count:

Abstract: 250

Body: 3373

Tables: 4

Figures: 0

Abstract

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to moderately reduce prostate cancer risk. However, evidence is limited on whether NSAIDs protect against prostate cancer mortality (death from prostate cancer among men without a cancer history) and case-fatality (death from prostate cancer among men with prostate cancer), and whether benefits are consistent in white and black men. This study investigated associations of aspirin and non-aspirin (NA)-NSAID use with prostate cancer incidence, mortality, and case-fatality in a population-based cohort of white and black men.

Methods: We included 6,594 men (5,060 white, 1,534 black) from the Atherosclerosis Risk in Communities study without a cancer history at enrollment in 1987-89. NSAID use was assessed at four study visits (1987-98). Cancer outcomes were ascertained through 2012. Cox proportional hazards regression was used to estimate adjusted hazard ratios (HRs), overall and by race.

Results: Aspirin use was not associated with prostate cancer incidence. However, aspirin use was inversely associated with prostate cancer mortality (HR: 0.59, 95% confidence interval [CI]: 0.36-0.96). This association was consistent among white and black men and appeared restricted to men using aspirin daily and/or for cardiovascular disease prevention. Aspirin use was inversely associated with case-fatality (HR: 0.45, 95% CI: 0.22-0.94). NA-NSAID use was not associated with these endpoints.

Conclusion: Aspirin use was inversely associated with prostate cancer mortality and case-fatality among white and black men.

Impact: If confirmed by additional studies, benefits of aspirin for preventing prostate cancer mortality may need to be factored into risk-benefit calculations of men considering an aspirin regimen.

Introduction

Unlike other leading causes of cancer, little is known about how to prevent prostate cancer. Older age, African-American race, and a positive family history are established prostate cancer risk factors, but these risk factors are non-modifiable. Cigarette smoking and obesity appear associated with advanced and/or lethal prostate cancer (1,2), but these risk factors are difficult to modify. There is a need to identify additional modifiable factors for prostate cancer incidence and mortality so that preventive strategies can be developed and morbidity and mortality can be reduced.

One potential modifiable factor is regular use of aspirin and non-aspirin (NA) nonsteroidal anti-inflammatory drugs (NSAIDs), which are hypothesized to prevent cancer development and progression via anti-inflammatory and anti-platelet mechanisms (3,4). Secondary analyses of randomized controlled trials (RCTs) of aspirin for cardiovascular disease (CVD) prevention have shown that daily aspirin reduces overall cancer incidence, development of cancer metastases, and cancer mortality, particularly after ≥5 years of use (5-7). However, RCTs have not investigated NSAID use and prostate cancer endpoints specifically.

In observational studies, NSAID use has been inversely associated with prostate cancer risk (pooled odds ratio [POR] and 95% confidence interval [CI] for aspirin: 0.83 [0.77-0.89]; for NA-NSAIDs: 0.89 [0.78-1.02]) (8). Aspirin use has also been inversely associated with advanced prostate cancer risk (POR: 0.81 [0.72-0.92]) (8). However, most studies have defined advanced prostate cancer based on diagnostic stage and/or histologic grade, which are imperfect indicators of disease lethality, particularly in settings with routine prostate-specific antigen (PSA) screening (9,10). Evidence also conflicts on whether NSAID use pre- or post-diagnosis protects against case-fatality (i.e. death from prostate cancer among men diagnosed with prostate cancer) (11), and additional studies are thus needed to determine whether NSAIDs may protect against development or progression of prostate cancers with a lethal

phenotype. Furthermore, previous studies have been conducted primarily among white men, and generalizability to other groups is unknown.

The goal of this study was to investigate associations between aspirin and NA-NSAID use and prostate cancer incidence and mortality among white and black men without a cancer history in the Atherosclerosis Risk in Communities (ARIC) study. This study also examined associations between pre-diagnostic aspirin and NA-NSAID use and case-fatality among men diagnosed with prostate cancer during ARIC follow-up.

Methods

Study Population

This study included men enrolled in ARIC, a prospective cohort study designed to assess the etiology and natural history of CVD (12). A total of 15,792 participants ages 45-64 years were recruited from four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; Washington County, Maryland). Participants attended up to six in-person study visits (Visit 1: 1987-89, 2: 1990-92, 3: 1993-95, 4: 1996-98, 5: 2011-13, 6: 2016-17). All study sites received institutional review board approval, ~~and~~ all participants provided written informed consent, and the ARIC study is conducted in accordance with recognized ethical guidelines.

For analyses of prostate cancer incidence and mortality, the study population was restricted to men without a history of cancer at baseline. The study population was further restricted to men who self-reported as white or black, since there were not enough men of other racial/ethnic groups to examine them separately. Few black men were enrolled from the Washington County and Minneapolis field centers; these men were excluded as well, to avoid confounding by race/geography. Lastly, men with missing baseline medications data were excluded (Supplemental Figure 1).

