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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Aspirin Use Reduces the Risk of Aggressive Prostate Cancer and Disease Recurrence in African-American Men

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Abstract

Background: Men of African descent experience a disproportionately high prostate cancer mortality. Intratumoral inflammation was found to be associated with aggressive prostate cancer. We and others have shown that prostate tumors in African-American (AA) patients harbor a distinct immune and inflammation signature when compared with European-American (EA) patients. These observations suggest that inflammation could be a driver of aggressive disease in men of African descent, leading to the hypothesis that an anti-inflammatory drug like aspirin could prevent disease progression.

Methods: We examined the relationship between aspirin use and prostate cancer in the NCI-Maryland Prostate Cancer Case-Control Study consisting of 823 men with incident prostate cancer (422 AA and 401 EA) and 1,034 population-based men without the disease diagnosis (486 AA and 548 EA).

Results: We observed a significant inverse association between regular aspirin use and prostate cancer among AA men. Stratification of AA patients by disease stage showed that daily and long-term (>3 years) aspirin use significantly decreased the risk of advanced disease [adjusted ORs for T3/T4 disease: 0.35, 95% confidence interval (CI), 0.17–0.73; and 0.22, 95% CI, 0.08–0.60, respectively], but not early-stage disease (T1/T2). Regular aspirin use also reduced disease recurrence in AA men.

Conclusions: Regular aspirin use is associated with a decreased risk of advanced stage prostate cancer and increased disease-free survival in AA men.

Impact: Regular aspirin use before and after a prostate cancer diagnosis may prevent the development of aggressive disease in AA men who are at risk of a lethal malignancy. *Cancer Epidemiol Biomarkers Prev; 26(6); 845–53. ©2017 AACR.*

Introduction

Prostate cancer mortality rates are the highest among men of African descent in the United States and globally (1, 2). Although prostate cancer deaths have declined for both African-American (AA) and European-American (EA) men in the United States, AA men continue to experience a greater mortality burden (3). The reasons for the disparities in prostate cancer incidence and mortality are multifactorial and include differences in access to healthcare and lifestyle exposures, a delayed disease diagnosis in socioeconomically deprived communities, tumor biological differences, and intrinsic factors related to ancestry (1, 2, 4–10).

Inflammation is a putative risk factor for prostate cancer (11) and is associated with aggressive disease (12, 13). We and others have previously described a distinct immune-inflammation signature in prostate tumors of AA patients (14–17) that is absent in most EA patients. Race/ethnic differences in prostatic inflammation also exist in noncancerous tissues (18, 19). Consistent with these observations, anti-inflammatory drugs may reduce the burden of prostate cancer in AA men. Several investigations of mainly European or EA men observed that aspirin use decreases the risk of prostate cancer development and progression; however, findings across studies were heterogeneous, and the risk reduction by aspirin was generally modest (20–30). Here, we pursued the hypothesis that use of aspirin reduces the risk of aggressive prostate cancer among AA men because of the immune-inflammation signature that AA patients harbor in their tumors. To test the hypothesis, we examined the relationship between aspirin use and prostate cancer in the NCI-Maryland Prostate Cancer Case-Control Study, which recruited AA and EA patients and population-based controls between 2005 and 2015.

Materials and Methods

NCI-Maryland prostate cancer case-control study

This study was initiated to test the primary hypothesis that environmental exposures (including infections and medical history) and ancestry-related factors modify prostate cancer susceptibility and contribute to the excessive disease burden among AA men. The catchment area for the cases and the population-based male controls included Maryland, Washington DC, and few neighboring counties in Pennsylvania, Delaware, and Virginia, but the majority of the recruited men resided in four Maryland counties: Anne Arundel, Baltimore City, Baltimore County, and Howard. The study was initiated in 2005 after approval by the NCI (protocol # 05-C-N021) and the University of Maryland (protocol #0298229) Institutional Review Boards. Recruitment ended in

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

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2015. Cases were recruited at two hospitals, the Baltimore Veterans Affairs Medical Center and the University of Maryland Medical Center, and had a prostate cancer diagnosis within the last 2 years prior to recruitment. These men self-reported to be either AA or EA and signed an informed consent to participate in the study. Other inclusion criteria required that the men were 40 to 90 years old, were born in the United States, and spoke English well enough to be interviewed. Severely ill men or men residing in an institution were not eligible for the study. Of the 976 cases that were recruited into the study, 489 were AAs and 487 were EAs. We defined 823 patients as incident cases (422 AAs, 401 EAs) because they were recruited into the study within 1 year after the disease diagnosis with an average interval between diagnosis and enrollment into our study of 4.8 months (4.4 months for AA and 5.2 months for EA men). The male controls were identified through the Maryland Department of Motor Vehicle database and were frequency-matched by age and race to cases. Recruitment of these controls has previously been described (31), as they had double eligibility for this study and the NCI-Maryland Lung Cancer Case-Control Study, with the exception that subjects who had a known hepatitis C virus (HCV); hepatitis B virus (HBV); human immunodeficiency virus (HIV) infection or were taking antibiotics or steroid medications were eligible for the prostate cancer study but not the lung cancer study. Controls were men without a history of cancer other than nonmelanomic skin cancer, had a residential working phone number, were born in the United States, and spoke English well enough to be interviewed. Controls were not eligible for the study when they had a history of radiotherapy or chemotherapy, or when they were severely ill or resided in an institution. They were by self-report either AA or EA and signed an informed consent to participate in the study. Of the 1,034 population controls recruited, 486 were AA and 548 were EA men. The study involved the administration of a survey at time of enrollment given by a trained interviewer and the collection of blood, peripheral blood monocytes, and urine from all study subjects. The survey evaluated family cancer history, medication and medical history, occupational history, socioeconomic status, anthropometry, known risk factors for prostate cancer, tobacco use, sexual history, and had a nutrition section. We obtained additional information on cases from pathology reports and medical records [e.g., prostate-specific antigen (PSA) levels at diagnosis, disease stage and grade, disease recurrence]. Disease staging followed the stage grouping as defined by the 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis system for anatomic stage/prognostic groups, abbreviated as T1–T4. Information on disease-free survival for up to 100 months was attained for 218 patients. Thirty-seven patients experienced a disease recurrence (by biochemistry and/or diagnostic imaging), whereas 181 patients remained disease-free with a follow-up of at least 12 months and a mean follow-up time of 56 months for these patients.

