Research Article

Cancer Epidemiology, Biomarkers & Prevention

Racial and Ethnic Differences in the Relationship between Aspirin Use and Non–Small Cell Lung Cancer Risk and Survival

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Abstract

Background: African Americans (AA) experience higher incidence and mortality of lung cancer as compared with European Americans (EA). Inflammation is associated with lung cancer, many aspects of which differ between AA and EA. We investigated whether use, frequency, and duration of the anti-inflammatory drug aspirin were associated with lung cancer risk and survival, separately among AA and EA populations.

Methods: Using data from the Maryland Non–Small Cell Lung Cancer (NSCLC) Case–Control Study (1,220 cases [404 AA and 816 EA] and 1,634 controls [1,004 EA and 630 AA]), we estimated the adjusted odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) of the associations between aspirin use and NSCLC risk and survival, respectively.

Results: Any aspirin use (OR: 0.66; 95% CI, 0.49–0.89), daily use of $\geq$ 1 tablet (OR: 0.68; 95% CI, 0.50–0.90), and use for $\geq$ 3 years (OR: 0.61; 95% CI, 0.44–0.85) was associated with lower NSCLC risk only among men, even after adjustment for covariates including body mass index and global genetic ancestry. These variables were also associated with improved survival, but only among AA (HR: 0.64; 95% CI, 0.46–0.91; HR: 0.61; 95% CI, 0.42–0.90; and HR: 0.60; 95% CI, 0.39–0.92, respectively). Tylenol and other NSAIDs were either associated with elevated or no NSCLC risk.

Conclusions: Aspirin use is associated with lower risk of NSCLC among men and improved survival among AA.

Impact: Preventive regular aspirin use could be considered among men and AA. *Cancer Epidemiol Biomarkers Prev; 27(12); 1518–26. ©2018 AACR.*

Introduction

Lung cancer is the leading cause of cancer mortality in the United States, accounting for more than 25% of all cancer deaths (1, 2). Non–small cell lung cancer (NSCLC) constitutes 75% to 85% of all diagnosed lung cancers and includes adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma (3). Despite advances in therapy, the 5-year survival for lung cancer cases is only 16% (1). In the United States, racial differences in lung cancer risk and survival are observed between African Americans (AA) and European Americans (EA; refs. 1, 4). AA experience incidence rates 50% higher than their EA counterparts and worse survival outcomes (2, 5). In searching for explanations for these health disparities, investigators have considered cultural, socioeconomic, genetic, and biological differences, as well as differences in tobacco exposure (6). Research has also focused on the role of inflammation processes in lung cancer and differences between AA and EA, which may contribute to the observed health disparities (7).

The US Preventive Services Task Force recommends low-dose aspirin for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (8–14)—current data estimate daily aspirin use for the prevention of CVD at approximately 30% (15). It is not yet clear whether such a preventive effect exists for NSCLC.

Inflammation can result in high cell turnover rates leading to DNA damage, mutations, and ultimately tumor growth (16). Aspirin inhibits inflammation by preventing the production of prostaglandins via COX-2. COX-2 is overexpressed in many cancers including lung cancer (17–20). Data suggest that aspirin may have a protective effect against lung cancer development (21). In a meta-analysis of aspirin use and lung cancer risk, overall results indicated a protective effect of aspirin, though strong differences were observed between studies (8, 21–25). Duration of use was somewhat related to decreased