For analyses of case-fatality, the study population included white and black men without a cancer history at baseline who were diagnosed with prostate cancer during follow-up (1987-2012), irrespective of whether prostate cancer was the first or subsequent primary. Cases missing stage or identified by death certificate only were excluded.

Assessment of NSAID Use

At each study visit, participants were asked to bring containers of all prescribed and over-the-counter medications they had used within the past two weeks. This information was used to classify men as current aspirin and NA-NSAID users at each visit. Additional detailed information on regular aspirin use, defined as use ≥ once/week for several months, was collected at Visit 4, including information on dose (low-dose [<300 mg], regular-strength [300-499 mg], extra-strength [≥500 mg]), days/week of use, and indication for use (CVD prevention, other).

Outcome Ascertainment

Cancer diagnoses and deaths among ARIC participants were identified and adjudicated as previously described (13) and are currently ascertained through 2012. This study had four primary outcomes: (1) incident prostate cancer, defined as diagnosis of a first primary prostate cancer, (2) prostate cancer mortality, defined as death from prostate cancer as the underlying cause, irrespective of whether other cancers were also diagnosed during follow-up, (3) incident lethal prostate cancer, defined as diagnosis of a first primary prostate cancer with metastasis to any organ at diagnosis (pathologic TNM stage 4 or SEER summary stage 3, 4, or 7), or diagnosis of a first primary prostate cancer that resulted in prostate cancer death during follow-up; and (4) case-fatality, defined as death from prostate cancer as the underlying cause among men diagnosed with prostate cancer during follow-up, irrespective of whether other cancers were diagnosed after the prostate cancer diagnosis. Results for incident lethal prostate cancer

(Supplemental Table 1) and prostate cancer mortality were generally similar; thus we focus on prostate cancer mortality throughout.

Statistical analysis

For each outcome, hazard ratios (HRs) and 95% confidence intervals (CIs) comparing aspirin and NA-NSAID users to non-users were calculated using Cox proportional hazards regression. For analyses of prostate cancer incidence, men were censored if lost-to-follow-up, if diagnosed with a first primary cancer of another site, at death, or administratively in 2012. For analyses of prostate cancer mortality and case-fatality, men were censored at date of death from a cause other than prostate cancer or administratively in 2012. The proportional hazards assumption was verified via Schoenfeld residuals.

For analyses of prostate cancer incidence and mortality, the time metric was age. Current aspirin and NA-NSAID use were included as dichotomous exposures and updated at each visit (through Visit 4). Time-fixed covariates included race/center (White/Forsyth, Black/Forsyth, Black/Jackson, White/Minneapolis, White/Washington County), year of birth (in 5-year categories), education (basic [≤11 years completed], intermediate [12-16 years], advanced [≥17 years]), and family history of prostate cancer in 1st degree relatives (yes, no). Time-updated covariates included cigarette smoking status (never, quit >10 years ago, quit within 10 years or current smoker), body mass index (BMI, continuous), statin use (yes, no), diabetes (diagnosed diabetes [self-reported physician-diagnosed diabetes or use of diabetes medications], undiagnosed diabetes [fasting serum glucose ≥126 mg/dL or non-fasting serum glucose ≥200 mg/dL], prediabetes [100 mg/dL ≤ fasting serum glucose <126 mg/dL or 140 mg/dL ≤ non-fasting serum glucose <200 mg/dL], no diabetes [fasting serum glucose <100 mg/dL or non-fasting serum glucose <140 mg/dL]), and prevalent coronary heart disease (CHD, yes, no). Time-updated covariates were carried forward from the prior visit when missing. When time-updated covariates were missing at Visit 1 or when time-fixed covariates were missing

(0.2% for BMI, 0.2% for education, 2.0% for CHD, 7.4% for family history of prostate cancer, and 0.1% for diabetes), data were imputed using simple mean imputation.

Among men still at risk for each outcome at Visit 4, similar analyses were conducted using information on regular aspirin use collected at Visit 4. Specifically, HRs were calculated comparing regular aspirin use by dose, indication, and frequency of use to non-use, adjusting for the same covariates as above.

For analyses of case-fatality, the primary exposures were aspirin and NA-NSAID use at the visit prior to prostate cancer diagnosis. Time since diagnosis was the time metric, and covariates were the same as above, with the addition of age (continuous), stage (T1, T2, T3, T4 or N1 or M1), grade (low, moderate, high, missing), and years between the prior visit and diagnosis (continuous).

To explore possible effect modification by race (white, black) and frequency of routine physical examinations (≥once every 5 years, <once every 5 years), analyses were repeated, stratified by these variables. Statistical interaction was tested via likelihood ratio tests.