Assessment of pain reliever use

Our survey evaluated aspirin use with four questions: (i) Have you taken aspirin or aspirin-containing compounds (such as Bufferin, Anacin, Ascriptin, Excederin) regularly—at least one pill per week for 2 months during the past 5 years—no, yes, or do not know. (ii) Did you take aspirin or aspirin-containing compounds regularly 1 year prior to interview—no, yes, or do not know. (iii) How many pills per day or week did you take regularly, during the past 5 years—number of pills per day, number of pills per week, or do not know. (iv) How long did you take aspirin regularly or aspirin-containing compounds, during the past 5 years—number of weeks, number of months, number of years, or do not know. More than 90% of the participants answered these questions. The use of aspirin or aspirin-containing compounds was defined as "aspirin use" in the study. These same questions were also asked with respect to the use of Tylenol and acetaminophen-containing compounds (e.g., Tylenol, or aspirin-free Anacin, or Excedrin-PM), defined as "Tylenol use" in our study, and use of pain relievers not containing either aspirin or Tylenol (such as Aleve, Ibuprofen, Motrin, Advil, Nuprin, Naprosyn, Feldene, Indocin, Clinoril). We created the aspirin category "In the past 5 years, did you take at least 1 tablet daily," from the number of pills taken daily and weekly over the 5 years. Use was then categorized as either "no" or "yes." The "no" category included both nonusers and those who took less than 1 aspirin tablet daily. Duration of aspirin use was calculated by summing up length of aspirin use in weeks, months, and years. Duration was then categorized as either "did not use," "less than or equal to 3 years," or "more than three years," The "did not use" category included all nonusers of aspirin. The aspirin category, "Among users who took at least 1 tablet daily, how long did they regularly take aspirin," was created by selecting participants who took at least 1 tablet daily in the past 5 years and assessing the duration of their aspirin use categorized as "less than or equal to 3 years" or "more than 3 years," compared with nonusers and users of less than 1 tablet daily as the reference group.

Plasma C-reactive protein measurement

We assayed plasma C-reactive protein (CRP) using an ELISA assay (cat# ab99995; Abcam) according to the manufacturer's instructions. Two microliters of plasma samples were added to 398 μL of 1x Diluent D, followed by a second 1: 200 dilution step for each sample (1: 40,000 final dilution). One-hundred microliters of CRP standard (0 to 600 pg/mL) and the diluted samples were loaded as duplicates into precoated 96-well plates. Samples were incubated overnight at 4°C with gentle shaking, followed by incubations with the anti-human CRP antibody and the horseradish peroxidase–streptavidin solution. CRP was quantified measuring absorbance at 450 nm with a microplate reader.

Statistical analysis

Data analysis was performed using the Stata/SE 14.0 statistical software package (Stata Corp). All statistical tests were two-sided, and an association was considered statistically significant with $P < 0.05$. Initially, we assessed associations between the use of nonsteroidal anti-inflammatory drugs (NSAID; aspirin, Tylenol, pain relievers not containing aspirin or Tylenol) and related exposures with prostate cancer, disease characteristics, or patient characteristics using χ^2 statistics, the t test, or the Mann–Whitney U test, with exposures being assessed as categorical or continuous metrics. These examinations were followed by analyses with unconditional logistic regression models to calculate ORs. For the main analysis, cases and controls were assessed in single models with adjustment for presumed (e.g., age) and statistically identified confounding variables that had a 10% or greater change in the OR for the association of aspirin with prostate cancer. Tests for trend were conducted by calculating P values in logistic regression models with aspirin use coded as an ordinal variable. The Cox proportional hazards model was used to estimate HRs and 95% confidence intervals (CI) for disease-free survival. In our models, the proportional hazards assumption was not violated.

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We calculated disease-free survival from the date of treatment with curative intent ("disease free" after radiotherapy, surgery, or hormone treatment) to recurrent disease, or to the date of last follow-up without recurrent disease.