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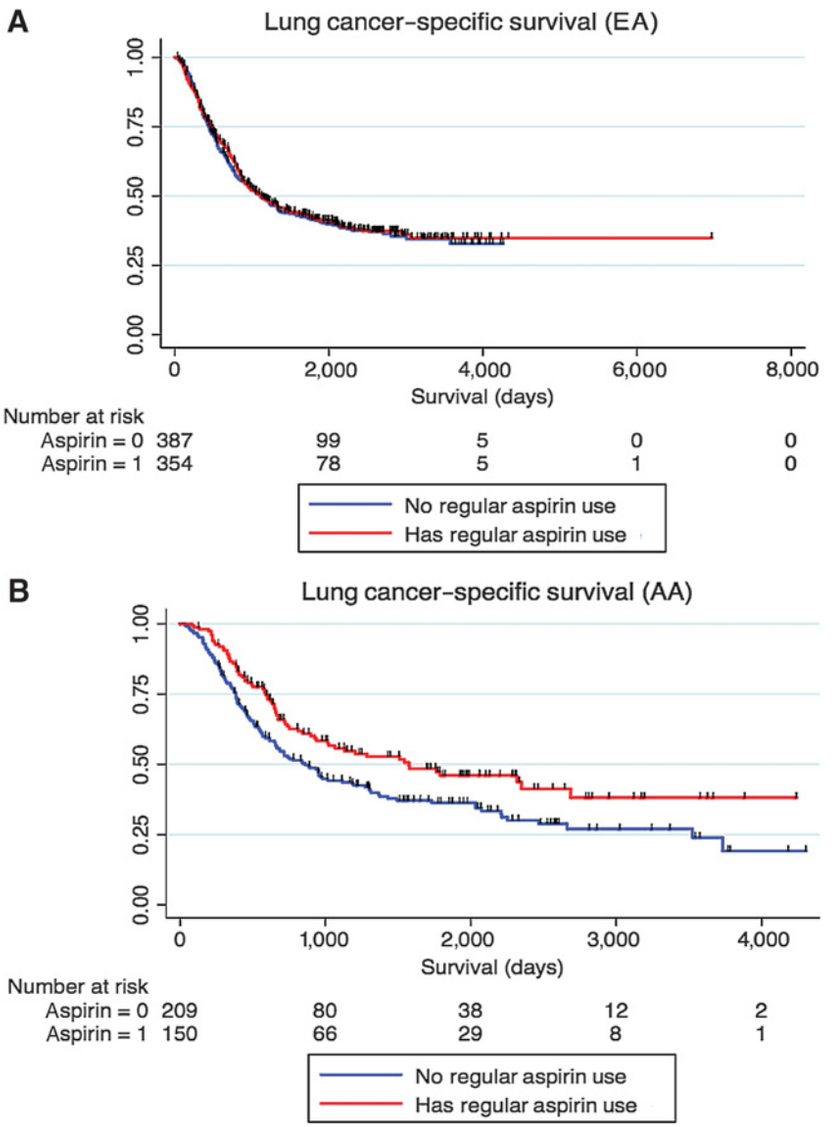

Figure 1.
Kaplan–Meier curves showing the relationship between aspirin use and lung cancer–specific survival. A, The relationship among EA. B, The relationship in AA.

mortality (9, 10). Studies of aspirin and lung cancer survival have also yielded mixed results. Animal studies suggest that aspirin reduces lung cancer metastasis (22), but in a large cohort study, aspirin use did not affect overall survival (26, 27).

Smith and colleagues recently found that aspirin use was associated with a reduced risk of prostate cancer and protective against disease recurrence among AA, but not EA (28), suggesting that racial differences in the effect of aspirin on cancer prevention could be one factor that drives heterogeneity across studies. Recently, we described racial differences in cytokines and inflammatory markers between AA and EA with lung cancer (7). In addition, we identified differences in the inflammatory cell population between EA and AA in lung tumors (29). Therefore, in this study, our goal was to examine the relationship between aspirin use and NSCLC risk and survival, and to specifically address any differences between AA and EA populations.

Materials and Methods

Data were obtained from the NCI-Maryland Lung Cancer Case–Control Study, an ongoing study of AA and EA from the greater Baltimore and Eastern Shore regions of Maryland that started in 1998 (30). Cases, recruited from seven hospitals in the greater Baltimore metropolitan area, were diagnosed with histologically confirmed NSCLC at any stage (i.e., AJCC stages I, II, III, and IV). The histologic type and stage of the malignancy were recorded and available for the present study. Population controls, frequency matched to cases on age, race, and sex, were recruited from Maryland Department of Motor Vehicles records. Both case and control participants were required to have been born in the United States, speak English well enough to be interviewed, be between the ages of 40 and 90 years, and not be severely ill or reside in an institution.

Trained interviewers administered a standardized questionnaire to capture information regarding demographics, socioeconomic characteristics, tobacco smoking history [current, former (those

who reported to have quit smoking one year prior to the interview), or never (those who smoked less than 100 cigarettes over their lifetime)], as well as pack-years of smoked cigarettes, alcohol history, medical history, family history of cancer, reproductive history, and occupational history. All data were self-reported unless otherwise noted. As of 2005, questions about the use of nonsteroidal anti-inflammatory drugs (NSAID) such as aspirin and other NSAIDs (i.e., ibuprofen, Advil, Naprosyn, Feldene, Celebrex, and others), and Tylenol (including other acetaminophen containing compounds) were added. Body mass index (BMI) was determined using self-reported measures of height and weight.

Assessment of aspirin, Tylenol, and other NSAID use

Aspirin use was defined as any regular use of aspirin or aspirin-containing compounds. Specifically, information on any use, frequency, and duration was obtained by asking three questions: (i) have you taken aspirin or aspirin-containing compounds regularly? (defined as at least one pill per week for 2 months during the past 5 years; yes, no, don't know); (ii) 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 don't know); (iii) how long did you take aspirin or aspirin-containing products regularly during the past 5 years? (number of weeks, number of months, number of years, or don't know). Similar questions were asked for Tylenol and other NSAIDs.

