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Regular Adult Aspirin Use Decreases the Risk of Non-Small Cell Lung Cancer among Women

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Abstract

Background—Prior studies indicate that use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAID) is associated with a decreased risk of non-small cell lung cancer (NSCLC); however, results have been contradictory in part because of variation in study design. Few studies have examined the use of aspirin or other NSAIDs on risk of NSCLC in women.

Methods—Through a case-control study of African American and Caucasian women with and without NSCLC, we examined the relationship between use of aspirin, NSAIDs, and acetaminophen and risk of NSCLC. Risk was estimated by calculating odds ratios and 95% confidence intervals for ever/never use, duration of use, and duration of use category (never, 1–5 years, >5 years) after adjusting for major risk factors for lung cancer. Risk estimates were stratified by race, age, smoking history, and body mass index.

Results—Ever use of adult-strength aspirin was associated with a significant reduction in risk of NSCLC (odds ratio, 0.66; 95% confidence interval, 0.46–0.94). Additionally, there was a significant trend toward a reduced risk of NSCLC in adult-strength aspirin users with increasing duration of use (P_{trend} = 0.02). In stratified analyses, aspirin use was associated with a significantly reduced risk of lung cancer among Caucasians and 55- to 64-year-olds. Baby aspirin and NSAID use was associated with a significant reduction in risk of NSCLC only among 65- to 74-year-olds.

Conclusion—Our results suggest that long-term use of adult-strength aspirin may reduce the risk of NSCLC in women.

Introduction

Lung cancer is the second leading form of cancer in both men and women in the United States, expected to affect 213,380 persons in 2007, and is the leading type of cancer-related death in the United States (1). Whereas lung cancer incidence and mortality among men have been decreasing for several years, mortality rates among women steadily increased from 1995 to 2002 (2). As the 5-year survival rate for lung cancer is only 15%, identification of methods of chemoprevention and chemotherapeutics is needed.

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One set of attractive targets for chemoprevention and therapy are the cyclooxygenase (COX) enzymes, COX-1 and COX-2. COX-1 is constitutively expressed, whereas COX-2 expression is induced by growth factors, oncogenes, cytokines, carcinogens, and phorbol esters. COX enzymes catalyze the production of prostaglandins, including prostaglandin E_2, the tumorigenic effects of which include immunosuppression, stimulation of angiogenesis, antiapoptotic effects, stimulating estrogen synthesis, promoting cell motility, and a synergistic effect with EGFR. Aspirin and some nonsteroidal anti-inflammatory drugs (NSAID) non-selectively block COX-1 and COX-2, whereas other NSAIDs, such as celecoxib, selectively block COX-2. These agents may provide an inexpensive means of chemoprevention and therapy with fewer side effects in comparison with the toxicity associated with established chemotherapies.

As these agents have different mechanisms of action, it is important to study their association with non-small cell lung cancer (NSCLC) separately. Whereas aspirin irreversibly inactivates COX-1 and COX-2 via acetylation, other NSAIDs are competitive antagonists, reversibly inhibiting COX enzymes. Furthermore, aspirin may have a dose-response relationship with risk of NSCLC; subsequently, the association between baby aspirin and adult-strength aspirin and NSCLC should be examined separately.

Studies investigating the expression of COX-2 in lung tumors have consistently found increased expression of COX-2 in lung tumor tissue in comparison with non-neoplastic tissue or samples from healthy smokers (3–9). Moreover, high COX-2 tumor expression has been associated with poorer patient survival even after taking into consideration histologic type (10–12).

Four of the five published studies examining the relationship between the *COX2* T8473C polymorphism and risk of lung cancer report a protective effect of the C allele although findings were not always statistically significant (13–17). These data suggest that COX-2 is a potential target for chemoprevention.

Several studies have been conducted examining whether aspirin and NSAIDs are effective in reducing the risk of lung cancer. The studies analyzing aspirin use and lung cancer risk vary by design, age of participants, measure of aspirin use, aspirin use classifications, and whether smoking was taken into consideration in analyses. The only randomized controlled trial, conducted as part of the Women's Health Study, reported a nonsignificant trend toward reduced lung cancer in the aspirin group; however, their smoking classification (past/current/never) did not capture dose or duration of smoking (18). Of the six prospective cohort and five case-control studies conducted to date, results have been mixed (19–29).

Similarly, inconsistent results have been obtained for studies examining the relationship between aspirin use and mortality from lung cancer (30–32). A randomized trial conducted by Peto et al. involving 5,139 British male physicians assigned to either placebo or 500 mg/d aspirin for 6 years revealed a nonsignificant 22% reduction in lung cancer mortality in the aspirin group (30). A prospective cohort study following over 635,000 U.S. participants for 6 years reported no effect of frequency of aspirin use on the relative risk (RR) of fatal respiratory cancer in men and women combined and a reduced risk in women but not men (31). Alternatively, Ratnasinghe et al. detected a reduced risk of mortality from lung cancer in men but not in women (32). Shortcomings of these studies include not adjusting for smoking dose or duration, age, and/or dose or duration of aspirin used in analyses.

Conflicting results have also been reported in the nine studies analyzing the relationship between NSAID use and risk of lung cancer. A meta-analysis by Harris et al. revealed a nearly significant 36% decreased risk of lung cancer with daily NSAID use [RR, 0.64; 95% confidence interval (95% CI), 0.40–1.03; ref. 33]. No study to date has addressed dose,

duration, and frequency of aspirin or NSAID use simultaneously in estimation of risk of lung cancer. Only four studies addressing this issue have focused on women (18, 24, 25, 29). The inconsistency between the studies in terms of definition of regular aspirin or NSAID use makes cross-comparisons difficult. Additionally, many of these studies did not adjust for smoking in their analyses.