Results

Characteristics of the participants in the NCI-Maryland prostate cancer case-control study

Demographic characteristics of all enrolled subjects and the clinicopathologic features of the cases are presented in Table 1 and Supplementary Table S1. The study enrolled a total of 976 cases and 1,034 controls from the greater Baltimore area in Maryland, with 50% (489/976) of the cases and 47% (486/1034) of the controls being self-identified AA men (Supplementary Table S1). Table 1 summarizes the characteristics of the 823 incident cases in the study (average interval between enrollment and diagnosis: 4.8 months) versus the population-based controls. Cases and controls had a similar age distribution and prevalence of diabetes. Yet, AA participants more often reported a diabetes diagnosis than EA participants ($P < 0.05$). More cases than controls were affected by a family history of prostate cancer ($P < 0.05$). Cases also had a lower average body mass index (BMI; 27.6 vs. 29.0 in controls; $P < 0.05$) and were current smokers more frequently than controls (26% vs. 15% in controls; $P < 0.05$). Lastly, fewer cases than controls had either a college or graduate degree (combined 32% vs. 50% in controls; $P < 0.05$). These differences were observed among both AA and EA men. Cases presented with prostate cancer at all disease stages (Table 1). Among the 823 incident cases, 116 men (14%) had advanced disease with T3 or T4 prostate cancer (AA men: 55, EA men: 61). One hundred and forty-six men (18%) had a Gleason score higher than 7 (AA men: 76, EA men: 70). To further delineate clinical disease, we decided to additionally categorize men into nonaggressive (T1 or T2 and Gleason score $\leq$7) and aggressive prostate cancer (T3 or T4 and Gleason score >7). The disease pathology of 53 patients (AA men: 27, EA men: 26) met this definition of aggressive disease. The median PSA (ng/mL) was 6.4 for all cases, but 7.0 and 6.0 for AA and EA cases, respectively ($P < 0.05$ for AA vs. EA).

Use of pain relievers

We assessed self-reported use of aspirin, Tylenol, and pain relievers not containing either aspirin or Tylenol in our

Table 1. Characteristics of incident cases and population controls

	Cases[a]			Population controls		
Demographics	**All ($n = 823$)**	**AA ($n = 422$)**	**EA ($n = 401$)**	**All ($n = 1,034$)**	**AA ($n = 486$)**	**EA ($n = 548$)**
Age[b] (y), median (IQR)[c]	64 (10)	63 (11)	65 (10)	65 (12)	64 (10)	66 (13)
BMI (kg/m^2), mean (SD)[d]	27.6 (5.7)	27.7 (6.9)	27.4 (5.2)	29.0 (5.3)	29.8 (5.5)	28.3 (5.0)
Education, *N (%)*						
$\leq$High school	298 (36)	196 (47)	102 (25)	250 (24)	145 (30)	105 (19)
Some college	267 (32)	157 (37)	110 (27)	268 (26)	144 (30)	124 (22)
College	145 (18)	48 (11)	97 (24)	262 (25)	105 (21)	157 (29)
Graduate	112 (14)	20 (5)	92 (24)	253 (25)	91 (19)	162 (30)
Baseline health factors						
Family history of prostate cancer[e], *N (%)*						
No	730 (89)	377 (89)	353 (88)	963 (93)	455 (94)	508 (93)
Yes	93 (11)	45 (11)	48 (12)	71 (7)	31 (6)	40 (7)
Smoking status[f], *N (%)*						
Current	210 (26)	147 (35)	63 (16)	151 (15)	98 (20)	53 (10)
Former	330 (40)	150 (36)	180 (45)	466 (45)	201 (42)	265 (49)
Never	275 (33)	120 (28)	155 (39)	408 (40)	184 (38)	224 (41)
Did not provide	8 (1)	5 (1)	3 (<1)	9 (<1)	3 (<1)	6 (<1)
Diabetes, *N (%)*						
No	634 (77)	298 (71)	336 (84)	784 (76)	336 (69)	448 (82)
Yes	189 (23)	124 (29)	65 (16)	250 (24)	150 (31)	100 (18)
Stage[g], *N (%)*						
T1	156 (19)	67 (16)	89 (22)			
T2	551 (67)	300 (71)	251 (63)			
T3	67 (8)	25 (6)	42 (10)			
T4	49 (6)	30 (7)	19 (5)			
Gleason score, *N (%)*						
$\leq$7	677 (82)	346 (82)	331 (83)			
>7	146 (18)	76 (18)	70 (17)			
Disease aggressiveness, *N (%)*						
Nonaggressive disease[h]	614 (92)	318 (92)	296 (92)			
Aggressive disease[i]	53 (8)	27 (8)	26 (8)			
PSA (ng/mL), median (IQR)	6.4 (5.6)	7.0 (7.4)	6.0 (4.5)			

[a]Cases recruited within 1 year after disease diagnosis with an average interval between diagnosis and enrollment of 4.8 months.
[b]Age at study interview.
[c]IQR, interquartile range.
[d]SD, standard deviation.
[e]First-degree relative with prostate cancer.
[f]Smoking status describes cigarette smoking.
[g]Pathologically confirmed using AJCC 7th Edition.
[h]Cases with pathologically confirmed T1 or T2 and Gleason score $\leq$7.
[i]Cases with pathologically confirmed T3 or T4 and Gleason score >7.