The following variables were created: (i) regular aspirin use (based on response to whether participants had taken aspirin regularly and characterized as yes/no); (ii) daily number of aspirin tablets (none, < 1, or ≥ 1 tablet); and (iii) duration of aspirin use (never, < 3, and ≥ 3 years). Similar variables were generated for Tylenol and acetaminophen containing compounds and for other NSAIDs use.

The National Death Index was used to obtain data on lung cancer–specific mortality, which was defined as lung cancer listed as the primary, secondary, or tertiary cause of death on the death certificate.

Global genetic ancestry

Genetic ancestry analysis was performed as previously described (31). Briefly, DNA from buffy coat was genotyped for 100 ancestry informative markers (AIM) using the Sequenom MassARRAY iPLEX platform, according to the manufacturer's recommendations. The AIMs panel consisted of carefully selected autosomal markers that were previously identified and validated for estimating continental ancestry information in admixed populations (32, 33). Individual single-nucleotide polymorphism (SNP) genotype calls were generated using Sequenom TYPER software, which automatically calls allele-specific peaks according to their expected masses. Genotyping quality control for all SNPs was assessed. A genotype concordance rate of 99.5% was observed for all markers. Genotyping call rates exceeded 97% for all individuals included in the analyses.

Individual admixture estimates for each study participant were calculated using a model-based clustering method as implemented in the program STRUCTURE v2.3 (34). STRUCTURE 2.3 was run using parental population genotypes from West Africans, Europeans, and Native Americans (32) under the admixture model using the Bayesian Markov chain Monte Carlo method ($K = 3$, assuming three founding populations) and a burn-in length of 30,000 for 70,000 repetitions.

A continuous global genetic ancestry variable was used in regression and survival models and consisted of the percentage of West African, European, and Native American ancestry.

Measurement of inflammatory proteins

Serum was prepared from a blood draw from consenting individuals and used to determine circulating cytokine concentrations in AA. The following inflammatory proteins were measured in serum specimens using the Mesoscale VPlex assay: CRP, TNF, CXCL8 (IL8), IL6, IL4, IL2, IL13, IL12A, IL10, IFNG, VEGFA, LTA, IL7, IL5, IL1A, IL17A, IL16, IL15, IL12B, CSF2, CCL17, CCL4, CCL3, CCL22, CCL13, CCL2, CXCL10, CCL26, CCL11, and IL1B.

Statistical analysis

Descriptive statistics were generated to examine differences in participant characteristics, aspirin, Tylenol, and other NSAIDs use between AA and EA cases and controls, using χ^2 tests. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI), before and after adjustment for known and potential confounders, including BMI, which was previously reported to be inversely associated with lung cancer diagnosis (31, 32). Tests for trends were also performed.

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% CI for disease-free survival after adjustment for relevant covariates including the histologic type and stage of the NSCLC. Survival was calculated using the difference in time between the date of surgery or diagnosis and the date of last known follow-up or death from lung cancer. Causes of death other than lung cancer were censored ($n = 22$ among AA). We performed a competing risks regression based on the method of Fine and Gray (35) using the stcrreg function in STATA. Differences in inflammatory protein expression between AA aspirin users and nonusers were assessed using Kruskal–Wallis tests.

We conducted analyses of the study sample before and after stratification by race and gender. All statistical tests were two-sided, and a P value of 0.05 was used to assess significance. We used Stata version 14 to perform all analyses.

Results

Participant population characteristics

Between 2005 and 2015, a total of 2,854 participants were included in the study: 1,820 EA (816 cases and 1,004 controls) and 1,034 AA (404 cases and 630 controls). Demographics of the study population are presented in Table 1. Compared with the AA population, the EA population was slightly older. More AA (40%) than EA (26%) cases were current smokers, but the latter smoked more pack-years of cigarettes than the former. The distribution of NSCLC by gender was similar in both EA and AA populations. EA cases had a higher prevalence of family members with a history of lung cancer. Differences in education level and BMI were noted between the two populations (Table 1). In addition, among the cases, the main histologic subtype was adenocarcinoma with a similar distribution of tumor histology between AA and EA (Table 1).