The effects of acetaminophen, an antipyretic and analgesic without anti-inflammatory properties, on COX remain controversial. The two previously conducted case-control studies examining the relationship between acetaminophen use and risk of lung cancer found no association (29, 34). This result is consistent with the consensus to date that acetaminophen acts to block central nervous system COX with only weak activity peripherally (35–37).

Our *a priori* hypotheses were that use of aspirin and other NSAIDs would be associated with reduced risk of NSCLC and that acetaminophen use would not be associated with NSCLC risk. In this large population-based case-control study of women, we examined risk of lung cancer associated with regular aspirin, NSAID, and acetaminophen use, taking into account dose, duration, and frequency in our analyses, and we adjusted for smoking history based on pack-years.

Materials and Methods

Study Subjects

Subjects were identified through the population-based Metropolitan Detroit Cancer Surveillance System, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Women ages 18 to 74 years, diagnosed with primary NSCLC in the tri-county (Wayne, Macomb, and Oakland) area between November 1, 2001 and October 31, 2005, were eligible to participate. Ascertainment was originally focused on adenocarcinoma histology but was broadened after November 1, 2004 to include all NSCLC histologies because many histologic diagnoses at the time of rapid case ascertainment were not more specific. Seventy-two percent of cases had adenocarcinoma histology, 9% were squamous cell carcinoma, 3% large cell carcinoma, and 16% were NSCLC unspecified, reflecting this sampling method.

Due to the detailed nature of the questionnaire, particularly with respect to the extensive medication history included, no proxy interviews were conducted; therefore, women deceased at ascertainment or first contact were ineligible. Five hundred and ninety-seven (55%) women completed an interview. The rapidly fatal nature of lung cancer and the likelihood of a late-stage diagnosis meant that many women were too ill ($n = 135$) at the time of first contact and could not complete the interview. We could not locate a working phone number for another 90 women, and 270 women refused. Women self-reporting race other than African American or Caucasian ($n = 16$) were excluded from this analysis because there were too few for race-specific analyses. In total, 581 women with NSCLC were available for analysis.

Population-based controls were identified through random-digit dialing. Control women were frequency matched to cases on race and 5-year age group. Of the households willing to complete the brief eligibility screening questionnaire, 70.8% ($n = 552$) have participated. Eleven controls reporting race other than African American or Caucasian were excluded, leaving 541 controls for analysis.

Data Collection

All local institutional and review boards approved this study. Informed consent was obtained from each subject before study participation. Trained interviewers conducted in-person

interviews to collect demographic information, medication history (aspirin, acetaminophen, and NSAID), smoking history, health history, and lifetime estimates of environmental tobacco smoke exposure. Ex-smokers were individuals quitting more than 2 years before diagnosis/interview. Never smokers included those who smoked less than 100 cigarettes in their lifetime. Demographic information included age at diagnosis/interview, year of first diagnosis, date and place of birth, residence at time of diagnosis/interview, marital status, race, and number of years of education completed. Medical history included self-report of physician diagnoses of asthma, emphysema, allergies, pneumonia, bronchitis, chronic obstructive pulmonary disease, tuberculosis, and cancer. Participants with diagnoses of lung diseases reported within 1 year of lung cancer diagnosis (for cases) or interview (for the controls) were coded as not having the disease. Emphysema, chronic obstructive pulmonary disease, and chronic bronchitis were combined to create a broad chronic obstructive lung disease (COLD) variable.

Additionally, history of myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis was collected. Smoking history included age began and quit smoking, years of smoking, average number of cigarettes per day, type of cigarette, and total years of smoking interruption. Participants were asked about their environmental tobacco smoke exposure at home (as a child and as an adult) and within the workplace as well as hours and years of exposure for each situation. Family history of lung cancer was coded as yes or no based on the detailed first-degree family history information collected. Lung cancer diagnosis dates and histology information for cases were obtained through the Metropolitan Detroit Cancer Surveillance System.

Regular pill use (aspirin, acetaminophen, and NSAID) was defined as taking at least one pill three times per week or more for at least 1 month during the participant's lifetime. For each type of pill and period of use, participants were asked ages at which they started and stopped pill use and number of pills per week taken. For aspirin, participants were asked whether they took baby/senior citizen aspirin (81 mg) or regular-strength aspirin (325 mg). Pill use 1 year before diagnosis/interview was excluded from analysis.

We created the variable pill-years, which is defined as one pill-year being equal to one pill per day for 1 year. To calculate this variable, the total number of weeks the pills were taken was multiplied by the number of pills per week to equal the total number of pills. This number was divided by 364 (7 days/wk × 52 weeks/y) to equal the number of pill-years. As pill-years of use was similar to duration of use and not frequency of use in our analysis, results were presented as years of use, either years of use as a continuous variable or in categories (never, 1–5 years, >5 years).