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study (see Materials and Methods). Aspirin is the most commonly used NSAID, and the frequency of aspirin intake was 57% and 49% among controls and cases, respectively, in this greater Baltimore population ($P < 0.05$ for controls vs. cases), with a significantly higher intake among EA than AA men (Table 2; Supplementary Table S2). Fifty-two percent of the controls and 43% of the cases were regular users of aspirin 1 year prior to interview ($P < 0.05$ for controls vs. cases), and 54% of the controls and 47% of the cases reported taking at least 1 or more tablets daily of aspirin or aspirin-containing tablets ($P < 0.05$ for controls vs. cases). In contrast, more than 90% of the participants reported that they do not use Tylenol regularly, and Tylenol intake was not different between cases and controls. Consumption of pain relievers not containing aspirin or Tylenol was also uncommon in this population of men, but their use was higher among cases than controls ($P < 0.05$).

Aspirin use and prostate cancer risk

We analyzed the relationship between use of pain relievers and prostate cancer based on the responses to four survey questions (see Materials and Methods). In this analysis, we did not find significant associations between prostate cancer and the use of Tylenol or pain relievers not containing aspirin or Tylenol, likely due to their infrequent intake in this population. For aspirin use, regular use for more than 3 years was associated with a reduced risk of developing prostate cancer in the unstratified analysis (Table 3; Supplementary Table S3). When we stratified participants into AA and EA men, significant inverse associations of regular aspirin use with prostate cancer were observed among AA but not EA men (Table 3). AA men who regularly used aspirin 1 year prior to interview, or used at least one tablet daily in the past 5 years, or used aspirin for more than 3 years, or who took at least one tablet daily for more than 3 years were at a significantly reduced risk of prostate cancer in the adjusted logistic regression analysis. Aspirin use among AA men was protective in both the analysis that only included incident cases (Table 3) and the analysis that included all 976 cases (Supplementary Table S3). Because we previously observed a prevalent immune-inflammation signature in prostate tumors of AA men (14), we next asked the question whether aspirin may protect against disease progression, theorizing that aspirin would suppress tissue inflammation in these men. Therefore, we stratified patients into those with either early-stage (T1 or T2) or advanced stage (T3 or T4) disease and assessed the association of aspirin use with disease progression among AA and EA men. We did not find that aspirin intake significantly protected against the development of early-stage disease, neither among all participants nor in the subgroups of AA and EA men, although a trend toward an inverse relationship between aspirin use and early-stage disease existed among AA men (20% to 30% reduced odds of a disease diagnosis, Table 4 and Supplementary Table S4, respectively). Yet, regular aspirin intake significantly protected AA men, but not EA men, from being diagnosed with the advanced disease (Table 5; Supplementary Table S5). Regular use of aspirin 1 year prior to interview (adjusted OR, 0.26; 95% CI, 0.11–0.60), daily use of at least 1 tablet daily during the past 5 years (adjusted OR, 0.35; 95% CI, 0.17–0.73), aspirin use for more than 3 years (adjusted OR, 0.22; 95% CI, 0.08–0.60), or daily

Table 2. Pain reliever use of participants in the NCI Maryland Prostate Cancer Case-Control Study

	Cases[a]			Population controls		
	All ($n = 823$)	**AA ($n = 422$)**	**EA ($n = 401$)**	**All ($n = 1{,}034$)**	**AA ($n = 486$)**	**EA ($n = 548$)**
Regular aspirin[b] use[c], *N (%)*						
No	418 (51)	244 (58)	174 (43)	446 (43)	236 (49)	210 (38)
Yes	405 (49)	178 (42)	227 (57)	588 (57)	250 (51)	338 (62)
Regular aspirin use 1 year prior to interview, *N (%)*						
No	418 (51)	244 (58)	174 (43)	446 (43)	236 (49)	210 (38)
Yes	354 (43)	151 (36)	203 (51)	534 (52)	221 (45)	313 (57)
Did not provide	51 (6)	27 (6)	24 (6)	54 (5)	29 (6)	25 (5)
In the past 5 years, did you take at least 1 tablet daily? *N (%)*						
No	435 (53)	254 (60)	181 (45)	472 (46)	245 (50)	227 (41)
Yes	387 (47)	168 (40)	219 (55)	561 (54)	240 (49)	321 (59)
Did not provide	1	—	1	1	1 (<1)	—
In the past 5 years, how long did you regularly take aspirin? *N (%)*						
Did not use	418 (51)	244 (58)	174 (43)	446 (43)	236 (49)	210 (38)
≤3 years	148 (18)	72 (17)	76 (19)	177 (17)	90 (18)	87 (16)
>3 years	251 (30)	103 (24)	148 (37)	403 (39)	157 (32)	246 (45)
Did not provide	6 (1)	3 (1)	3 (1)	8 (1)	3 (1)	5 (1)
Regular Tylenol use, *N (%)*						
No	763 (93)	395 (94)	368 (92)	962 (93)	463 (95)	499 (91)
Yes	59 (7)	26 (6)	33 (8)	72 (7)	23 (5)	49 (9)
Did not provide	1 (<1)	1 (<1)	—	—	—	—
Regular pain reliever[d] use, *N (%)*						
No	686 (83)	362 (86)	324 (81)	916 (89)	450 (93)	466 (85)
Yes	137 (17)	60 (14)	77 (19)	118 (11)	36 (7)	82 (15)

[a]Cases recruited within 1 year after disease diagnosis with an average interval between diagnosis and enrollment of 4.8 months.
[b]Aspirin or aspirin-containing compounds such as Bufferin, Anacin, Ascriptin, and Exedrin.
[c]Regular use of pain relievers is defined as taking pain relievers at least 1 per week for 2 months during the past 5 years.
[d]Pain reliever not containing aspirin, aspirin-containing compounds, or Tylenol.