Finally, several sensitivity analyses were conducted to verify findings for aspirin use. First, because it was hypothesized that the influence of aspirin on cancer endpoints would not be immediate, analyses were repeated with current aspirin use lagged one year. Current aspirin use was updated every three years and thus already lagged to an extent in the primary analysis, but this sensitivity analysis was conducted to test whether additional lagging altered the findings. Second, because aspirin is often used concurrently with statins, and because statins have been associated with a reduced risk of prostate cancer mortality in ARIC (14) and other studies (15) analyses were repeated restricted to non-statins users only. Too few men reported using both statins and aspirin to examine their joint effects. Third, to test the assumption that carrying forward the last observed value was an adequate approach for handling missing data on time-updated covariates, analyses were repeated with missing data imputed using multiple imputation by chained equations (MICE). Ten imputed datasets were derived, based on ten

iterations each, with missing data predicted using all other covariates in this analysis. Finally, to examine the impact of aspirin use on the cumulative incidence of each outcome, in the presence of competing events, subdistribution hazard ratios were calculated using Fine and Grey regression (16). Analyses were conducted in SAS Version 9.4 (Cary, NC) and R Version 3.4.

Results

Current Aspirin and NA-NSAID Use at Visits 1-4 and Prostate Cancer Incidence and Mortality

Among 6,594 eligible men, we ascertained 817 incident prostate cancers and 90 prostate cancer deaths. At Visits 1, 2, 3, and 4, 29% 33%, 37%, and 44% of men reported current aspirin use, respectively, and 13%, 16%, 20%, and 23% of men reported current NA-NSAID use. Compared to non-users at Visit 1, aspirin and NA-NSAID users were more likely to be white than black and receive frequent physical examinations (Table 1). Aspirin users were also more likely to have prevalent CHD.

After adjusting for potential confounders, current aspirin use was not associated with prostate cancer incidence (HR: 1.05, 95% CI: 0.91-1.22, Table 2). However, current aspirin use was inversely associated with prostate cancer mortality (HR: 0.59, 95% CI: 0.36-0.96, Table 2). Results were consistent when aspirin use was lagged by one additional year, when analyses were restricted to non-users of statins, when missing data were imputed, and when sub-distribution HRs were calculated to account for competing risks (Supplemental Table 2).

In race-stratified analyses, the association for prostate cancer incidence appeared null for white men (HR: 0.97, 95% CI: 0.82-1.16) but nominally positive for black men (HR: 1.30, 95% CI: 0.98-1.72, *p*-interaction=0.13, Table 3). For prostate cancer mortality, results were consistent across race (HR: 0.67, 95% CI: 0.38-1.19 for white men; HR: 0.41, 95% CI: 0.14-1.20 for black men, *p*-interaction=0.32).

When stratified by frequency of routine physical examinations, aspirin use appeared nominally positively associated with prostate cancer incidence among men who reported frequent physical examinations (HR: 1.18, 95% CI: 0.98-1.41, Table 3). In contrast, aspirin use had a non-significant inverse association with prostate cancer incidence among men who reported infrequent examinations (HR: 0.85, 95% CI: 0.65-1.10, *p*-interaction=0.07). Associations with prostate cancer mortality did not differ by examination frequency (*p*-interaction=0.49).

In analyses stratified by both race and exam frequency, the positive association between aspirin use and prostate cancer incidence observed for black men was restricted to black men who reported frequent physical examinations (HR: 1.39, 95% CI: 0.98-1.96) and attenuated among black men who reported infrequent physical examinations (HR: 1.08, 95% CI: 0.64-1.80, Supplemental Table 3).

No statistically significant associations were observed for NA-NSAID use and prostate cancer incidence and mortality (Table 2). No effect modification by race or frequency of routine physical examinations was observed (Supplemental Table 4).

Regular Aspirin Use at Visit 4 and Prostate Cancer Incidence and Mortality

Among the 4,527 men who attended Visit 4, completed items on regular aspirin use, and were not yet diagnosed with cancer, 37% reported regular aspirin use. Of these men, 24% used low-dose, 68% used regular-strength, and 4% used extra-strength aspirin. Seventy-nine percent used aspirin for CVD prevention and 77% used aspirin daily. After Visit 4, 506 incident prostate cancers and 36 prostate cancer deaths were ascertained.

Overall, regular aspirin use at Visit 4 was not associated with prostate cancer incidence (HR: 1.08, 95% CI: 0.89-1.32) or mortality (HR: 0.81, 95% CI: 0.38-1.70, Table 4). However, associations appeared to differ by indication, dose, and frequency of use. Specifically, aspirin used for CVD prevention, low- and regular-strength aspirin, and daily aspirin use appeared

inversely associated with prostate cancer mortality (Table 4). In contrast, aspirin used for other indications, extra-strength aspirin, and non-daily use appeared positively associated with prostate cancer mortality. Use of extra-strength aspirin was also positively associated with prostate cancer incidence (HR: 1.84, 95% CI: 1.03-3.30).