Aspirin, Tylenol, and other NSAID use

Among EA participants, 47.9% of cases reported regular aspirin use, compared with 42.3% of AA cases (Table 2). More EA cases reported use of ≥ 1 aspirin tablet per day than AA cases (46.5% and

Table 1. Participant characteristics in the NCI-Maryland NSCLC Case–Control Study

	EA			AA		
	Controls *N* = 1,004	**Cases *N* = 816**	***P***	**Controls *N* = 630**	**Cases *N* = 404**	***P***
Age (years) (mean, standard deviation)	66 (8.6)	66 (10.5)	<0.0001	64 (8.5)	64 (9.5)	0.01
Gender (*N*, %)			0.50			<0.0001
Males	561 (55.9)	444 (54.4)		496 (78.7)	221 (54.7)	
Females	443 (44.0)	372 (45.6)		134 (21.3)	183 (45.3)	
BMI (kg/m^2) (*N*, %)			<0.0001			<0.0001
<18.5	6 (1.0)	46 (5.6)		1 (<1.0)	159 (39.7)	
18.5–24.9	314 (31.5)	357 (43.8)		112 (17.8)	127 (31.7)	
25.0–30.0	388 (38.9)	274 (33.6)		229 (36.4)	84 (21.0)	
>30.0	293 (29.5)	138 (17.9)		288 (45.7)	31 (7.7)	
Missing	3	1		0	0	
Smoking (*N*, %)			<0.0001			<0.0001
Never smoker	473 (47.1)	87 (10.7)		260 (41.3)	28 (6.9)	
Former Smoker: Quit more than 1 year before interview	424 (42.2)	386 (47.3)		255 (40.5)	146 (36.1)	
Current Smoker	93 (9.3)	209 (25.6)		99 (15.7)	163 (40.4)	
Former Smoker: Quit within 1 year before interview	13 (1.3)	133 (16.3)		15 (2.4)	67 (16.6)	
Former Smoker: Quit unknown amount of time before interview	1	1		1	0	
Pack-years of smoking (median, IQR)	3.3 (0–28.75)	40.6 (21.7–63.1)	<0.0001	6.4 (0–24.1)	30.1 (14.6–47.0)	<0.0001
Education (*N*, %)			<0.0001			<0.0001
Less than 11th grade	35 (3.5)	132 (16.2)		51 (8.1)	130 (32.2)	
High school or GED (12th grade)	179 (17.9)	276 (33.8)		135 (21.5)	122 (30.2)	
Some college (includes AA degree)	214 (21.3)	166 (20.3)		177 (28.2)	92 (22.8)	
Technical school	23 (2.3)	29 (3.6)		10 (1.6)	5 (1.2)	
College	279 (27.8)	129 (15.8)		134 (21.2)	33 (8.2)	
Professional school (includes MS, PhD, MD, etc.)	273 (27.2)	84 (10.3)		121 (19.2)	22 (5.5)	
Missing	1	0		2	0	
Family history of lung cancer (*N*, %)			<0.0001			<0.0001
No	636 (63.4)	436 (53.4)		445 (70.6)	241 (59.7)	
Yes	238 (23.7)	297 (36.4)		104 (16.5)	100 (24.8)	
Missing	130	83		81	63	
Histology (*N*, %)						Per
Adenocarcinoma		370 (46.3)			185 (46.3)	
Squamous cell carcinoma		204 (25.5)			99 (24.8)	
NSCLC[a]		88 (10.8)			45 (11.3)	
Other		61 (7.6)			29 (7.3)	
Missing		93			46	

[a]This classification includes largely adenocarcinomas, squamous cell carcinomas, and large-cell carcinomas; however, the pathologic classification at the time of diagnosis was NSCLC.

Percentages may not add up to 100% due to missing observations.

39.6%, respectively). Overall, aspirin use was similar between EA and AA, although EA were more likely to have longer-term use (≥3 years; Table 2).

Regular Tylenol use was reported by 13.5% of EA cases and 12.4% of AA cases, and significant differences were present between cases and controls in both populations ($P = 0.004$ [EA] and $P = 0.001$ [AA]; Table 2). Regular use of other NSAIDs was more common than regular Tylenol use, but less common than regular aspirin use, with 19.8% of EA cases and 14.6% of AA cases reporting it (Table 2). Daily use of one or more other NSAIDs tablets was less common among AA cases (11.6%) compared with EA cases (16.0%).

Aspirin use and NSCLC risk

In the total study sample, aspirin use, frequency, and duration were associated with reduced odds of having NSCLC, even after adjustment for relevant covariates, including age, gender, smoking, pack-years, education, family history of lung cancer, marital status, year of interview, use of Tylenol and other NSAIDs (Supplementary Table S1) and genetic ancestry (Table 3). After stratification by race, the associations remained statistically significant among AA: aspirin use (OR: 0.59; 95% CI, 0.40–0.87); daily use ≥ 1 tablet (OR: 0.60; 95% CI, 0.37–0.82); and duration of use ≥3 years (OR: 0.54; 95% CI, 0.34–0.84; Table 3). A similar, but less robust relationship was also observed among EA: aspirin use (OR: 0.71; 95% CI, 0.54–0.93); daily use ≥ 1 tablet (OR: 0.75; 95% CI, 0.57–0.98); and duration of use ≥ 3 years (OR: 0.72; 95% CI, 0.54–0.97; Table 3).