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Table 3. Adjusted[a] ORs and 95% CIs for associations of regular aspirin use with prostate cancer in the NCI Maryland prostate cancer case-control study

	Total			AA			EA		
	Control	Case[b]	OR (95% CI)	Control	Case	OR (95% CI)	Control	Case	OR (95% CI)
Did you take aspirin regularly 1 year prior to interview?									
No	441 (46)	410 (54)	Ref.	233 (52)	238 (61)	Ref.	208 (40)	172 (46)	Ref.
Yes	529 (54)	351 (46)	0.81 (0.66–1.00)	220 (48)	150 (39)	**0.71 (0.52–0.97)**	309 (60)	201 (54)	0.88 (0.66–1.17)
In the past 5 years, did you take at least 1 tablet daily?									
No	467 (46)	427 (53)	Ref.	242 (50)	248 (60)	Ref.	225 (42)	179 (45)	Ref.
Yes	556 (54)	384 (47)	0.86 (0.71–1.06)	239 (50)	167 (40)	**0.70 (0.52–0.95)**	317 (58)	217 (55)	0.99 (0.74–1.31)
In the past 5 years, how long did you regularly take aspirin?									
Did not use	441 (43)	410 (51)	Ref.	233 (49)	238 (58)	Ref.	208 (39)	172 (44)	Ref.
≤3 years	174 (17)	146 (18)	0.94 (0.72–1.23)	89 (19)	71 (17)	0.79 (0.53–1.17)	85 (16)	75 (19)	1.12 (0.76–1.64)
>3 years	401 (39)	250 (31)	**0.79 (0.63–0.99)**	157 (33)	103 (25)	**0.68 (0.48–0.96)**	244 (45)	147 (37)	0.84 (0.62–1.15)
			$P_{trend} = 0.04$			$P_{trend} = 0.03$			$P_{trend} = 0.28$
Among users who took at least 1 tablet daily, how long did they regularly take aspirin?									
Did not use	467 (46)	427 (53)	Ref.	242 (51)	248 (59)	Ref.	225 (42)	179 (45)	Ref.
≤3 years	158 (16)	138 (17)	1.00 (0.76–1.32)	82 (17)	65 (16)	0.78 (0.52–1.17)	76 (14)	73 (19)	1.28 (0.87–1.90)
>3 years	390 (38)	240 (30)	**0.79 (0.63–0.99)**	154 (32)	99 (25)	**0.65 (0.46–0.92)**	236 (44)	141 (36)	0.87 (0.64–1.18)
			$P_{trend} = 0.04$			$P_{trend} = 0.01$			$P_{trend} = 0.39$

NOTE: Column total sums that differ are due to missing data, *N* (%). Bolded data indicate significant associations in the logistic regression analysis.
[a]Unconditional logistic regression adjusted for age at study entry, BMI (kg/m^2), diabetes (yes/no), education (high school or less, some college, college, professional school), family history of prostate cancer (first-degree relatives, yes/no), race (not included in stratified analysis), smoking history (never, former, current), Tylenol (yes/no), and pain relievers not containing Tylenol or aspirin-containing compounds (yes/no).
[b]Cases recruited within 1 year after disease diagnosis with an average interval between diagnosis and enrollment of 4.8 months.

tablet use of aspirin for more than 3 years (adjusted OR, 0.24; 95% CI, 0.09–0.62) were each inversely associated with advanced stage disease among AA men in the analysis of incident cases (Table 5). Very similar associations were obtained when all cases were included in the same analysis (Supplementary Table S5). To further extend our observations, we stratified patients using a different definition of advanced/aggressive disease [Gleason score >7 and T3 or T4 disease, instead of T3 or T4 only; Table 1; Supplementary Table S1]. Again, aspirin intake was inversely associated with aggressive prostate cancer only among AA men (Supplementary Table S6). It did not protect against the development of nonaggressive disease (Gleason score ≤7 and T1 or T2) among all participants or the subgroup of EA men, but a trend toward a protective effect remained in AA men (Supplementary Table S7).

Aspirin use and disease recurrence

Because of our findings that aspirin intake is inversely associated with advanced/aggressive disease among AA men, we asked if aspirin use also reduces the risk of disease recurrence among these men. We attained disease recurrence data for 85 AA patients and 133 EA patients in the study. Twenty of the AA patients and 17 of the EA patients experienced a recurrent disease. A Kaplan–Meier analysis (Fig. 1) and Cox proportional

Table 4. Adjusted[a] OR and 95% CIs for associations of regular aspirin use with prostate cancer in men with low stage[b] disease compared with population controls