Aspirin and NA-NSAID Use and Prostate Cancer Case-Fatality

Among 676 eligible men with prostate cancer (Supplemental Table 5), 65 died of their prostate cancer. After multivariable adjustment, current aspirin use prior to diagnosis was inversely associated with case-fatality (HR: 0.45, 95% CI: 0.22-0.94, Supplemental Table 6). NA-NSAID use was not significantly associated with case-fatality (HR: 0.69, 95% CI: 0.28-1.65).

Discussion

In this study, current aspirin use was not associated with prostate cancer incidence but was inversely associated with prostate cancer mortality. Aspirin use pre-diagnosis was also inversely associated with case-fatality. Current NA-NSAID use was not significantly associated with these endpoints.

The magnitude of the association for aspirin and prostate cancer mortality was large, with current aspirin users exhibiting a 41% reduced risk relative to non-users. Results were similar for incident lethal prostate cancer (Supplemental Table 1). These results are consistent with previous observational studies of lethal prostate cancer: in the Health Professionals Follow-up Study, the HR for lethal prostate cancer comparing current aspirin use to non-use was 0.84 (95% CI: 0.69-1.02) (17), and in the Physicians' Health Study, the HR was 0.68 (95% CI: 0.52-0.89) (18). Our results are also similar in magnitude to secondary analyses of RCTs. In a pooled analysis of six CVD trials, men allocated to daily aspirin had a non-significant reduced risk of prostate cancer mortality after five or more years of follow-up (HR: 0.52, 95% CI: 0.20-1.34), though only 37 prostate cancer deaths were observed during the study period of these trials (5).

These prior studies were conducted in primarily white study populations. Importantly, our study extends these findings to black men, who are more likely than other racial/ethnic groups to develop and die from prostate cancer (19). According to this study and others (20,21), black men may also be less likely to use aspirin regularly. Encouraging guideline-concordant use of aspirin among black men may thus help attenuate the current racial disparity, if the association between aspirin use and prostate cancer lethality proves to be causal.

In analyses of regular aspirin use at Visit 4, a significant inverse association with prostate cancer mortality was not observed, possibly due to the limited follow-up time after Visit 4 and small number of events. However, aspirin used regularly for CVD prevention, low- and regular-strength aspirin, and daily aspirin appeared inversely associated with prostate cancer mortality, consistent with our primary findings. Though CIs in these analyses were wide, these patterns suggest that protective effects of aspirin may be confined to daily and/or low-dose use, a finding that warrants further investigation.

At first glance, our finding of no association between aspirin and prostate cancer incidence appears inconsistent with prior studies, which have most often reported inverse associations (8). However, our primary analysis did not account for detection bias resulting from the fact that aspirin users may be more health-conscious, or in greater contact with the healthcare system, and thus more likely to be screened for prostate cancer (22). To account for this bias, we stratified by frequency of routine visits to the doctor, a proxy for opportunity to undergo prostate cancer screening. Of note, the association among men who frequently visited the doctor was positive, consistent with the expected effect of detection bias. In contrast, the association was moderately inverse among men who infrequently visited the doctor for routine examinations, and who thus had limited opportunity to be screened. Though not significant, this inverse association is most consistent with prior studies and suggests that aspirin may protect against prostate cancer incidence once the influence of detection bias is reduced.

Aspirin use pre-diagnosis was also associated with a 57% reduction in case-fatality, even after adjustment for cancer stage and grade, suggesting that aspirin use may have specifically influenced risk of early cancer spread. Other studies have reported null associations for pre-diagnostic aspirin use and prostate cancer case-fatality (23-27). Our results may differ due to differing time intervals between measurement of aspirin use and prostate cancer diagnosis (median=5.7 years in our study vs. 1-3 years in most previous studies) or differing study time frames (our study overlapped the pre-PSA era, while previous studies were conducted solely in the PSA era). There could also be unmeasured confounding in our study by access to or receipt of treatment, a determinant of prostate cancer mortality that might differ by aspirin use. Finally, our case-fatality analysis was limited by a small number of events, and further research is needed to explore whether our results were spurious, confounded, or indicative of a true causal relationship.

In this study, current NA-NSAID use was not associated with any of our outcomes. The null associations for NA-NSAIDs, in contrast to the inverse associations for aspirin, could have several explanations. First, there may have been inadequate power to observe more moderate associations for NA-NSAID use. Second, NA-NSAID users were likely a heterogeneous group, consisting of men using NA-NSAIDs for different indications and durations. The mixing of regular and sporadic users could bias results towards the null, as short-term use is unlikely to influence cancer outcomes. Third, discordant findings for aspirin and NA-NSAIDs might indicate that any chemopreventive effects of aspirin are due to an aspirin-specific biological mechanism. For example, unlike NA-NSAIDs, aspirin has a prolonged inhibitory effect on platelets, which are thought to facilitate metastases through the bloodstream (28). If platelet inhibition is the primary mechanism through which aspirin protects against prostate cancer lethality, then similar effects for NA-NSAIDs would not be expected. Additional studies with greater power and detailed assessment of NA-NSAID use are needed to rule out the first two explanations and provide support for or against the third.

