Aspirin Use and Prostate Cancer among African-American Men in the Southern Community Cohort Study

Wei Tang[1], Jay H. Fowke[2], Lauren M. Hurwitz[3], Mark Steinwandel[4], William J. Blot[4,5], and Stefan Ambs[1]

ABSTRACT

Background: The association of aspirin use with prostate cancer has been investigated, but few studies included African-American men. Here, we analyzed the relationship of aspirin intake with prostate cancer risk and mortality among African-American men in the Southern Community Cohort Study (SCCS).

Methods: SCCS recruited 22,426 African-American men between 2002 and 2009. Aspirin use was assessed at enrollment. Our exposures of interest were any aspirin use (regular strength, low-dose or baby aspirin, or half tablets of aspirin) and regular strength aspirin. Each exposure variable was compared with non-users. Associations between aspirin use and prostate cancer risk and mortality were examined with Cox proportional hazards models.

Results: At enrollment, 5,486 men (25.1%) reported taking any aspirin and 2,634 men (12.1%) reported regular strength aspirin use. During follow-up (median, 13 years), 1,058 men developed prostate cancer, including 103 prostate cancer–specific deaths. Aspirin use was not associated with prostate cancer development [adjusted HR, 1.07; 95% confidence interval (CI), 0.92–1.25 for any aspirin use and HR, 0.97; 95% CI, 0.78–1.19 for regular strength aspirin], but was suggestively associated with reduced prostate cancer mortality (HR, 0.66; 95% CI, 0.39–1.14 for any aspirin use and HR, 0.41; 95% CI, 0.17–1.00 for regular strength aspirin).

Conclusions: Aspirin use at enrollment was tentatively associated with reduced prostate cancer mortality, but not risk, among African-American men in SCCS.

Impact: Prospective SCCS data suggest that aspirin use may help prevent lethal prostate cancer among this high-risk group of men.

Introduction

Men of African ancestry have an excess risk of developing and dying from prostate cancer (1–6). We have had limited success in reducing this health disparity. Our group and others have described previously an immune inflammation signature that is prevalent in prostate tumors of African-American men, but absent in most European-American men (7–12). This gene signature associated with an increased risk of recurrent disease (11), suggesting that potential inhibitors of this inflammation-related signature, such as an anti-inflammatory drug like aspirin, may prevent prostate cancer progression in African-American men. In agreement with the hypothesis, we reported that aspirin use at time of disease diagnosis was associated with fewer cases having advanced-stage prostate cancer and a lower risk of disease recurrence among African-American men in the NCI-Maryland Prostate Cancer Case–Control Study (13). There have been numerous studies investigating the association of regular aspirin intake with prostate cancer risk (14–17) and disease mortality and survival (18–21) among European-American men, with several reporting an association with reduced mortality, but few studies have included African-American men. Here, we pursued the hypothesis that use of aspirin prior to a disease diagnosis reduces prostate cancer risk and mortality among African-American men in the Southern Community Cohort Study (SCCS), a large cohort study that prospectively recruited low-income and predominately African-American participants to investigate the causes of cancer health disparities (22).

Materials and Methods

SCCS

SCCS focused on the recruitment of a low-income, predominantly African-American population from a 12-state area of the Southeast (22). Accordingly, 59% of the recruited African-American men came from households with less than $15,000 of annual household income and 21% from households with annual incomes between $15,000 and $25,000 at time of recruitment (23). Recruitment began in March 2002 and was completed in September 2009. Informed consent was obtained from all study participants, and the study was approved by the institutional review boards of the involved institutions. Participants were asked to complete an in-person interview at enrollment. About 85,000 men and women ages 40–79 years were recruited into this study. To obtain follow-up data on cancer development, procedures for data linkage, processing, and quality control were established with the 12-state cancer registries covering the SCCS catchment area (Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia). These registries provide the primary source of identifying incident cancer diagnoses and disease characteristics. Information on disease staging followed the 7th edition of the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) system for clinical stage, abbreviated as I–IV. We

[1]Laboratory of Human Carcinogenesis, Center for Cancer Research, NCI, NIH, Bethesda, Maryland. [2]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee. [3]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, NIH, Rockville, Maryland. [4]International Epidemiology Institute, Rockville, Maryland. [5]Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, Tennessee.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Stefan Ambs, NCI, Building 37, Room 3050B, MSC Convent Drive 4258, Bethesda, MD 20892. Phone: 240-760-6836; E-mail: ambss@mail.nih.gov