	Total			AA			EA		
	Control	Case[c]	OR (95% CI)	Control	Case	OR (95% CI)	Control	Case	OR (95% CI)
Did you take aspirin regularly 1 year prior to interview?									
No	441 (46)	347 (53)	Ref.	233 (52)	199 (61)	Ref.	208 (40)	148 (47)	Ref.
Yes	529 (54)	310 (47)	0.84 (0.68–1.04)	220 (48)	140 (39)	0.79 (0.57–1.09)	309 (60)	170 (53)	0.84 (0.62–1.14)
In the past 5 years, did you take at least 1 tablet daily?									
No	467 (46)	362 (52)	Ref.	242 (50)	209 (58)	Ref.	225 (42)	153 (46)	Ref.
Yes	556 (54)	336 (48)	0.88 (0.72–1.09)	239 (50)	153 (42)	0.76 (0.56–1.03)	317 (58)	183 (54)	0.95 (0.71–1.28)
In the past 5 years, how long did you regularly take aspirin?									
Did not use	441 (43)	347 (50)	Ref.	233 (49)	199 (55)	Ref.	208 (39)	148 (45)	Ref.
≤3 years	174 (17)	126 (18)	0.95 (0.72–1.26)	89 (19)	64 (18)	0.84 (0.56–1.26)	85 (16)	62 (18)	1.06 (0.71–1.59)
>3 years	401 (39)	222 (32)	0.82 (0.65–1.03)	157 (33)	97 (27)	0.76 (0.53–1.09)	244 (45)	125 (37)	0.81 (0.59–1.12)
			$P_{trend} = 0.10$			$P_{trend} = 0.13$			$P_{trend} = 0.20$
Among users who took at least 1 tablet daily, how long did they regularly take aspirin?									
Did not use	467 (46)	362 (51)	Ref.	242 (51)	209 (58)	Ref.	225 (42)	153 (46)	Ref.
≤3 years	158 (16)	118 (17)	1.01 (0.76–1.35)	82 (17)	58 (16)	0.81 (0.54–1.24)	76 (14)	60 (18)	1.22 (0.81–1.83)
>3 years	390 (38)	214 (32)	0.82 (0.65–1.04)	154 (32)	93 (26)	0.72 (0.50–1.03)	236 (44)	121 (36)	0.85 (0.62–1.18)
			$P_{trend} = 0.10$			$P_{trend} = 0.06$			$P_{trend} = 0.34$

NOTE: Column total sums that differ are due to missing data, *N* (%).
[a]Unconditional logistic regression adjusted for age at study entry, BMI (kg/m^2), diabetes (yes/no), education (high school or less, some college, college, professional school), family history of prostate cancer (first-degree relatives, yes/no), race (not included in stratified analysis), smoking history (never, former, current), Tylenol (yes/no), and pain relievers not containing Tylenol or aspirin-containing compounds (yes/no).
[b]Low stage includes men with pathologically confirmed T1 or T2 disease.
[c]Cases recruited within 1 year after disease diagnosis with an average interval between diagnosis and enrollment of 4.8 months.

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Table 5. Adjusted[a] ORs and 95% CIs for associations of regular aspirin use with prostate cancer in men with high stage[b] disease compared with population controls

	Total			AA			EA		
	Control	**Case[c]**	**OR (95% CI)**	**Control**	**Case**	**OR (95% CI)**	**Control**	**Case**	**OR (95% CI)**
Did you take aspirin regularly 1 year prior to interview?									
No	441 (46)	63 (61)	Ref.	233 (52)	39 (80)	Ref.	208 (40)	24 (44)	Ref.
Yes	529 (54)	41 (39)	**0.62 (0.39–0.97)**	220 (48)	10 (20)	**0.26 (0.11–0.60)**	309 (60)	31 (56)	1.10 (0.60–2.03)
In the past 5 years, did you take at least 1 tablet daily?									
No	467 (46)	65 (58)	Ref.	242 (50)	39 (74)	Ref.	225 (42)	26 (43)	Ref.
Yes	556 (54)	48 (42)	0.75 (0.49–1.15)	239 (50)	14 (26)	**0.35 (0.17–0.73)**	317 (58)	34 (57)	1.25 (0.69–2.25)
In the past 5 years, how long did you regularly take aspirin?									
Did not use	441 (43)	63 (57)	Ref.	233 (49)	39 (75)	Ref.	208 (39)	24 (41)	Ref.
≤3 years	174 (17)	20 (18)	0.86 (0.49–1.51)	89 (19)	7 (13)	0.48 (0.19–1.23)	85 (16)	13 (22)	1.54 (0.72–3.29)
>3 years	401 (39)	28 (25)	**0.59 (0.35–0.97)**	157 (33)	6 (12)	**0.22 (0.08–0.60)**	244 (45)	22 (37)	1.06 (0.55–2.05
			$P_{trend} = 0.04$			$P_{Trend}<0.01$			$P_{trend} = 0.99$
Among users who took at least 1 tablet daily, how long did they regularly take aspirin?									
Did not use	467 (46)	65 (59)	Ref.	242 (51)	39 (75)	Ref.	225 (42)	26 (42)	Ref.
≤3 years	158 (16)	20 (18)	1.04 (0.59–1.82)	82 (17)	7 (13)	0.54 (0.21–1.38)	76 (14)	13 (23)	1.83 (0.86–3.91)
>3 years	390 (38)	26 (23)	**0.58 (0.35–0.98)**	154 (33)	6 (12)	**0.24 (0.09–0.62)**	236 (44)	20 (35)	1.01 (0.52–1.96)
			$P_{trend} = 0.05$			$P_{Trend}<0.01$			$P_{trend} = 0.95$