Statistical Analysis

Comparisons of dichotomous risk factors were made between cases and controls using χ^2 tests, and comparisons of means were conducted using Student's *t* tests. χ^2 analysis was also conducted for comorbidities between cases and controls, including history of arthritis, ulcer, and cardiovascular disease. A multivariate unconditional logistic regression model was used to estimate odds ratios (OR) and 95% CI. The initial model was developed based on age, race, and nonmedication factors associated with lung cancer in univariate analysis. These factors included age at diagnosis/interview (continuous variable), race, years of education, pack-years of smoking (continuous variable), history of COLD, current body mass index (BMI; continuous variable), and family history of lung cancer, all independent predictors of lung cancer risk ($P < 0.05$). Additionally, comorbidities significantly different between cases and controls were included in the model. Tests for interactions were done, and the one interaction term significant in the full model (education × BMI) was also included. This

model was then applied to medication use (ever/never and pill-years). To further analyze the effects of duration of use, years of use were categorized as never, 1 to 5 years, and >5 years. Adjusted ORs and 95% CIs were calculated and a test for trend was done for each type of pill. Stratified analyses were done based on smoking pack-year history, age, race, BMI, cardiovascular disease, and arthritis. To analyze the effects of combined NSAID use, cases and controls were categorized on whether they had taken baby aspirin and/or adult-strength aspirin and on whether they used any aspirin (baby or adult-strength) in addition to NSAIDs. Finally, whether regular use of aspirin and/or other NSAIDs was associated with risk of NSCLC in the absence of the influence of use of other pill types, ever/never use was reanalyzed, including only cases and controls who took either only a given pill type or who took neither NSAIDs nor acetaminophen on a regular basis. All statistical analyses were done using SAS version 9.1 (SAS Institute).

Results

Participant characteristics are displayed in Table 1. Age and race did not differ between cases and controls ($P = 0.07$ and 0.75, respectively). Approximately 25% of the cases and controls were African American. Cases were more likely to be current smokers ($P < 0.0001$) and reported significantly higher mean pack-years of smoking than controls ($P < 0.0001$). Cases also were less likely to have completed high school ($P = 0.02$) and had lower BMI at the time of interview than controls ($P < 0.0001$). In addition, 31.5% of cases reported a history of COLD at least 1 year before diagnosis, whereas only 14.2% of controls reported such a history ($P < 0.0001$). A family history of lung cancer in a first-degree relative was more than twice as likely to be reported by cases than by controls ($P < 0.0001$). In univariate analyses, duration of use of aspirin, acetaminophen, and NSAIDs did not differ between cases and controls.

Comorbidities potentially affecting use of aspirin, acetaminophen, and NSAIDs are reported in Table 2. In unadjusted analyses, cases were more likely to report a physician diagnosis of any history of arthritis (including not otherwise specified type) and rheumatoid arthritis than were controls. After adjusting for age, only the difference between cases and controls in history of arthritis was sustained (OR, 1.28; 95% CI, 1.00–1.63; $P = 0.05$). In unadjusted analyses, cases and controls differed significantly in reporting a history of all cardiovascular diseases and specifically for stroke, myocardial infarction, congestive heart failure, and peripheral vascular disease. After adjusting for age and smoking pack-years, only history of stroke remained significantly different between cases and controls (OR, 1.75; 95% CI, 1.03–2.95). Although history of any cardiovascular disease (including stroke) was no longer significant after adjustment, it was included in the multivariate unconditional logistic models evaluating aspirin and NSAID use because it is potentially an important moderator of aspirin or NSAID use. There was no difference between cases and controls in the frequency of reporting a history of ulcers (16.4% versus 13.2%; $P = 0.13$).

The relationships between regular use of aspirin, acetaminophen, and NSAIDs and risk of lung cancer were evaluated using three different measures of use: ever/never, pill-years as a continuous variable, and years of regular use categorized as never, 1 to 5 years, and >5 years (Table 3). Regular aspirin use (ever/never) was associated with a significantly reduced risk of lung cancer (OR, 0.66; 95% CI, 0.46–0.94), as was duration of use based on pill-years (data not shown). The analysis by years of use categories also showed this reduced risk ($P_{trend} = 0.02$). These associations remained significant even after adjusting for BMI, family history of lung cancer, history of COLD, arthritis or cardiovascular disease, and a BMI × education interaction term.

In fully adjusted models, regular baby aspirin use, acetaminophen use, and NSAID use (as measured by ever/never use or years of use) were not significantly associated with risk of lung cancer. Although not statistically significant, regular baby aspirin and NSAID use and duration of baby aspirin and NSAID use were associated with reduced risk of lung cancer of a similar magnitude to that seen for regular aspirin use.

Among cases, users of NSAIDs were less likely to be baby aspirin users ($P = 0.01$) and more likely to be adult aspirin users ($P = 0.0006$) than non-NSAID users. However, the results for baby aspirin, adult-strength aspirin, and NSAIDs were independent of each other in the full models. Inclusion of either ever/never use or duration of use for combinations of the medications did not alter the results. Ever use of any aspirin (adult or baby-strength) was associated with a significant reduction in risk of NSCLC (OR, 0.58; 95% CI, 0.42–0.79). Ever use of any aspirin and other NSAIDs further reduced the risk of NSCLC (OR, 0.47; 95% CI, 0.29–0.75).

We restricted analysis to cases and controls who had either used no pills or who used only the pill type of interest. Similar results were obtained: adult aspirin only (OR, 0.51; 95% CI, 0.29–0.87), adult and/or baby aspirin only (OR, 0.57; 95% CI, 0.40–0.81), and combined aspirin plus other NSAIDs (OR, 0.37; 95% CI, 0.22–0.64). No significant reduction in risk of NSCLC was seen for baby aspirin alone or acetaminophen alone.