Individuals taking aspirin are more likely than those who did not to have a higher BMI (36); therefore, we conducted an adjustment for BMI at the time of diagnosis. As shown in Supplementary Table S1, most of the associations between aspirin use variables and lung cancer risk remained in the same direction, but their strengths were reduced (Supplementary Table S2).

We next stratified the analysis by gender. Aspirin use was associated with lower NSCLC risk only in men (OR: 0.61; 95% CI, 0.48–0.79), even after adjustment for both BMI and global genetic ancestry (OR: 0.66; 95% CI, 0.49–0.89; Table 4; Supplementary Table S3). Supplementary Table S4 shows results in

Table 2. Use, frequency, and duration of aspirin, Tylenol, and Other NSAIDs in the NCI-Maryland NSCLC Case–Control Study

	EA			AA		
	Controls, *N* (%)	**Cases, *N* (%)**	***P***	**Controls, *N* (%)**	**Cases, *N* (%)**	***P***
Regular aspirin use[a]			0.29			0.10
No	498 (49.6)	425 (52.1)		328 (52.1)	233 (57.7)	
Yes	506 (50.4)	391 (47.9)		302 (47.9)	171 (42.3)	
Daily aspirin use			0.004			0.08
Never	498 (49.7)	425 (52.1)		328 (52.1)	233 (57.7)	
<1 tablet per day	39 (3.9)	11 (1.34)		11 (1.7)	11 (2.7)	
≥1 tablet per day	466 (46.5)	380 (46.6)		290 (46.0)	160 (39.6)	
Missing	1	0		1	0	
Duration of aspirin use			0.21			0.06
Never	498 (50.6)	425 (52.2)		328 (52.1)	233 (59.6)	
<3 years	106 (10.8)	79 (9.6)		70 (11.6)	51 (13.0)	
≥3 years	381 (38.7)	273 (33.4)		208 (30.3)	107 (27.4)	
Missing	19	39		24	13	
Regular Tylenol use[a]			0.004			0.001
No	912 (90.9)	706 (86.5)		592 (94.0)	354 (87.6)	
Yes	92 (9.2)	110 (13.5)		38 (6.0)	50 (12.4)	
Daily Tylenol use			0.01			0.001
Never	912 (90.9)	706 (86.5)		592 (94.1)	354 (87.6)	
<1 tablet per day	27 (27.8)	25 (3.1)		9 (1.4)	10 (2.5)	
≥1 tablet per day	64 (6.4)	85 (10.4)		28 (4.5)	40 (9.9)	
Missing	10	8		9	6	
Duration of Tylenol use			<0.0001			<0.0001
Never	912 (90.8)	709 (86.5)		592 (93.8)	354 (87.6)	
<3 years	28 (2.8)	69 (8.4)		13 (2.1)	29 (7.2)	
≥3 years	54 (5.4)	33 (4.0)		16 (2.5)	15 (3.7)	
Missing	10	8		9	6	
Daily other NSAIDs use			<0.0001			0.01
Never	830 (82.9)	654 (80.5)		570 (90.5)	345 (85.4)	
<1 tablet per day	67 (6.7)	27 (3.3)		21 (3.3)	12 (3.0)	
≥1 tablet per day	104 (10.4)	131 (16.1)		39 (6.2)	47 (11.6)	
Missing/don't know	3	4		0	0	
Duration of other NSAIDs use			0.01			<0.0001
Never	830 (82.8)	654 (80.2)		570 (90.5)	345 (85.4)	
<3 years	68 (6.8)	88 (10.8)		22 (3.5)	38 (9.4)	
≥3 years	105 (10.5)	74 (9.1)		38 (6.0)	21 (5.2)	
Missing/don't know	1	0		0	0	

[a]Regular use is defined as at least one pill per week for 2 months during the past 5 years.
Percentages may not add up to 100% due to missing observations.

women. In the fully adjusted model, the *P* value for the interaction term between aspirin use and gender was 0.054.