NOTE: Column total sums that differ are due to missing data, *N* (%). Bolded data indicate significant associations in the logistic regression analysis.
[a]Unconditional logistic regression adjusted for age at study entry, BMI (kg/m^2), diabetes (yes/no), education (high school or less, some college, college, professional school), family history of prostate cancer (first-degree relatives, yes/no), race (not included in stratified analysis), smoking history (never, former, current), Tylenol (yes/no), and pain relievers not containing Tylenol or aspirin-containing compounds (yes/no).
[b]High stage includes men with pathologically confirmed T3 or T4 disease.
[c]Cases recruited within 1 year after disease diagnosis with an average interval between diagnosis and enrollment of 4.8 months.

hazards models adjusting for age, race/ethnicity, Gleason score, disease stage, smoking, and education were used to investigate the association between aspirin use and disease-free survival. In the unstratified analysis, regular aspirin use during the past 5 years and use of aspirin 1 year prior to interview was not significantly associated with disease-free survival (Fig. 1A and B; adjusted HR: 0.59, 95% CI, 0.28–1.27 for regular aspirin use, yes vs. no; and HR: 0.57, 95% CI, 0.26–1.23 for regular use of aspirin 1 year prior to interview, yes vs.no). In contrast, the same aspirin intake was associated with a markedly reduced risk of a disease recurrence among AA men (Fig. 1C and D; adjusted HR: 0.26, 95% CI, 0.07–1.0 for regular aspirin use, yes vs. no; and HR: 0.17, 95% CI, 0.03–0.84 for regular use of aspirin 1 year prior to interview, yes vs. no), consistent with our

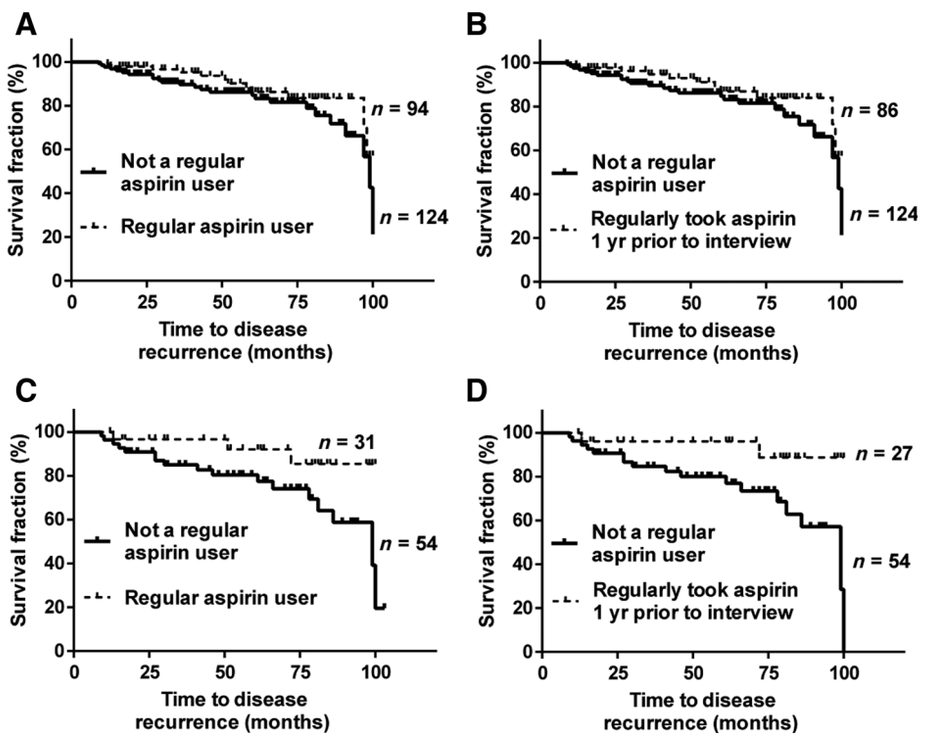

Figure 1.
Regular aspirin use decreases disease recurrence in AA men. Shown are Kaplan–Meier curves for disease-free survival. Disease recurrence information was obtained for 218 patients (133 EA and 85 AA). Thirty-seven experienced a disease recurrence (17 EA and 20 AA). Survival of regular aspirin users (**A**), or users, who took aspirin regularly 1 year prior to interview (**B**), was not markedly increased when compared with patients who were not regular aspirin users ($P = 0.17$ and $P = 0.16$, respectively, log-rank test). Disease-free survival of AA patients who were regular aspirin users (**C**) or who took aspirin regularly 1 year prior to interview (**D**) was markedly increased when compared with patients who were not regular aspirin users ($P = 0.04$ and $P = 0.02$, respectively, log-rank test).

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observations that regular aspirin intake prevents advanced/aggressive disease in AA patients.

Discussion

In our analysis of the relationship between aspirin and prostate cancer in the NCI-Maryland Prostate Cancer Case-Control Study, we found that regular intake of aspirin is inversely associated with advanced prostate cancer and disease recurrence among AA men using case-control and case-only designs, indicating that regular aspirin use could prevent a lethal malignancy among AA men. Our observation that aspirin, an anti-inflammatory drug, increases disease-free survival among AA patients confirms a similar observation in a previous study (32). These results are quite plausible because earlier data from us and others have shown that prostate tumors in AA men harbor a distinct immune signature and molecular alterations (10, 14–17, 33–36), and measurements of blood CRP showed that AA men tend to have higher CRP levels than EA men (37, 38), indicating increased inflammation, which we confirmed in our study population (Supplementary Fig. S1). High blood CRP is associated with an increased prostate cancer mortality, although it is neither a marker for disease risk (39–42) nor a good surrogate for the anti-inflammatory effects of aspirin (43, 44). Together, these observations argue that AA patients experience an increased occurrence of a low-grade chronic inflammation in their tumors and systemically, that is associated with disease progression, but can be prevented with the regular use of an anti-inflammatory drug, like aspirin, thereby leading to a reduced risk of advanced disease and disease mortality in this high-risk group of patients.