Because of the potential for confounding and/or effect modification due to comorbidities related to smoking, age, race, and obesity, stratified analyses were conducted examining the relationship between years of aspirin, acetaminophen and NSAID use, and lung cancer by presence or absence of a history of cardiovascular disease and presence or absence of a history of arthritis (Table 4). Regular aspirin use was associated with a significantly reduced risk of lung cancer among patients without a history of cardiovascular disease (OR, 0.65; 95% CI, 0.43–0.98). A similar but not statistically significant reduction in risk was observed among patients with a history of cardiovascular disease (OR, 0.67; 95% CI, 0.32–1.42). A reduced risk of lung cancer was observed among regular adult-strength aspirin users (OR, 0.61; 95% CI, 0.38–0.96) and NSAID users (OR, 0.60; 95% CI, 0.39–0.91) who had arthritis. Again, a similar but not statistically significant reduction with regular adult-strength aspirin use was seen among people who reported no history of arthritis. No statistically significant relationships between years of regular baby aspirin use or acetaminophen use and lung cancer were found among patients regardless of presence or absence of cardiovascular disease or arthritis. Similar results for each pill type were obtained when duration of use was evaluated (data not shown).

In addition to the education × BMI interaction included in the models, the following statistically significant interactions were noted: acetaminophen duration × arthritis ($P = 0.003$) and duration of NSAID use × age at diagnosis/interview ($P = 0.01$). To address these interactions, additional stratified analyses of pill use (ever/never) were conducted by smoking pack-year history (nonsmoker, 1–20 pack-years, >20 pack-years), age category (<55, 55–64, and 65–74 years), race, and BMI (Table 5). Significant reductions in risk of lung cancer with regular aspirin use were seen specifically for Caucasians (OR, 0.63; 95% CI, 0.42–0.95) and women ages 55 to 64 years (OR, 0.43; 95% CI, 0.22–0.82).

Nonsignificant reductions in risk of lung cancer with regular adult aspirin use were reported for smokers with a >20 pack-year history (OR, 0.66; 95% CI, 0.40–1.07) and for women in the lowest BMI category (OR, 0.53; 95% CI, 0.27–1.03), and there was a trend for decreasing risk with increasing years of use in each of these categories ($P_{trend} = 0.04$ and 0.01, respectively). Significant reductions in risk of lung cancer were also observed for baby aspirin use (OR, 0.53; 95% CI, 0.30–0.95) and NSAIDs (OR, 0.41; 95% CI, 0.22–0.77)

among the oldest age group, 65- to 74-year-olds. Finally, baby aspirin use was associated with a reduced risk of lung cancer among women in the middle BMI category (OR, 0.46; 95% CI, 0.23–0.90). When a test for trend was performed on duration of pill use, women with a BMI of 25 to 29 kg/m^2 or a BMI of ≥30 kg/m^2 had similar reductions in risk with increasing years of baby aspirin use (P_{trend} = 0.04 and 0.04, respectively).

Discussion

Regular-Strength Aspirin

Our findings suggest that, overall, regular adult aspirin use is protective against NSCLC in women. Whether analyzed by ever/never use, pill-years of use, or duration of use, regular aspirin use was associated with a statistically significant decreased risk of lung cancer after adjustment for potential confounders. Similar to our findings, results from a large case-control study of both men and women showed a lower risk for individuals who used aspirin at least once a week for at least 1 year, compared with nonusers, after adjustment for age, pack-years of smoking, and education (OR, 0.57; 95% CI, 0.41–0.78; ref. 26). Harris et al. reported significant reductions in risk of lung cancer with use of at least two or more pills per week in a case-control study (29). In a nested case-control study, Akhmedkhanov et al. reported that women enrolled in the New York University Women's Health Study who reported aspirin use three or more times per week for at least 6 months were at decreased risk of NSCLC compared with non-aspirin users (OR, 0.39; 95% CI, 0.16–0.96) after adjustment for smoking and education (25). A similar study of low-dose (100 mg) aspirin in a randomized controlled trial that took place as part of the Women's Health Study also reported a borderline significant reduction in risk of lung cancer among aspirin users compared with the placebo group (RR, 0.78; 95% CI, 0.59–1.03) and a significant reduction in lung cancer mortality (RR, 0.70; 95% CI, 0.50–0.99) among users compared with the placebo group (18). However, these estimates were not adjusted for confounding variables specific to NSCLC, and smoking was classified as former, current, or never instead of pack-year history.

Schreinemachers and Everson reported a decreased risk of lung cancer among individuals who had used aspirin during the 30 days before their participation in the National Health and Nutrition Examination Survey (NHANES) I (incidence rate ratio, 0.68; 95% CI, 0.49–0.94; ref. 19). However, once these data were stratified by gender and age, this protective effect was only seen in men over the age of 65 years. These findings were later confirmed in NHANES II in an analysis of risk of mortality from lung cancer (32). Other cohort studies reported no association between aspirin use and lung cancer risk or risk of mortality from lung cancer (20–23, 31); however, many of the previous studies lack the detailed information necessary to examine duration of use or particular subgroups of individuals who may benefit most from aspirin use.

Our current study is the first to report that duration of aspirin use was associated with decreased risk of lung cancer overall and specifically among women who are Caucasian and 55- to 64-year-olds. We also report nonsignificant reductions in lung cancer risk among heavy smokers and normal-weight participants. Schreinemachers and Everson detected the greatest effects overall at 7 to 10 years of follow-up (19). Similarly, results from the New York University Women's Health Study indicate a significant trend toward a reduced risk of lung cancer with increasing duration of aspirin use (25). This trend was repeated in a hospital-based case-control study that indicated a reduced risk with increasing duration of use among men (26). These results agree with our finding of a significant trend for decreased risk of lung cancer with increasing duration of adult aspirin use.