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defined aggressive prostate cancer as stage IV (T4) or N1 or M1 by AJCC, or Gleason score ≥ 8 (high grade), as described previously (24). Cohort member deaths were identified through annual linkages with both the Social Security Administration and the National Death Index (NDI). For this study, SCCS state cancer registries reporting was completed through December 31, 2016 and NDI reporting through December 31, 2018. We examined the SCCS dataset for all self-reported African-American men ($n = 22{,}426$). Of these men, 1,058 developed prostate cancer. During the study follow-up (median, 13 years; maximum, 16.8 years), a total of 6,627 deaths occurred, including 103 prostate cancer–related deaths as defined by International Classification of Diseases 10th criteria using NDI data. All participants provided written informed consent for the studies that were conducted. The research followed the ethical guidelines set by the Declaration of Helsinki.

Assessment of aspirin use

We pursued two exposures of interests, any aspirin use and regular strength aspirin use. The SCCS baseline survey evaluated aspirin use with the following questions: (i) in the past year, have you taken the following medication regularly? By regularly, we mean at least two times per week for 1 month or more: regular aspirin (such as Anacin, Bayer, Bufferin, Excedrin, etc.) with no or yes; low-dose aspirin, baby aspirin, or half tablets of aspirin with no or yes. (ii) How many years have you taken this type of medication regularly? Number of years was calculated. (iii) When you took this regularly, what is the average number of pills you took per week? Number of pills was calculated. A total of 97.4% of the participants (21,851/22,426) answered the questions on aspirin use at enrollment. We created aspirin use categories on the basis of question (i). The use of regular aspirin was defined as "regular strength aspirin use" in the study, whereas "any aspirin use" was defined as taking either regular aspirin, low-dose or baby aspirin, or half tablets of aspirin. Use was then categorized as either "no" or "yes." For all analyses, nonusers of aspirin were men who did not report any aspirin use. The aspirin category was further categorized as either "taken more than seven pills per week" or "taken seven pills per week or less" based on question (iii). Duration of aspirin use was based on question (ii). Duration was then categorized as either "less than or equal to 3 years," or "more than 3 years," as done previously (13).

Statistical analysis

Cox proportional hazards regression models with age as the time scale were used to calculate HRs for disease risk and disease-specific mortality. Our exposures of interest were any aspirin use and regular strength aspirin use. Each exposure variable was separately compared with nonusers. Models to assess disease risk and mortality contained the same covariates [age, year of enrollment (categorical), education (without high school degree, high school degree, college degree, and graduate degree), household income (<$15,000, $15,000–25,000, >$25,000–50,000, >$50,000–100,000, and >$100,000), family history of prostate cancer including father and brother (yes/no), smoking status (current, former, and never), diabetes (yes/no), body mass index (BMI; as six categories <18.5, 18.5–25, 25–30, 30–35, 35–40, and >40 kg/m^2), benign prostate hyperplasia (BPH) (yes/no), prostate cancer screening by PSA test (yes/no) and digital rectal exam (DRE; yes/no), acetaminophen (yes/no), and other NSAID use (yes/no)]. In the analysis of disease risk, men contributed follow-up time from enrollment until incident cancer, death, or last follow-up. We performed additional secondary analyses after grouping patients by disease stage (TNM I/II vs. III/IV), by Gleason score [≤7 (low/medium grade) vs. ≥8 (high grade)], and by disease aggressiveness (T4 or N1 or M1 or Gleason score ≥ 8). In these stratified analyses, the other cases were removed (e.g., when data for early-stage disease were analyzed, cases with late-stage disease were removed). Models were adjusted for potential confounders, as aforementioned. Individuals who did not answer the aspirin survey questions or with missing values for the two exposure variables were excluded from the analysis. Missing data for covariates were imputed as mean values. Because PSA levels were measured in a subset of men at baseline, we compared these PSA levels between aspirin users and nonusers to evaluate an aspirin effect.

In the mortality analysis, we compared the risk of fatal prostate cancer by aspirin use among men without prostate cancer at enrollment. Men contributed follow-up time from enrollment until death or last follow-up at December 31, 2018. Deaths from causes other than prostate cancer were censored. Subdistribution HRs (SHR) were calculated using Fine and Grey regression to examine the impact of aspirin use on the cumulative probability of prostate cancer–related death in the presence of competing events.