There has been suggestive, but not conclusive, evidence from multiple reports that regular aspirin intake reduces the risk of prostate cancer (45–47). The association of other NSAIDs with prostate cancer has been less consistent (20, 45, 48, 49). Several studies reported a more robust inverse relationship between aspirin intake and aggressive than nonaggressive disease (21, 29, 48). Yet, other reports did not find an association of aspirin with advanced prostate cancer (50), and a European study reported a modest increased risk of prostate cancer among aspirin users (51). Most of these reports investigated men from Europe and North America and found an overall modest protective effect by aspirin (10%–20% reduced risk) among these men of mainly European descent. We observed a comparable protective effect among EA men in our study, who were regular aspirin users, for overall prostate cancer, although the association was not statistically significant. However, we did not find that aspirin protected against the advanced disease among them. On the other hand, aspirin intake had a significant protective effect among AA men in a similarly powered analysis, and decreased their risk of developing advanced/aggressive disease and disease recurrence. To our best knowledge, only very few studies have previously explored the relationship between aspirin use and prostate cancer in men other than European/EA men. Almost all of these studies were underpowered to examine this relationship in AA men (45, 49). Osborn and colleagues investigated biochemical failure-free survival in 289 AA patients undergoing radiotherapy and reported that aspirin significantly increased survival (32). This observation is consistent with the data from our study showing a significant reduction of disease recurrence among AA patients who regularly used aspirin. The findings by Osborn and colleagues and us, together with comparable findings from different groups of prostate cancer patients (23, 24, 27), strongly suggest that regular aspirin use following a disease diagnosis will increase prostate cancer survival. Thus, aspirin should be further evaluated as an opportunity to develop improved therapeutic strategies to decrease lethal prostate cancer in AA men.

There are several limitations to our study. The study population consisted of men from the greater Baltimore area, who used aspirin more regularly and had a higher educational attainment than US adults in general. Cases were more likely to be current smokers but less likely to attain a college or graduate degree than controls. These differences between cases and controls were observed among both AA and EA men. We controlled for these differences in the logistic regression models. We assessed aspirin usage with four questions in our survey, allowing us to examine the duration, frequency, and quantity of aspirin intake over a time period of 5 years, but we did not obtain the same granular assessment of aspirin intake that few other studies did, e.g., an estimate of the 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.

Secondly, some studies have reported that aspirin use leads to lower PSA blood levels, which can introduce a bias, because prostate cancer is mostly detected through a PSA test, leading to a potential under-estimate of disease occurrence among men who are regular aspirin users. Long-term use of NSAIDs was estimated to lower PSA levels by modest 6% (52). We observed an average 5% reduction in PSA levels among EA men (6.0 to 5.7 ng/mL) and a similar 5.7% reduction among AA men (7.0 to 6.6) who were regular aspirin users. Thus, this bias would affect both groups similarly and would not lead to a spurious association among AA men but not EA men. In addition, men with advanced disease or AA men, who have higher PSA blood levels than men with early-stage disease or EA men, should not experience as much of a detection bias because their increased PSA levels would still lead to a disease diagnosis even if aspirin usage modestly decreases these levels. Thus, the finding that aspirin reduces the risk of advanced/aggressive disease, but not early-stage disease, among AA men, and increases disease-free survival is very unlikely due to an aspirin-caused disease detection bias.

Lastly, we used a case-control design in which recall bias is an inherent limitation. However, it is unlikely that men in the general population are aware of the hypothesis of aspirin's potentially anticancer properties in the context of prostate cancer. Furthermore, the inverse association of regular aspirin use with advanced and recurrent disease only among AA men, but not with early-stage disease or among the EA men, makes it unlikely that a recall bias contributed to these findings. Finally, a case-only analysis confirmed the case-control findings.

In conclusion, regular aspirin use was found to be associated with a decreased risk of advanced stage prostate cancer and disease recurrence in AA men. Our observations are consistent with data showing that AA men have a distinct immune-inflammation signature in their tumors (14–17) and support the hypothesis that aspirin targets inflammation as a driver of disease progression in AA men, thereby reducing lethal prostate cancer in this high-risk group of patients. Recently, a large randomized trial assessing the effects of aspirin on disease recurrence for prostate cancer and other solid cancers has been initiated in the United Kingdom (53). Our findings suggest that men of African descent should be part of the 2,120 men recruited into the prostate cancer arm of the trial.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.J. Smith, S. Ambs
Development of methodology: C.J. Smith, C.A. Loffredo, S. Ambs
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.J. Smith, C.A. Loffredo
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.J. Smith, W. Tang, S.V. Jordan, C.A. Loffredo, S. Ambs
Writing, review, and/or revision of the manuscript: C.J. Smith, S.V. Jordan, C.A. Loffredo, S. Ambs
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.J. Smith, T.H. Dorsey, S.V. Jordan
Study supervision: C.J. Smith, S.V. Jordan, S. Ambs

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