Primary study limitations included the small number of events other than prostate cancer incidence and the potential for misclassification of NSAID use. Current medication use was based on medication bottles brought to each visit; failure to bring in bottles could have resulted in underreporting of use. Medication use was also only assessed at each study visit and assumed to remain constant between visits, or indefinitely after Visit 4. Moreover, though regular, long-term use was of most interest, our definitions of current NSAID use likely captured both short- and long-term users. Additional information on dose, frequency of use, indication, and lifetime cumulative duration of use would have been informative, but these data were only available for aspirin at Visit 4. There was also limited data available on prostate cancer treatment, and so we were unable to adjust for this potential confounder in our case-fatality analyses. Finally, race and location of residence were highly collinear in this cohort, limiting our ability to tease apart the influence of these factors.

Despite this collinearity, the racial and geographic diversity of the cohort was a major strength that improves generalizability of the results. There was also thorough, time-updated assessment of potential CVD-related confounders. For example, weight and height were measured at each visit instead of self-reported, and diabetes status was assessed using a combination of self-report and glycemic markers. Given that NSAIDs are used for specific indications and that these indications may share risk factors with prostate cancer, careful adjustment is necessary to minimize confounding.

In conclusion, this prospective, community-based study of white and black men provides evidence that aspirin may protect against prostate cancer mortality. Additional studies are needed to confirm these findings, build support for a causal relationship, and assess the influence of dose, frequency, and timing of aspirin use. Collectively, such research may eventually help inform whether benefits of aspirin pertaining to prostate cancer lethality may need to be incorporated into clinical guidelines or factored into individual risk-benefit calculations of men considering starting an aspirin regimen.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

Cancer incidence data have been provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Maryland Department of Health, 201 W. Preston Street, Room 400, Baltimore, MD 21201. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the Centers for Disease Control and Prevention for the funds that helped support the availability of the cancer registry data.

References

1. World Cancer Research Fund International/Continuous Update Project. Diet, nutrition, physical activity, and prostate cancer. 2014.
2. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
3. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol **2012**;9(5):259-67. doi: 10.1038/nrclinonc.2011.199.
4. Ulrich CM, Bigler J, Potter JD. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. Nat Rev Cancer **2006**;6(2):130-40.
5. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet **2011**;377(9759):31-41. doi: 10.1016/S0140-6736(10)62110-1. Epub 2010 Dec 6.
6. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G*, et al.* Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet **2012**;379(9826):1602-12. doi: 10.016/S0140-6736(11)61720-0. Epub 2012 Mar 21.
7. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet **2012**;379(9826):1591-601. doi: 10.016/S0140-6736(12)60209-8. Epub 2012 Mar 21.
8. Mahmud SM, Franco EL, Aprikian AG. Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis. Int J Cancer **2010**;127(7):1680-91. doi: 10.002/ijc.25186.
9. Assel M, Dahlin A, Ulmert D, Bergh A, Stattin P, Lilja H*, et al.* Association Between Lead Time and Prostate Cancer Grade: Evidence of Grade Progression from Long-term Follow-up of Large Population-based Cohorts Not Subject to Prostate-specific Antigen Screening. Eur Urol **2017**;21(17):30860-6.
10. Helgstrand JT, Roder MA, Klemann N, Toft BG, Brasso K, Vainer B*, et al.* Diagnostic characteristics of lethal prostate cancer. Eur J Cancer **2017**;84:18-26.(doi):10.1016/j.ejca.2017.07.007. Epub Aug 2.
11. Thakker D, Raval AD, Raval N, Vyas A. Nonsteroidal anti-inflammatory drugs and clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. J Med Paediatr Oncol **2018**;39:127-41.
12. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol **1989**;129(4):687-702.
13. Joshu CE, Barber JR, Coresh J, Couper DJ, Mosley TH, Vitolins MZ*, et al.* Enhancing the Infrastructure of the Atherosclerosis Risk in Communities (ARIC) Study for Cancer Epidemiology Research: ARIC Cancer. Cancer Epidemiol Biomarkers Prev **2017**;20:1055-9965.
14. Mondul AM, Joshu CE, Barber JR, Prizment AE, Bhavsar NA, Selvin E*, et al.* Lipid-lowering drug use and risk of fatal prostate cancer in black and white men in the Atherosclerosis Risk in Communities (ARIC) Study. **(submitted)**.
15. Alfaqih MA, Allott EH, Hamilton RJ, Freeman MR, Freedland SJ. The current evidence on statin use and prostate cancer prevention: are we there yet? Nat Rev Urol **2017**;14(2):107-19. doi: 10.1038/nrurol.2016.199. Epub Oct 25.
16. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association **1999**;94(446):496-509 doi 10.2307/2670170.