Tests for trend related to frequency and duration of aspirin use were performed by calculating P values in regression models, with aspirin use coded as an ordinal variable. Data analysis was performed using the R statistical software, version 3.6.0. All statistical tests were two-sided. An association was considered statistically significant with $P < 0.05$.

Data availability

The data underlying this article were obtained through a data access agreement with the SCCS (https://www.southerncommunitystudy.org/research-opportunities.html). These and derived data generated in this research will be shared in agreement with data access rules set by the SCCS and can be obtained from the corresponding author upon request.

Results

Demographics and clinicopathologic features

The study recruited 22,426 African-American men, of whom 1,058 developed prostate cancer on follow-up. At enrollment, 5,486 men (25.1%) reported taking any aspirin and 2,634 men (12.1%) reported taking regular strength aspirin. Characteristics of the African-American men by aspirin use are shown in **Table 1**. The median age at enrollment was 49 (interquartile range, 11) years, with a median follow-up time of 13 years. Baseline characteristics of men who used or did not use aspirin differed significantly with respect to age, education, and smoking status (**Table 1**). Aspirin users were more likely to have an elevated BMI (28.5 vs. 26.1 for any aspirin and 28.1 vs. 26.1 for regular strength aspirin), a history of diabetes (33.8% vs. 12.9% for any aspirin and 27.5% vs. 12.9% for regular strength aspirin), BPH (9.4% vs. 3.8% for any aspirin and 7.2% vs. 3.8% for regular strength aspirin), or family history of prostate cancer (6% vs. 4.3% for any aspirin and 5.9% vs. 4.3% for regular strength aspirin). Among men who were diagnosed with prostate cancer, 120 (11.3%) men with disease stage information presented with an advanced-stage disease (TNM III/IV) and 169 (16%) with an aggressive disease (T4 or N1 or M1 or Gleason score ≥ 8).

Aspirin use and prostate cancer risk

In the multivariable-adjusted Cox regression analysis, aspirin use at enrollment was not associated with prostate cancer risk [HR, 1.07; 95% confidence interval (CI), 0.92–1.25 for any aspirin use and HR, 0.97; 95% CI, 0.78–1.19 for regular strength aspirin use; **Table 2**]. Associations remained null when examined by frequency of use (HR, 1.03; 95% CI, 0.77–1.39 for less than daily use and HR, 1.07; 95% CI, 0.91–

Table 1. Baseline characteristics of African-American men in the SCCS by aspirin use.

	No aspirin		Any aspirin		Regular strength aspirin	
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Total	16,365	74.9[a]	5,486	25.1	2,634	12.1
Age median (IQR)	48 (10)		53 (13)		52 (12)	
BMI median (IQR)	26.1 (7)		28.5 (7.8)		28.1 (7.8)	
Education						
Less than high school	5,526	33.8[b]	1,823	33.2	913	34.7
High school	6,903	42.2	2,028	37.0	991	37.6
College	2,751	16.8	992	18.1	471	17.9
More than college	1,085	6.6	548	10.0	227	8.6
Household income						
<15,000	10,138	61.9	2,900	52.9	1,477	56.1
15,000–25,000	3,453	21.1	1,176	21.4	539	20.5
25,000–50,000	1,840	11.2	855	15.6	386	14.7
50,000–100,000	620	3.8	381	6.9	156	5.9
>100,000	153	0.9	113	2.1	38	1.4
Family history of prostate cancer						
No	15,606	95.4	5,123	93.4	2,460	93.4
Yes	703	4.3	331	6.0	156	5.9
Tobacco use						
Current	10,017	61.2	2,457	44.8	1,343	51.0
Former	2,814	17.2	1,640	29.9	701	26.6
Never	3,475	21.2	1,335	24.3	559	21.2
Diabetes						
No	14,242	87.0	3,629	66.2	1,906	72.4
Yes	2,112	12.9	1,853	33.8	725	27.5
BPH						
No	15,689	95.9	4,936	90.0	2,432	92.3
Yes	627	3.8	516	9.4	189	7.2
PSA screening						
No	9,076	55.5	2,067	37.7	1,180	44.8
Yes	6,402	39.1	3,109	56.7	1,299	49.3
DRE screening						
No	7,611	46.5	1,760	32.1	978	37.1
Yes	8,666	53.0	3,681	67.1	1,636	62.1

Abbreviation: IQR, interquartile range.
[a]Percentage of all men in study ($n = 21,851$).
[b]Percentage of men within aspirin group [no aspirin ($n = 16,365$), any aspirin ($n = 5,486$), and regular strength aspirin ($n = 2,634$)] for all listed variables. Missing data not included in percentages.