Low-Dose/Baby Aspirin

In our study, ever use of baby aspirin and duration of baby aspirin use were associated with a reduced risk of lung cancer among 64- to 75-year-olds and among women with a BMI of ≥25. Overall, there was a nonsignificant trend toward decreased risk of lung cancer with increasing duration of baby aspirin use. Of the studies that distinguish between baby and adult-strength aspirin, a Danish prescription-based study that examined prescriptions of a maximum dose of 150 mg found no association between low-dose aspirin use and risk of lung cancer (21). Similarly, the only randomized controlled trial addressing this issue was conducted through the Women's Health Study and used a dose of 100 mg adult aspirin versus placebo every other day (18). Cook et al. reported a borderline decreased risk of lung cancer in the aspirin group. Furthermore, Harris et al. observed a nonsignificant trend toward a reduced risk of lung cancer in participants taking two or more baby aspirins a week (29). These results and those of previous studies raise the question of whether there is a dose-response effect in the relationship between aspirin use and lung cancer. It is possible that the doses tested in these studies may not have been high enough to have a protective effect against lung cancer.

Acetaminophen Use

Regular use of acetaminophen and duration of acetaminophen use were not associated with risk of NSCLC. Two previously published studies that analyzed the association between use of acetaminophen and risk of lung cancer obtained similar results (29, 34). Unlike the other NSAIDs that act on COX-1 and/or COX-2, this analgesic and antipyretic has been proposed to act on COX-3. COX-3 is an alternative splice variant of COX-1 that retains intron 1, with only weak inhibition of COX-1 and COX-2 (36). Acetaminophen passes through the blood-brain barrier and inhibits COX-3, which is constitutively expressed in the central nervous system, affecting central prostaglandin E_2 synthesis (35–37). However, this mechanism remains controversial, and it has been suggested that acetaminophen acts on COX-2 centrally (38–40). Thus, whereas other NSAIDs decrease the production of prostaglandin E_2 peripherally, acetaminophen has a putative effect on prostaglandin E_2 production only centrally. Subsequently, it is not expected to have a peripheral anti-inflammatory effect and therefore is less likely to be associated with risk of NSCLC.

Other NSAID Use

In our population, only NSAID users ages 64 to 75 years had a decreased risk of lung cancer compared with non-NSAID users, and increasing duration of NSAID use was also associated with a diminished risk of lung cancer, although this trend was not statistically significant. A recent meta-analysis of 14 studies suggested that NSAID use lowered the risk of lung cancer (RR, 0.79; 95% CI, 0.66–0.95) and the risk was further reduced when the analysis was limited to the nine studies that adjusted for the effects of smoking in case-control studies (RR, 0.63; 95% CI, 0.47–0.86) and cohort studies (RR, 0.78; 95% CI, 0.62–0.98; ref. 41). There is wide variation in the estimates of effect for NSAIDs, with some studies finding a protective association (27–29, 34), others finding an increase in lung cancer risk among NSAID users (42, 43), and other studies finding no association (24, 44–46). Additionally, the study by Muscat et al. suggests that smoking modifies the association between NSAID use and risk of lung cancer, with only NSAID use in nonsmokers but not smokers, showing a protective effect (OR, 0.60; 95% CI, 0.45–0.80; ref. 28). In our sample population, we did not see an association between duration of pill use and risk of lung cancer among nonsmokers. Likewise, Harris et al. reported a significant reduction in risk with regular use of selective COX-2 inhibitors among chronic smokers (OR, 0.24; 95% CI, 0.12–0.45); however, this reduced risk was not significant among nonsmokers (OR, 0.50; 95% CI, 0.22–1.12; ref. 29).

Sex, Age, and Pill Use

Several epidemiologic studies suggest that the relationship between lung cancer and aspirin use is sex specific and possibly age specific. In a study of retirement community residents, Paganini-Hill et al. observed a nonsignificant decrease in risk of lung cancer with aspirin use among women but not men, consistent with our findings (20). Analysis of the Cancer Prevention Study II revealed marginally significant decreased risk of fatal respiratory cancer among women taking aspirin <16 times per month but not among men; however, they did not include smoking in their analysis of lung cancer risk (31). Similarly, Akhmedkhanov et al. reported an inverse relationship between lung cancer and aspirin use among women; however, only 15 cases were coded as regular aspirin users, suggesting that this study was underpowered for subgroup analyses (25). Other studies suggest that regular aspirin use may reduce the risk in men but not in women. Moysich et al. observed a reduced risk of lung cancer among men but not women; however, aspirin dose was not measured and hospital-based controls were sampled (26).

In a comparison of 492 invasive lung cancer patients with 984 controls, Harris et al. found a significant reduction in risk of lung cancer in men (OR, 0.26; 95% CI, 0.10–0.62) but not in women (OR, 0.52; 95% CI, 0.24–1.13; ref. 29). In a younger sample (average age of 49 years) from NHANES I, aspirin appeared to reduce the risk of lung cancer in men but not in women (19). In contrast to these findings, the Health Professionals Follow-up Study did not observe an association between lung cancer and aspirin use among men (22). Similarly, a prospective cohort study analyzing the NHANES I and II databases involving over 22,000 participants observed that risk of mortality from lung cancer was reduced in men but not in women after adjusting for BMI, race, education, poverty index, and smoking (32); however, the authors did not adjust for aspirin dose or duration of use. Thus, whether there is a sex-specific effect of aspirin on lung cancer risk and whether this risk may vary with age remain to be determined.