17. Dhillon PK, Kenfield SA, Stampfer MJ, Giovannucci EL. Long-term aspirin use and the risk of total, high-grade, regionally advanced and lethal prostate cancer in a prospective cohort of health professionals, 1988-2006. Int J Cancer **2011**;128(10):2444-52. doi: 10.1002/ijc.25811. Epub 2011 Feb 26.
18. Downer MK, Allard CB, Preston MA, Gaziano JM, Stampfer MJ, Mucci LA*, et al.* Regular Aspirin Use and the Risk of Lethal Prostate Cancer in the Physicians' Health Study. Eur Urol **2017**;8(17):30069-6.
19. American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018.
20. Sanchez DR, Diez Roux AV, Michos ED, Blumenthal RS, Schreiner PJ, Burke GL*, et al.* Comparison of the racial/ethnic prevalence of regular aspirin use for the primary prevention of coronary heart disease from the multi-ethnic study of atherosclerosis. Am J Cardiol **2011**;107(1):41-6. doi: 10.1016/j.amjcard.2010.08.041.
21. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacoepidemiol Drug Saf **2014**;23(1):43-50. doi: 10.1002/pds.3463. Epub 2013 May 30.
22. Tangen CM, Goodman PJ, Till C, Schenk JM, Lucia MS, Thompson IM, Jr. Biases in Recommendations for and Acceptance of Prostate Biopsy Significantly Affect Assessment of Prostate Cancer Risk Factors: Results From Two Large Randomized Clinical Trials. J Clin Oncol **2016**;34(36):4338-44. Epub 2016 Oct 28.
23. Cardwell CR, Flahavan EM, Hughes CM, Coleman HG, O'Sullivan JM, Powe DG*, et al.* Low-dose aspirin and survival in men with prostate cancer: a study using the UK Clinical Practice Research Datalink. Cancer Causes Control **2014**;25(1):33-43. doi: 10.1007/s10552-013-0306-x. Epub 2013 Dec 6.
24. 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(1):154-9. doi: 10.1093/annonc/mdt428.
25. Jacobs EJ, Newton CC, Stevens VL, Campbell PT, Freedland SJ, Gapstur SM. Daily aspirin use and prostate cancer-specific mortality in a large cohort of men with nonmetastatic prostate cancer. J Clin Oncol **2014**;32(33):3716-22. doi: 10.1200/JCO.2013.54.8875. Epub 2014 Oct 20.
26. Veitonmaki T, Murtola TJ, Maattanen L, Taari K, Stenman UH, Tammela TL*, et al.* Use of non-steroidal anti-inflammatory drugs and prostate cancer survival in the finnish prostate cancer screening trial. Prostate **2015**;75(13):1394-402. doi: 10.002/pros.23020. Epub 2015 Jun 12.
27. Zhou CK, Daugherty SE, Liao LM, Freedman ND, Abnet CC, Pfeiffer R*, et al.* Do Aspirin and Other NSAIDs Confer a Survival Benefit in Men Diagnosed with Prostate Cancer? A Pooled Analysis of NIH-AARP and PLCO Cohorts. Cancer Prev Res (Phila) **2017**;10(7):410-20. doi: 10.1158/940-6207.CAPR-17-0033. Epub 2017 May 15.
28. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer **2011**;11(2):123-34. doi: 10.1038/nrc3004.

Author Manuscript Published OnlineFirst on November 28, 2018; DOI: 10.1158/1055-9965.EPI-18-0965
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Tables

Table 1. Baseline (1987-1989) demographic and clinical characteristics of 6,594 men in the ARIC study, by current aspirin and NA-NSAID use at Visit 1