1.26 for daily use; $P_{trend} = 0.41$) and duration of use (HR, 1.07; 95% CI, 0.89–1.28 for ≤3 years of use and HR, 1.05; 95% CI, 0.84–1.30 for >3 years of use; $P_{trend} = 0.45$). No significant association was observed between any aspirin use and risk of advanced-stage, high-grade, or aggressive disease. Only use of regular strength aspirin showed a suggestive association with a reduced risk of advanced-stage disease (HR, 0.70; 95% CI, 0.34–1.41), but this association was not statistically significant.

Aspirin use and disease-specific mortality

In this analysis, we assessed the risk of fatal prostate cancer related to baseline aspirin use among men without prostate cancer. During follow-up, 103 men developed fatal prostate cancer. In the multivariable-adjusted Cox regression analysis, aspirin use at enrollment tentatively associated with a reduced prostate cancer mortality (HR, 0.66; 95% CI, 0.39–1.14 for any aspirin use and HR, 0.41; 95% CI, 0.17–1 for regular strength aspirin use; **Table 3**). There was not much of an influence of competing risks of death on the risk of fatal prostate cancer, as shown by the SHRs in the Fine–Gray competing risk regression model (**Table 3**).

Discussion

Men of African ancestry are a high-risk population for prostate cancer and have an excess risk of developing lethal disease (1, 2, 25, 26). Using the NCI-Maryland Prostate Cancer Case–Control Study, we reported previously that intake of aspirin at diagnosis was inversely associated with advanced-stage prostate cancer and disease recurrence among these men (13). Here, we extended this study and examined the relationship between self-reported aspirin use at enrollment in SCCS and prostate cancer risk and mortality among African-American men. We did not observe an association between aspirin use and prostate cancer risk, but aspirin use tended to be associated with a lower prostate cancer mortality. Our observations are plausible as recent mechanistic observations and epidemiologic data showed that aspirin could have promising effects on reducing metastasis and cancer mortality (27, 28).

This is the first study that specifically investigated the relationship between aspirin use and prostate cancer mortality among African-American men using a prospective design. SCCS recruited both African-American and European-American men from a predominantly

Table 2. Associations between aspirin use at enrollment and prostate cancer risk among African-American men in SCCS.

	Events	PY	HR (95% CI)[a]	*P*	HR (95% CI)[b]	*P*
Overall						
No use	690	162,857	Reference		Reference	
Any use	332	50,057	1.11 (0.97–1.27)	0.14	1.07 (0.92–1.25)	0.40
Regular strength	136	25,091	1.01 (0.84–1.21)	0.95	0.97 (0.78–1.19)	0.75
Less than daily	54	10,934	1.00 (0.75–1.32)	0.97	1.03 (0.77–1.39)	0.84
Daily and more	269	37,850	1.13 (0.98–1.31)	0.09	1.07 (0.91–1.26)	0.42
					P_{trend}	0.41
≤3 years	189	30,283	1.09 (0.92–1.28)	0.31	1.07 (0.89–1.28)	0.48
>3 years	135	18,417	1.12 (0.93–1.36)	0.24	1.05 (0.84–1.30)	0.68
					P_{trend}	0.45
TNM stage I/II						
No use	420	162,857	Reference		Reference	
Any use	214	50,057	1.12 (0.94–1.32)	0.21	1.03 (0.85–1.26)	0.74
Regular strength	90	25,091	1.06 (0.84–1.34)	0.61	0.98 (0.75–1.28)	0.88
TNM stage III/IV						
No use	90	162,857	Reference		Reference	
Any use	30	50,057	0.83 (0.54–1.28)	0.40	1.00 (0.63–1.60)	0.98
Regular strength	9	25,091	0.54 (0.27–1.07)	0.08	0.70 (0.34–1.41)	0.31
Gleason ≤ 7						
No use	404	162,857	Reference		Reference	
Any use	181	50,057	1.08 (0.90–1.29)	0.41	0.95 (0.77–1.17)	0.64
Regular strength	76	25,091	0.98 (0.77–1.26)	0.88	0.90 (0.68–1.20)	0.48
Gleason ≥ 8						
No use	86	162,857				
Any use	44	50,057	1.15 (0.79–1.68)	0.46	1.36 (0.89–2.08)	0.15
Regular strength	16	25,091	0.93 (0.54–1.59)	0.78	0.95 (0.51–1.75)	0.87
Aggressive[c]						
No use	116	162,857	Reference		Reference	
Any use	53	50,057	1.04 (0.74–1.46)	0.80	1.17 (0.80–1.71)	0.42
Regular strength	19	25,091	0.82 (0.51–1.34)	0.44	0.84 (0.49–1.46)	0.54