Tylenol and other NSAID associations with NSCLC risk

Tylenol use was associated with increased odds of having NSCLC (OR: 1.51; 95% CI, 1.13–2.03) overall. Although a similar (albeit nonsignificant) trend was observed in EA (Supplementary Table S5), the effect was stronger among AA (OR: 2.13; 95% CI, 1.23–3.67). Use of ≥1 other NSAID tablet per day (vs. never use) was associated with an increased risk of NSCLC (OR: 1.54; 95% CI, 1.16–2.04). No consistent racial differences were observed with use of other NSAIDs (Supplementary Table S6).

Aspirin use and NSCLC survival

We assessed the relationship between aspirin use and survival using lung cancer–specific death as the outcome, before and after stratification by race (Supplementary Table S6). Aspirin use, frequency, and duration were associated with reduced HR only among AA participants, even after adjustment for relevant covariates, including BMI and global genetic ancestry: AA: aspirin use (HR: 0.64; 95% CI, 0.45–0.91); daily use ≥1 tablet (HR: 0.61; 95% CI, 0.42–0.90); and duration of use ≥3 years (HR: 0.60; 95% CI, 0.39–0.92; 95% CI; Table 5; Supplementary Table S7; Fig. 1; ref. 1).

In our study, 22 AA patients died of causes other than lung cancer. We therefore conducted a competing risks analysis to address this potential factor and found that the association between aspirin use and lung cancer survival was not affected by censoring of the 22 individuals who died of causes other than lung cancer (fully adjusted model, for patients with aspirin use (HR: 0.64; 95% CI, 0.45–0.91).

Relationship between aspirin use and circulating levels of inflammatory cytokines

We also assessed the relationship between aspirin use and circulating inflammatory cytokines in 557 AA participants (219 NSCLC cases and 358 controls) by comparing serum cytokine concentrations. Among AA aspirin users, only IL4 concentrations were significantly elevated whether they were cases ($P = 0.02$) or controls ($P = 0.007$; Supplementary Table S8).

Discussion

We found that aspirin use was associated with lower NSCLC risk among men regardless of race, although the strength of the association was reduced after adjustment for BMI, and with improved survival only among AA. In addition, other NSAIDs

Table 3. Adjusted OR and 95% CI for the associations between aspirin use, frequency, and duration and NSCLC risk in the NCI-Maryland NSCLC Case–Control Study

	All		EA		AA	
Aspirin use	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
No	Reference		Reference		Reference	
Yes	0.69 (0.56–0.86)	**0.001**	0.71 (0.54–0.93)	**0.01**	0.59 (0.40–0.87)	**0.008**
Daily aspirin use						
Never	Reference		Reference		Reference	
<1 tablet per day	0.51 (0.24–1.08)	0.08	0.31 (0.12–0.77)	**0.004**	2.08 (0.55–7.86)	0.28
≥ 1 tablet per day	0.70 (0.56–0.87)	**0.001**	0.75 (0.57–0.98)	**0.03**	0.56 (0.37–0.82)	**0.004**
Trend		**0.001**		**0.03**		**0.004**
Duration of aspirin use						
Never	Reference		Reference		Reference	
<3 years	0.70 (0.49–0.99)	**0.05**	0.58 (0.37–0.91)	**0.02**	0.85 (0.46–1.58)	0.61
≥3 years	0.68 (0.54–0.87)	**0.002**	0.72 (0.54–0.97)	**0.03**	0.54 (0.34–0.84)	**0.007**
Trend		**0.001**		**0.02**		**0.008**

NOTE: Adjusted for age, gender, smoking, pack-years, education, family history of lung cancer, marital status, year of interview, genetic ancestry, and use of Tylenol and other NSAIDs.
Bold values denote statistical significance.

and Tylenol were either associated with elevated or no risk of NSCLC.

Our findings regarding the relationship between aspirin use and lung cancer are generally consistent with those of other studies (8, 24, 37, 38). Although several previous studies have reported a relationship between aspirin use and lung cancer risk (21, 38–46), not all studies have found significant associations (27, 47–51). Some studies adjusted for BMI (27, 47, 48), but others did not. Interestingly, among those studies that did not report adjustment for BMI, the associations were largely statistically significant (21, 38–44, 46). There is evidence that the excess risk of obesity on colon cancer risk is abrogated by aspirin use (52) and that aspirin may be more effective at preventing adenomas in individuals with a higher BMI (53). In our study, no such observations were seen. Indeed, we found the ORs and 95% CI for overweight and obese participants (adjusted for age gender, smoking and pack-years) to be 0.58 (0.47–0.72) and 0.30 (0.24–0.38), respectively, and to remain the same after including aspirin use in the model [0.58 (0.47–0.72) and 0.31 (0.24–0.39), respectively]. We also noted comparable results for the BMI categories after stratification by race, although the strength of such association was higher among AA than EA participants.