	Aspirin Use		NA-NSAID Use	
	No	Yes	No	Yes
N	4743	1851	5718	876
Age (years), mean (sd)	54.3 (5.8)	54.9 (5.6)	54.4 (5.8)	55.0 (5.8)
BMI (kg/m^2), mean (sd)	27.4 (4.2)	27.8 (4.3)	27.4 (4.2)	28.4 (4.6)
Race, n (%)				
White	3403 (72)	1675 (90)	4340 (76)	720 (82)
Black	1340 (28)	194 (10)	1378 (24)	156 (18)
Center, n (%)				
Forsyth	1207 (25)	524 (28)	1477 (26)	254 (29)
Jackson	1188 (25)	153 (8)	1459 (26)	261 (30)
Minneapolis	1136 (24)	666 (36)	1219 (21)	122 (14)
Washington County	1212 (26)	508 (27)	1563 (27)	239 (27)
Cigarette Smoking Status, n (%)				
Current/Recent (quit <10 years ago)	2084 (44)	810 (44)	2523 (44)	371 (42)
Former (quit ≥10 years ago)	1285 (27)	572 (31)	1570 (27)	287 (33)
Never	1374 (29)	469 (25)	1625 (28)	218 (25)
Education, n (%)				
Basic	1242 (26)	356 (19)	1371 (24)	277 (26)
Intermediate	1734 (37)	659 (36)	2059 (36)	334 (38)
Advanced	1756 (37)	834 (45)	2275 (40)	315 (36)
Missing	11 (0)	2 (0)	13 (0)	0 (0)
Family History of PCa[a], n (%)				
Yes	275 (6)	100 (5)	319 (6)	56 (6)
No	4121 (87)	1608 (87)	4977 (87)	752 (86)
Missing	347 (7)	143 (8)	422 (7)	68 (8)
Statin Use[b], n (%)				
Yes	17 (0)	20 (1)	29 (1)	8 (1)
No	4726 (100)	1831 (99)	5689 (99)	868 (99)
Prevalent CHD, n (%)				
Yes	209 (4)	322 (17)	441 (8)	90 (10)
No	4431 (93)	1501 (81)	5163 (90)	769 (88)
Missing	103 (2)	28 (2)	114 (2)	17 (2)
Diabetes, n (%)				
Diagnosed diabetes	342 (7)	138 (7)	401 (7)	79 (9)
Undiagnosed diabetes	213 (4)	80 (4)	245 (4)	48 (5)
Prediabetes	1790 (38)	809 (44)	2246 (39)	353 (40)

No diabetes	2391 (50)	824 (45)	2822 (49)	393 (45)
Missing			4 (0)	3 (0)
Frequency of Routine Physical Examinations				
≥Once every 5 years	2779 (59)	1230 (66)	3405 (60)	604 (69)
<Once every 5 years	1949 (41)	620 (34)	2299 (40)	270 (31)
Missing	15 (0)	1 (0)	14 (0)	2 (0)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; NA-NSAID, non-aspirin nonsteroidal anti-inflammatory drug; sd, standard deviation; BMI, body mass index; PCa, prostate cancer; CHD, coronary heart disease

[a]Reported at Visit 3

[b]Statin use is low at baseline because the first statin was not FDA approved until 1987

Table 2. Associations between current aspirin and NA-NSAID use and prostate cancer incidence and mortality among 6,594 men in the ARIC study, 1987-2012

	Prostate Cancer Incidence					Prostate Cancer Mortality				
		Age-Adjusted		Multivariable-Adjusted[a]			Age-Adjusted		Multivariable-Adjusted[a]	
	Events/ Person-years	HR	(95% CI)	HR	(95% CI)	Events/ Person-years	HR	(95% CI)	HR	(95% CI)
Aspirin Use										
No	503 / 75897	1	(Ref)	1	(Ref)	65 / 84565	1	(Ref)	1	(Ref)
Yes	314 / 43478	0.96	(0.84-1.11)	1.05	(0.91-1.22)	25 / 48951	0.52	(0.33-0.82)	0.59	(0.36-0.96)
NA-NSAID Use										
No	633 / 96626	1	(Ref)	1	(Ref)	71 / 107724	1	(Ref)	1	(Ref)
Yes	184 / 22749	1.15	(0.98-1.36)	1.16	(0.98-1.37)	19 / 25792	1.02	(0.62-1.70)	1.02	(0.62-1.71)

Abbreviations: NA-NSAID, non-aspirin nonsteroidal anti-inflammatory drug; ARIC, Atherosclerosis Risk in Communities; HR, hazard ratio; CI, confidence interval

[a]Adjusted for age, race/center, birth cohort, smoking status, BMI, current statin use, diabetes, prevalent CHD, education, family history of prostate cancer

Table 3. Associations between current aspirin use and prostate cancer incidence and mortality among 6,594 men in the ARIC study, 1987-2012, stratified by race and frequency of routine physical examinations