Abbreviation: PY, person-years.
[a]HR was adjusted for age.
[b]HR was adjusted for age, enrollment year, education, income, family history of prostate cancer, smoking status, diabetes, BMI, BPH, PSA and DRE screening, acetaminophen, and NSAIDs other than aspirin.
[c]T4 or N1 or M1 or Gleason score ≥ 8.

low-income background. Because only 22 of the European-American men progressed into fatal prostate cancer (vs. 103 African-American men), we did not examine the relationship of aspirin use with prostate cancer mortality among these men. There have been previous reports showing that regular aspirin intake may reduce the risk of prostate cancer (14–17), although a robust protective relationship may only exist with the aggressive disease (29–31) and disease mortality and survival (18–20). Nonetheless, data for men of African ancestry remain sparse. Hurwitz and colleagues investigated the relationship of aspirin use with prostate cancer in the Atherosclerosis Risk in Communities Study, a prospective study that included 5,060 European-American men and 1,534 African-American men (19). In this cohort, aspirin use was inversely associated with prostate cancer mortality, but did not associate with disease incidence, which is consistent with our findings in SCCS. An additional race-stratified analysis, although limited by the relative low number of African-American men who participated in this study, showed a suggestive protective effect of aspirin against prostate cancer mortality among the African-American men (adjusted HR, 0.41; 95% CI, 0.14–1.20). This observation is again consistent with our findings in this study.

Table 3. Association between aspirin use at enrollment and prostate cancer mortality among African-American men in SCCS.

	Events	PY	HR (95% CI)[a]	*P*	HR (95% CI)[b]	*P*	SHR (95% CI)	*P*
No aspirin use	74	2,368,439	Reference		Reference		Reference	
Any aspirin use[c]	25	744,964	0.65 (0.41–1.03)	0.07	0.66 (0.39–1.14)	0.14	0.69 (0.39–1.25)	0.22
Regular strength	6	369,317	0.36 (0.16–0.84)	0.02	0.41 (0.17–1.00)	0.05	0.43 (0.16–1.13)	0.09

Abbreviation: PY, person-years.
[a]HR was adjusted for age.
[b]HR was adjusted for age, enrollment year, education, income, family history of prostate cancer, smoking status, diabetes, BMI, BPH, PSA and DRE screening, acetaminophen, and NSAIDs other than aspirin.
[c]Any aspirin use category also includes regular strength events.

Aspirin may protect against lethal prostate cancer among African-American men by suppressing an immune inflammation signature in their cancerous prostate (7, 11, 12), as we hypothesize. Aspirin may also exert a more general protection by suppressing metastasis (32). Treating patients with prostate cancer with celecoxib, a selective cyclooxygenase-2 (COX2) inhibitor, did not confer a survival benefit in the STAMPEDE trial (33). Aspirin is thought to have cancer preventive activity by inhibiting the same pathway and prostaglandin synthesis. Yet, in contrast to COX2-specific inhibitors, aspirin irreversibly inhibits both COX1 and 2 activity by acetylation. Acetylation of COX1, which is the main enzyme activity in platelets, blocks the production of thromboxane A2. It has now been shown in an animal model of lung metastasis that aspirin inhibits the metastatic spread by blocking the formation of a metastatic intravascular niche that depends on platelet-derived thromboxane A2 (27), although comparable data for prostate cancer and bone metastasis are still missing. Still, such a mechanism would explain why aspirin may inhibit lethal prostate cancer more so than the localized disease, as observed in our study and the study by Hurwitz and colleagues (19). In addition to its ability to inhibit prostaglandin synthesis, aspirin can turn on the production of anti-inflammatory lipid mediators, lipoxins, which makes aspirin further distinct in function from other NSAIDs (34, 35). Finally, aspirin has additional anti-inflammatory actions that cannot be attributed to its ability to inhibit prostaglandin biosynthesis, such as blocking leukocyte trafficking to inflamed tissues. As such, aspirin may have unique cancer preventive activities and may distinctly inhibit metastasis and lethal cancer.