Race and Pill Use

Our study is the first to consider the relationship between patterns of use of aspirin and other NSAIDs and lung cancer by race; many of the previous studies involved primarily Caucasians. We observed that regular aspirin use was associated with a reduced risk of NSCLC among Caucasian women. No association between aspirin use and NSCLC was found among African American women. Although our study shows that similar numbers of Caucasian and African American controls took aspirin, among pill users Caucasians took aspirin for a significantly longer period of time (10.1 versus 6.2 years; $P = 0.04$). The lack of association between aspirin use and NSCLC among African Americans may reflect short duration of use and/or small sample size studied.

Pill Use and Smoking

We report a 34% reduction in risk of NSCLC with regular adult aspirin use among smokers with a greater than 20 pack-year smoking history. Of the four studies that also reported a protective effect of regular aspirin use for lung cancer, two did not stratify their analyses based on smoking pack-year history (19, 25) and a fourth only stratified on smoking status (chronic smoker versus nonsmoker; ref. 29). In contrast to our results, the third study by Moysich et al. reported a significant trend toward a reduced risk of NSCLC with increasing duration of use in the lowest tertile of pack-year distribution (1–34 pack-years; ref. 26). Interestingly, their lowest tertile of smoking pack-year history includes the median for our highest category of smoking pack-year history, and our study included only women. Like other aspirin studies, the study by Moysich et al. did not measure aspirin dose. It is possible that a higher proportion of this group of lighter smokers took regular aspirin than did the heavier smokers, biasing the results. One previous study of COX inhibition with NSAIDs

found a decreased risk of lung cancer in heavy smokers; however, dose and duration of NSAID use were not assessed (34). Thus, it could be argued that a basal level of inflammation as a result of heavy smoking is required to observe a beneficial effect of aspirin use.

Comment

Over the past two decades, researchers have attempted to address the question of whether regular use of aspirin and/or other NSAIDs decreases a person's risk of developing lung cancer with conflicting results. At the root of these contradictory results are variation in study design, age of participants, method of data collection (including the use of proxies), measure of aspirin use, aspirin use classifications, and whether and how smoking is taken into consideration in analyses. Furthermore, several studies have measured pill use indirectly through prescription databases (21, 27, 43, 45). This method of measurement fails to collect actual use and over-the-counter aspirin use and thus may misclassify aspirin use. Moreover, only one study analyzed comorbidities, such as cardiovascular disease and arthritis, which could affect use of aspirin or other NSAIDs (24), and only one study conducted analysis stratified by age and BMI (27).

The current study has several strengths. This study only included in-person interviews, increasing the reliability and validity of the data collected. Pill use was obtained directly from the participant, capturing over-the-counter and prescription NSAID use, as opposed to through a prescription database. Additionally, we calculated pill-years of use to create a pill use variable in an attempt to take into account both frequency and duration of use. We also separated the use of baby aspirin (81 mg) and adult-strength aspirin (325 mg) and considered confounders that might predicate use of aspirin or NSAIDS, such as presence of a history of cardiovascular disease or of arthritis. In addition, we were able to stratify or adjust for a variety of risk factors in our models, including pack-years of smoking. Analyses of individual pill use did not exclude users of other pill types; therefore, the analyses provide a conservative estimate of the association between pill use and NSCLC risk. Repeating the analysis by excluding other pill users from models of each pill type did not substantially alter risk estimates. Combined use of aspirin and other NSAIDs further reduced the risk of NSCLC. Other strengths of this study include its inclusion of a large proportion of African Americans and the collection of extensive medical histories.

The study design and analysis strategies also helped reduce several types of bias. The use of population-based controls as opposed to hospital-based controls decreased the likelihood of selection bias. Furthermore, the exclusion from analysis of medication use during the year before diagnosis/interview reduced the potential of protopathic bias.

There are several limitations that should be considered. As with any case-control study, there is the potential for recall bias. Various mechanisms were implemented to reduce this bias. First, the aspirin and other NSAID use was collected in the context of a questionnaire that included detailed medical history, history of hormone use and other reproductive variables, history of tobacco use and cigarette smoke exposure, extensive family history, and demographic information. Second, it is not common knowledge that aspirin and other NSAID use might be associated with lung cancer risk, and the study was not presented to participants as a study of NSAID use and risk of lung cancer. Lastly, as expected because acetaminophen has a different mechanism of action, we found no association between acetaminophen use and lung cancer risk, suggesting that there was no significant overreporting of medication use in the controls.

Our study is also limited in that the sample size and frequency distribution of histologic subtype of NSCLC did not permit analysis based on histology. This study included only

women; therefore, results cannot be generalized beyond risk of NSCLC in women. Another potential limitation is the somewhat low response rate among cases, typical of most lung cancer studies. The detailed and lengthy questionnaire required women to be well enough to participate in a 1- to 2-hour visit. Moreover, proxy interviews were not permitted, so only women living several months after their lung cancer diagnosis were eligible. Therefore, study results may only be applicable to a subset of all women with NSCLC.

Conclusion

Given the poor 5-year survival rate of lung cancer patients, finding a means of preventing lung cancer is imperative. Aside from smoking cessation, there are no known methods for preventing lung cancer. If effective in reducing a person's risk of lung cancer, regular use of aspirin and other NSAIDs presents an inexpensive and relatively nontoxic measure that could be implemented, especially among high-risk individuals such as long-term smokers. Our results suggest that long-term use of adult-strength aspirin may reduce risk of NSCLC among women.