Considering that both BMI and aspirin use were inversely associated with NSCLC risk, one might expect a possible additive effect. Interestingly, adding BMI to the model attenuated, rather than enhanced, the strength of the inverse association between aspirin use and NSCLC risk (Supplementary Table S2); and stratification by BMI categories resulted in similar estimates in all three strata (normal, overweight, and obese), thus revealing that BMI is not an effect modifier of the relationship between aspirin use and NSCLC risk, but possibly a confounder.

When we stratified by gender, aspirin use among men, but not women, was significantly associated with lower risk of NSCLC, even after adjustment for BMI and global genetic ancestry. Some studies have noted a protective effect of aspirin in both men and women (24, 25). However, National Health and Nutrition Examination Study data and a recent pooled analysis of aspirin use and lung cancer risk within the International Lung Cancer Consortium also found that the protective effect of aspirin on lung cancer risk was restricted to men (21, 54). The causes of these

Table 4. Adjusted OR and 95% CI for the associations between aspirin use, frequency, and duration and NSCLC risk in the NCI-Maryland NSCLC Case–Control Study, among only men

	Model[a]		Model[b]		Model[c]	
Aspirin use	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
No	Reference		Reference		Reference	
Yes	0.61 (0.48–0.79)	<**0.0001**	0.72 (0.55–0.93)	**0.01**	0.66 (0.49–0.89)	**0.006**
Daily aspirin use						
Never	Reference		Reference		Reference	
<1 tablet per day	0.37 (0.14–0.98)	**0.04**	0.33 (0.12–0.90)	**0.03**	0.40 (0.12–1.31)	0.13
≥1 tablet per day	0.63 (0.49–0.81)	<**0.0001**	0.74 (0.57–0.96)	**0.03**	0.68 (0.50–0.90)	**0.01**
Trend		<**0.0001**		**0.03**		**0.01**
Duration of aspirin use						
Never	Reference		Reference		Reference	
< 3 years	0.77 (0.52–1.15)	0.21	0.94 (0.62–1.42)	0.77	0.93 (0.58–1.45)	0.75
≥ 3 years	0.55 (0.42–0.72)	<**0.0001**	0.63 (0.47–0.85)	**0.002**	0.61 (0.44–0.85)	**0.003**
Trend		<**0.0001**		**0.002**		**0.003**

[a]Adjusted for age, smoking, pack-years, education, family history of lung cancer, marital status, year of interview, use of Tylenol, and other NSAIDs.
[b]Adjusted for age, smoking, pack-years, education, family history of lung cancer, marital status, year of interview, use of Tylenol and other NSAIDs, and BMI at diagnosis.
[c]Adjusted for age, smoking, pack-years, education, family history of lung cancer, marital status, year of interview, use of Tylenol and other NSAIDs, BMI at diagnosis, and global genetic ancestry.
Bold values denote statistical significance.

Table 5. Adjusted HR and 95% CI of aspirin use, frequency, and duration associated with NSCLC survival in the NCI-Maryland NSCLC Case–Control Study, among only AA

	Model[a]		Model[b]	
Aspirin use	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
No	Reference			Reference
Yes	0.66 (0.47–0.93)	**0.02**	0.64 (0.45–0.91)	**0.01**
Daily aspirin use				
Never	Reference			Reference
< 1 tablet per day	0.97 (0.38–2.47)	0.95	0.98 (0.38–2.54)	0.97
≥ 1 tablet per day	0.64 (0.44–0.91)	**0.01**	0.61 (0.42–0.90)	**0.01**
Trend		**0.01**		**0.01**
Duration of aspirin use				
Never	Reference			Reference
<3 years	0.55 (0.31–1.00)	**0.05**	0.53 (0.29–1.00)	**0.05**
≥3 years	0.62 (0.42–0.93)	**0.02**	0.60 (0.39–0.92)	**0.02**
Trend		**0.01**		**0.01**

[a]Adjusted for age, gender, smoking, pack-years, education, marital status, year of interview, use of Tylenol and other NSAIDs, stage, histology, and BMI at diagnosis.
[b]Adjusted for age, gender, smoking, pack-years, education, BMI, marital status, year of interview, use of Tylenol and other NSAIDs, stage, histology, BMI at diagnosis, and global genetic ancestry.
Bold values denote statistical significance.

differences could relate to the underlying physiologic reasons why men and women take aspirin, or it could reflect real biological differences (21). Given that BMI is higher among US men compared with US women at the time of lung cancer diagnosis, this could also perhaps explain why the relationship is restricted to men.

We found that aspirin use was associated with reduced risk of death from lung cancer only in AA. Long-term aspirin use (more than 5 years) was previously reported to be associated with a reduced risk of mortality from lung adenocarcinomas (9); however, another study of lung cancer survival and NSAIDs use found no association (26). The latter study predominantly involved EA using either aspirin or other NSAIDs.