Aspirin is commonly used in the U.S. population, which is primarily for prevention of cardiovascular disease. Its usage increases among the elderly population (36). A recent survey reported an estimated use of about 50% among U.S. adults ages 45–75 years (37). The observation indicates that aspirin use can be underreported when enrollment data are used. Aspirin effects in cancer prevention have been linked to dosage and duration, although a dosage or duration effect for the relationship of aspirin use with the risk of lethal prostate cancer remains to be determined (18–20). We stratified aspirin into any aspirin use and regular strength aspirin use, but could not stratify further because of inadequate statistical power. Regular strength aspirin is usually a 325 mg dose of aspirin (38), whereas our any aspirin use group comprised additional users of low-dose aspirin (about 50%). Accordingly, we found that the inverse relationship of aspirin use with prostate cancer mortality is somewhat stronger among regular strength aspirin users than any aspirin users, consistent with a dose effect, however, the CIs largely overlapped and there was no significant difference between the two groups.

There are several limitations to our study. First, we did not assess the exact daily dose of aspirin beyond the number of tablets per day. Also, we did not collect information on the reasons why participants were taking aspirin, however, most aspirin use is for prevention of cardiovascular disease among the elderly in the United States and follows recommendations by primary care physicians (37). Second, we did not receive information on disease characteristics for all men with prostate cancer. Accordingly, we had missing data on disease stage and Gleason score for 25%–30% of the patients, limiting our ability to analyze the relationship between aspirin use and advanced disease in this study. Third, studies have reported that aspirin leads to lower blood PSA, leading to a potential underestimate of disease occurrence among aspirin users in the prostate cancer risk analysis (39). We observed a rather modest effect of aspirin use on PSA levels in SCCS, with a median PSA reduction of 9.1% among all men who were regular strength aspirin users and only a 2.5% reduction among men who were aspirin users at baseline and later developed prostate cancer (Supplementary Fig. S1). Fourth, to abrogate a possible confounding effect of access to healthcare on the relationship between aspirin use and prostate cancer mortality, we adjusted a series of factors, such as age, socioeconomic status (education and income), smoking status, medical history of diabetes, BMI, BPH, acetaminophen, and other NSAID use, and PSA and DRE screening, in the multivariable Cox regression model. In our mortality analysis, we cannot adjust for received prostate cancer therapy. However, other studies have reported rather modest differences in obtained primary prostate cancer treatment comparing aspirin users with nonusers (40), and our adjustments for socioeconomic status and PSA screening should capture differences in primary care and treatment, if they exist. Nevertheless, we cannot exclude residual confounding as an underlying factor for our observations. We could not adjust for cardiovascular risk factors or some medications as these data were not collected in SCCS. Finally, the mortality analysis was limited by a small number of events, which may have prevented us to observe a more definite relationship between aspirin use and a reduced prostate cancer mortality. Additional studies are needed to replicate and strengthen our findings.

Conclusions

Self-reported aspirin use associated with a decreased prostate cancer–specific mortality among African-American men in SCCS. Yet, uncertainty remains about the strength of this association. In contrast, our data did not indicate an association between aspirin use and the risk of developing the disease. Our observations suggest that aspirin for prevention should be further evaluated as an opportunity to decrease lethal prostate cancer in these men.

Authors' Disclosures

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Authors' Contributions

W. Tang: Data curation, software, formal analysis, validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing. **J.H. Fowke:** Conceptualization, resources, supervision. **L.M. Hurwitz:** Supervision, investigation, methodology, writing-review and editing. **M. Steinwandel:** Resources, data curation. **W.J. Blot:** Conceptualization, resources, data curation, supervision. **S. Ambs:** Conceptualization, supervision, funding acquisition, investigation, project administration, writing-review and editing.

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