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Table 1

Characteristics of participants

Variable	Cases, *n* (%)	Controls, *n* (%)	*P*
n	581	541	
Age (y)	60.0 (9.3)	59.0 (9.4)	0.07
Race			
African American	136 (23.4)	131 (24.2)	0.75
Caucasian	445 (76.6)	410 (75.8)	
Smoking status			
Never	56 (9.7)	268 (49.9)	<0.0001
Former	191 (32.9)	168 (31.3)	
Current	333 (57.4)	101 (18.8)	
Pack-years among smokers	46.5 (29.3)	24.5 (22.6)	<0.0001
Smoking history level			
Never	56 (9.7)	268 (50.0)	<0.0001
1–20 Pack-years	90 (15.5)	146 (27.2)	
>20 Pack-years	433 (74.8)	122 (22.8)	
Education			
<12 y	108 (18.6)	46 (8.5)	<0.0001
High school or GED	239 (41.2)	166 (30.7)	
Beyond high school	233 (40.2)	329 (60.8)	
History of COLD			
No	398 (68.5)	464 (85.8)	<0.0001
Yes	183 (31.5)	77 (14.2)	
Family history of lung cancer			
No	431 (74.3)	478 (88.4)	<0.0001
Yes	149 (25.7)	63 (11.6)	
Current BMI (kg/m^2)	26.2 (5.9)	29.5 (7.3)	<0.0001
Pill use			
Baby aspirin	89	120	
Adult aspirin	129	132	
Acetaminophen	126	104	
NSAID	124	149	
Years of use (among pill users) *			
Baby aspirin	3.8 (3.5)	3.5 (3.5)	0.52
Adult aspirin	9.1 (9.7)	8.7 (9.9)	0.79
Acetaminophen	7.7 (9.4)	7.5 (8.6)	0.88
NSAID	5.9 (7.1)	4.7 (6.0)	0.15

* Outliers (>3 SD from the mean) were excluded from this analysis.

Table 2

Comorbidities in cases and controls and risk of lung cancer

Variable	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted OR*
Arthritis				
Yes	328 (56.5)	267 (49.3)	1.33 (1.05–1.68)	1.28 (1.00–1.63)
No	253 (43.6)	274 (50.7)		
Osteoarthritis				
Yes	127 (22.1)	137 (25.3)	0.83 (0.63–1.10)	0.79 (0.60–1.05)
No	449 (77.9)	404 (74.7)		
Rheumatoid arthritis				
Yes	64 (11.1)	41 (7.6)	1.52 (1.01–2.29)	1.48 (0.98–2.24)
No	514 (88.9)	500 (92.4)		
Systemic lupus erythematosus				
Yes	7 (1.2)	7 (1.3)	0.93 (0.32–2.67)	0.95 (0.33–2.72)
No	574 (98.8)	534 (98.7)		
Ulcer				
Yes	95 (16.4)	71 (13.2)	1.30 (0.93–1.81)	1.28 (0.92–1.79)
No	483 (83.6)	468 (86.8)		
Variable	**Cases *n* (%)**	**Controls *n* (%)**	**Crude OR (95% CI)**	**Adjusted OR† (95% CI)**
Cardiovascular disease				
Yes	136 (23.4)	69 (12.8)	2.09 (1.52–2.87)	1.25 (0.86–1.83)
No	445 (76.6)	472 (87.2)		
Stroke				
Yes	65 (11.3)	30 (5.6)	2.15 (1.37–3.36)	1.75 (1.03–2.95)
No	513 (88.7)	508 (94.4)		
Myocardial infarction				
Yes	55 (9.5)	25 (4.7)	2.19 (1.35–3.57)	1.48 (0.83–2.63)
No	524 (90.5)	513 (95.3)		
Congestive heart failure				
Yes	38 (6.6)	13 (2.4)	2.83 (1.49–5.38)	1.74 (0.84–3.59)
No	541 (93.4)	524 (97.6)		
Peripheral vascular disease				
Yes	27 (4.7)	12 (2.2)	2.15 (1.08–4.28)	0.99 (0.45–2.16)
No	551 (95.3)	526 (97.8)		

*Adjusted for age.

†Adjusted for age and smoking pack-years.

Table 3

Aspirin, acetaminophen, and NSAID use and risk of lung cancer

Variable	Cases *n* (%)	Controls *n* (%)	Adjusted OR*
Baby aspirin use			
Never	482 (83.1)	416 (76.9)	0.74 (0.50–1.08)
Ever	98 (16.9)	125 (23.1)	
Duration of baby aspirin use category			
0	482	416	1.00
1–5	59	92	0.69 (0.44–1.08)
>5	32	32	0.70 (0.37–1.32)
P_{trend}			0.09
Adult aspirin use			
Never	440 (75.9)	406 (75.0)	0.66 (0.46–0.94)
Ever	140 (24.1)	135 (25.0)	
Duration of adult aspirin use category			
0	440	406	1.00
1–5	64	73	0.60 (0.38–0.95)
>5	67	61	0.65 (0.40–1.06)
P_{trend}			0.02
Acetaminophen use			
Never	451 (77.8)	435 (80.4)	0.94 (0.65–1.36)
Ever	129 (22.2)	106 (19.6)	
Duration of acetaminophen use category			
0	451	435	1.00
1–5	74	59	1.03 (0.63–1.70)
>5	53	47	0.94 (0.72–1.22)
P_{trend}			0.63
NSAID use			
Never	454 (78.3)	388 (71.7)	0.77 (0.55–1.09)
Ever	126 (21.7)	153 (28.3)	
Duration of NSAID use category			
0	454	388	1.00
1–5	81	104	0.74 (0.49–1.10)
>5	44	48	0.87 (0.50–1.51)
P_{trend}			0.27

*Adjusted for age, race (African American or Caucasian), years of education level, smoking pack-years, BMI, family history of lung cancer, history of COLD, history of arthritis, history of cardiovascular disease, and BMI × years of education.