		Prostate Cancer Incidence					Prostate Cancer Mortality				
		Events/ Person-years	Age-Adjusted		Multivariable-Adjusted[a]		Events/ Person-years	Age-Adjusted		Multivariable-Adjusted[a]	
			HR	(95% CI)	HR	(95% CI)		HR	(95% CI)	HR	(95% CI)
Stratified by Race											
White	Aspirin Use										
	No	316 / 55777	1	(Ref)	1	(Ref)	36 / 62036	1	(Ref)	1	(Ref)
	Yes	243 / 38271	1.00	(0.85-1.18)	0.97	(0.82-1.16)	21 / 42823	0.66	(0.39-1.14)	0.67	(0.38-1.19)
Black	Aspirin Use										
	No	187 / 20120	1	(Ref)	1	(Ref)	29 / 22529	1	(Ref)	1	(Ref)
	Yes	71 / 5207	1.28	(0.97-1.68)	1.30	(0.98-1.72)	4 / 6127	0.39	(0.14-1.10)	0.41	(0.14-1.20)
p-value[b]				0.13					0.32		
Stratified by Frequency of Routine Physical Examinations[c]											
Frequent	Aspirin Use										
	No	298 / 43895	1	(Ref)	1	(Ref)	38 / 49264	1	(Ref)	1	(Ref)
	Yes	223 / 27806	1.06	(0.89-1.26)	1.18	(0.98-1.41)	14 / 31508	0.46	(0.25-0.86)	0.49	(0.26-0.94)
Infrequent	Aspirin Use										
	No	205 / 31730	1	(Ref)	1	(Ref)	27 / 35010	1	(Ref)	1	(Ref)
	Yes	91 / 15643	0.79	(0.62-1.02)	0.85	(0.65-1.10)	11 / 17412	0.62	(0.31-1.26)	0.78	(0.37-1.63)
p-value[b]				0.07					0.49		

Abbreviations: ARIC, Atherosclerosis Risk in Communities; HR, hazard ratio; CI, confidence interval

[a]Adjusted for age, race/center, birth cohort, smoking status, BMI, current statin use, diabetes, prevalent CHD, education, family history of prostate cancer

[b]*p*-value is from the likelihood ratio test comparing the multivariable model with vs. without an interaction term between aspirin use and race/frequency of routine physical exams

[c]Frequent routine physical examination defined as an examination at least once every 5 years, infrequent routine physical examination defined as an examination less that once every 5 years or no routine physical

Table 4. Associations between regular aspirin use at Visit 4 and prostate cancer incidence and mortality among 4,527 men in the ARIC study, 1996-2012

	Prostate Cancer Incidence					Prostate Cancer Mortality				
	Events/ Person-years	Age-Adjusted		Multivariable-Adjusted[a]		Events/ Person-years	Age-Adjusted		Multivariable-Adjusted[a]	
		HR	(95% CI)	HR	(95% CI)		HR	(95% CI)	HR	(95% CI)
Regular aspirin use										
No	321 / 34363	1	(Ref)	1	(Ref)	23 / 38667	1	(Ref)	1	(Ref)
Yes	185 / 19097	1.03	(0.86-1.23)	1.09	(0.89-1.32)	13 / 21663	0.86	(0.44-1.70)	0.81	(0.38-1.70)
Indication for use[b]										
No use	321 / 34363	1	(Ref)	1	(Ref)	23 / 38667	1	(Ref)	1	(Ref)
CVD prevention	142 / 15101	1.00	(0.82-1.21)	1.04	(0.84-1.29)	8 / 17140	0.65	(0.29-1.56)	0.57	(0.24-1.37)
Other	43 / 3925	1.16	(0.84-1.60)	1.25	(0.91-1.73)	5 / 4452	1.76	(0.67-4.63)	1.83	(0.68-4.89)
Dose[c]										
No use	321 / 34363	1	(Ref)	1	(Ref)	23 / 38667	1	(Ref)	1	(Ref)
<300 mg	47 / 4499	1.10	(0.84-1.58)	1.15	(0.84-1.58)	2 / 5211	0.56	(0.13-2.37)	0.49	(0.11-2.17)
300-499 mg	120 / 13170	0.97	(0.78-1.19)	1.03	(0.82-1.29)	8 / 14834	0.75	(0.34-1.69)	0.71	(0.30-1.71)
≥500 mg	12 / 800	1.58	(0.89-2.82)	1.85	(1.04-3.32)	2 / 922	3.33	(0.78-14.10)	3.38	(0.75-15.28)
Frequency of Use										
No use	321 / 34363	1	(Ref)	1	(Ref)	23 / 38667	1	(Ref)	1	(Ref)
Daily	142 / 14268	1.05	(0.86-1.28)	1.12	(0.90-1.39)	8 / 16270	0.68	(0.31-1.53)	0.60	(0.25-1.46)
Non-daily	43 / 4829	0.95	(0.69-1.31)	1.01	(0.73-1.40)	5 / 5393	1.45	(0.55-3.83)	1.44	(0.53-3.88)

Abbreviations: Atherosclerosis Risk in Communities; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; mg, milligrams

[a]Adjusted for age, race/center, birth cohort, smoking status at Visit 4, BMI at Visit 4, statin use at Visit 4, diabetes at Visit 4, prevalent CHD at Visit 4, education, family history of prostate cancer

[b]5 aspirin users of unknown indication excluded

[c]50 aspirin users of unknown dose excluded

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Aspirin and Non-Aspirin NSAID Use and Prostate Cancer Incidence, Mortality, and Case-Fatality in the Atherosclerosis Risk in Communities Study

Lauren M Hurwitz, Corinne E. Joshu, John R. Barber, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst November 28, 2018.