These observed racial differences may be partially explained by the somatic landscape of lung tumors. For example, aspirin use is associated with improved prognosis among colorectal cancer patients when tumors harbor somatic mutations in *PIK3CA*, a mutation that is also found in lung cancer (14). Racial differences in *PIK3CA* mutations are not well studied/described, and it is possible that the divergent relationship between aspirin use and lung cancer survival in EA and AA is related to divergent mutational profiles. If these findings are validated in other studies, both the mechanism of why this occurs, combined with the potential translation of these findings, should be explored.

There is evidence that chronic inflammation is involved in the development of lung cancer (55), and some studies have shown that inflammatory proteins are associated with lung cancer diagnosis (6, 18). Moreover, studies have shown racial differences in systemic immune-related proteins and tumor immune profiles in EA and AA (7, 29). These preliminary studies showing inflammation differences between these two populations could also partly explain why aspirin is associated with outcome in one population, but not the other. However, further work is needed. Of note, we found that AA using aspirin, both cases and controls, had higher serum concentrations of IL4 than nonusers. This finding was consistent with previous observations showing that aspirin modulates IL4 expression (56). Additionally, research has shown that IL4 inhibits COX-2 mRNA transcription and PGE_2 in lung cancer (57). It is not clear if this mechanism contributes to racial differences in aspirin use and cancer survival, but they need to be replicated and warrant further follow-up.

We found no association between NSCLC risk and use of NSAIDs, other than aspirin, and Tylenol. The latter is used as a pain reliever, even in the absence of inflammation; and the mechanism by which it relieves pain is not known. As for the NSAIDs, although they share a common mechanism of action, namely, inhibition of cyclo-oxygenase (COX) enzymes, they vary in their ability to inhibit COX isoforms and other functions such as platelet aggregation. Indeed, aspirin, with its active acetylsalicylic acid, is commonly used for its anticoagulant action.

Our study primarily relied on self-reported race, which is frequently used to capture an individual's race or ethnicity. However, it is clear from studies of genetic admixture that human genetic variation does not segregate into the same discrete groups as socially defined categories of race. The proportion of African ancestry can vary widely across the United States in self-reported AA and EA (58). Indeed, a recent study has suggested that the differences can vary as much as 10-fold across the United States (59). Given that few studies include an adjustment for genetic ancestry, as well as recent evidence for germline mutations that could influence the effect of aspirin and colon cancer risk (60), we included measures of genetic ancestry in our study. Our data suggest that global ancestry does not significantly modulate the relationship between aspirin and lung cancer risk or survival. To our knowledge, this is the first evidence to directly address this possibility. Although global genetic ancestry does not seem to modify the relationship between aspirin and lung cancer, future studies should focus on specific loci as there is significant evidence that the metabolism, tolerance, and response to aspirin are mediated by genetic variation. Key functional polymorphisms related to aspirin lie in *UGT1A6*, *ACSM2*, *CYP2C9*, and *PGTS1*, and SNPs may also modify whether aspirin affects the risk for certain cancers. For example, carriers of one or two T alleles of rs6983267 at 8q24 have a reduced colorectal cancer risk if they use aspirin, whereas carriers of the G allele show no evidence of a chemopreventive effect (60).

Our study has several limitations. Aspirin use was examined using three questions, which allowed us to capture use, duration and frequency; however, the nature of the questions did not allow for the same level of detail as in other studies. For example, it is not known what dose of aspirin was contained in each tablet. Moreover, no information was collected regarding why participants

used aspirin, which might have helped to address whether the associations we observed were attributable to aspirin itself or other underlying disease processes. Another limitation is the design of the study: case–control studies can be vulnerable to recall bias as cases may be more likely to recall their exposure, which in this study is aspirin use. However, if anything, recent use of pain medication would be expected to be higher among case patients, which is not the case in this study and is consistent with other observations also (21). Our data extend the literature regarding the relationship between aspirin use and lung cancer. We highlight several key racial differences in the relationship between aspirin use and lung cancer survival. In addition, we found BMI to have a significant inverse association with NSCLC risk, even after adjustment for aspirin use; and the strength of such association was higher among AA than EA participants (B.M. Ryan, unpublished observations). This could explain some of the previous heterogeneity in the literature, though the exact mechanism involved needs further study.

Our study also found that the main chemopreventive benefit of aspirin use may be confined to men. These conclusions require validation and follow-up, with particular emphasis on the potential translational impact of the findings for lung cancer survival in AA men due to existing health disparities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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