Table 4

Comoridities and ORs for lung cancer by pill use (ever/never)

Variable	No cardiovascular disease		Cardiovascular disease	
	Cases/controls	Adjusted OR*	Cases/controls	Adjusted OR* (95% CI)
Baby aspirin				
Never	376/374	0.81 (0.53–1.25)	106/42	0.52 (0.23–1.81)
Ever	68/98		30/27	
Adult aspirin				
Never	351/366	0.65 (0.43–0.98)	89/40	0.67 (0.32–1.42)
Ever	93/106		47/29	
Acetaminophen				
Never	350/381	0.91 (0.60–1.36)	101/54	1.08 (0.44–2.64)
Ever	94/91		35/15	
NSAID				
Never	348/334	0.72 (0.49–1.06)	106/54	1.13 (0.46–2.74)
Ever	96/138		30/15	

	No arthritis		Arthritis	
	Cases/controls	Adjusted OR† (95% CI)	Cases/controls	Adjusted OR† (95% CI)
Baby aspirin				
Never	219/216	0.64 (0.34–1.19)	263/200	0.78 (0.48–1.26)
Ever	34/58		64/67	
Adult aspirin				
Never	204/224	0.71 (0.40–1.27)	236/182	0.61 (0.38–0.96)
Ever	49/50		91/85	
Acetaminophen				
Never	206/250	1.95 (1.00–3.80)	245/185	0.67 (0.43–1.05)
Ever	47/24		82/82	
NSAID				
Never	212/230	1.31 (0.72–2.39)	242/158	0.60 (0.39–0.91)
Ever	41/44		85/109	

*Adjusted for age, race, years of education, smoking pack-years, BMI, history of COLD, family history of lung cancer, history of arthritis, and years of education × BMI interaction.

†Adjusted for age, race, years of education, smoking pack-years, BMI, history of COLD, family history of lung cancer, and history of cardiovascular disease, and years of education × BMI interaction.

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Table 5

ORs for pill use (ever/never) by smoking pack-years, age, race, and BMI

Variable	Baby aspirin		Adult aspirin		Acetaminophen		NSAID	
	Case/controls	OR*	Case/controls	OR* (95% CI)	Case/controls	OR* (95% CI)	Case/controls	OR* (95% CI)
Pack-years of smoking								
Nonsmoker								
Never	47/212	0.71 (0.31–1.60)	47/203	0.52 (0.23–1.20)	44/215	0.95 (0.44–2.02)	40/189	0.84 (0.42–1.66)
Ever	9/56		9/65		12/53		16/79	
1–20 pack-years								
Never	74/108	0.61 (0.28–1.35)	77/114	0.87 (0.38–1.95)	72/120	0.66 (0.29–1.51)	71/103	0.74 (0.35–1.55)
Ever	16/38		13/32		18/26		19/43	
>20 pack-years								
Never	361/93	0.72 (0.41–1.25)	315/84	0.66 (0.40–1.07)	333/96	1.02 (0.59–1.76)	342/92	0.76 (0.45–1.30)
Ever	71/29		117/38		99/26		90/30	
Age at diagnosis/interview								
<55 y								
Never	156/164	1.25 (0.49–3.20)	131/136	0.72 (0.38–1.35)	119/140	1.01 (0.55–1.87)	123/130	1.16 (0.64–2.10)
Ever	12/19		37/47		49/43		45/53	
55–64 y								
Never	156/132	0.80 (0.43–1.50)	150/136	0.43 (0.22–0.82)	157/146	0.67 (0.34–1.32)	154/134	0.92 (0.50–1.70)
Ever	41/49		47/45		40/35		43/47	
65–74 y								
Never	170/120	0.53 (0.30–0.95)	159/134	0.86 (0.46–1.60)	175/149	1.25 (0.64–2.44)	177/124	0.41 (0.22–0.77)
Ever	45/57		56/43		40/28		38/53	
Race								
Caucasians								
Never	364/308	0.68 (0.44–1.05)	328/304	0.63 (0.42–0.95)	349/334	0.93 (0.60–1.46)	341/283	0.78 (0.52–1.16)
Ever	80/102		116/106		95/76		103/127	
African Americans								
Never	118/108	0.86 (0.38–1.97)	112/102	0.74 (0.36–1.54)	102/101	0.89 (0.44–1.78)	113/105	0.73 (0.34–1.54)
Ever	18/23		24/29		34/30		23/26	

Variable	Baby aspirin		Adult aspirin		Acetaminophen		NSAID	
	Case/controls	OR*	Case/controls	OR* (95% CI)	Case/controls	OR* (95% CI)	Case/controls	OR* (95% CI)
BMI (kg/m^2)								
<25								
Never	222/130	1.46 (0.73–2.95)	209/124	0.53 (0.27–1.03)	214/130	0.92 (0.47–1.82)	219/113	0.65 (0.34–1.22)
Ever	47/27		60/33		55/27		50/44	
25–29								
Never	156/127	0.46 (0.23–0.90)	131/124	0.75 (0.41–1.37)	136/139	0.95 (0.49–1.82)	144/126	0.71 (0.38–1.32)
Ever	21/43		46/46		41/31		33/44	
≥30								
Never	103/158	0.67 (0.35–1.29)	99/155	0.63 (0.34–1.18)	100/163	1.04 (0.55–1.96)	90/147	0.89 (0.50–1.59)
Ever	30/53		34/56		33/48		43/64	

*Adjusted for age, race, years of education, smoking pack-years, BMI, history of COLD, family history of lung cancer, history of cardiovascular disease, history of arthritis, and education X BMI.