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Research Article

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Nonsteroidal Anti-Inflammatory Drug and Aspirin Use in Relation to Lung Cancer Risk among Postmenopausal Women

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Abstract

Background: Results from prospective studies suggest that nonsteroidal anti-inflammatory drugs (NSAID) may decrease lung cancer risk; however, any protective effect appears to be most evident in men.

Methods: We evaluated the associations between NSAID use and lung cancer incidence in postmenopausal women in the Women's Health Initiative (WHI) adjusting for female-specific potential confounders such as hormone therapy in addition to smoking histories and other potential confounders. We identified 143,841 women from ages 50 to 79 and 1,902 centrally confirmed lung cancer cases were included in the analysis. We used Cox regression models to estimate HRs and their 95% confidence intervals (CI).

Results: Compared with nonuse, regular NSAID use was not associated with overall lung cancer incidence (NSAID use >10 years HR 0.87; 95% CI, 0.71–1.08, $P_{trend} = 0.13$). No statistically significant associations were found when examined by histologic subtypes and although there was a trend of decreased risk with longer duration of NSAID use in the adenocarcinoma subtype, this was not statistically significant (NSAID use >10 years HR 0.80; 95% CI, 0.58–1.10; $P_{trend} = 0.07$).

Conclusion: Our study did not show that NSAID use is associated with lung cancer risk in women even after adjusting for female-specific confounders. There was a trend of decreased risk in the adenocarcinoma subtype; however, this was not statistically significant.

Impact: Future studies will need to take in account the various molecular subtypes of non–small cell lung cancer to further elucidate the role of NSAIDs in lung cancer, especially for the adenocarcinoma subtype. *Cancer Epidemiol Biomarkers Prev; 24(5); 790–7. ©2015 AACR.*

Introduction

The potential chemopreventive effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) on cancer has been reported since the 1980s with various observational studies suggesting beneficial effect on prevalent cancers such as colorectal, breast, and lung cancer (1, 2). Potential anticarcinogenic mechanisms of NSAIDs include inhibition of the COX pathway, which is involved in inflammation, apoptosis, and angiogenesis (3), and overexpression of COX2 has shown to increase the survival of lung adenocarcinoma *in vitro* (4). Also, NSAID-induced tumor regression has been observed in lung cancer mouse models (5). In addition, it has been reported that up to 70%–90% of non–small cell lung cancers, particularly adenocarcinoma subtype, overexpress COX2 enzyme (6, 7).

Several prospective cohort studies have investigated the relationship between NSAID use and lung cancer risk. Published cohort studies include the Vitamin and Lifestyle Study (VITAL), Iowa Women's Health Study (IWHS), Health Professional Follow-Up Study (HPFS), National Health and Nutrition Examination Survey (NHANES), Cancer Prevention Study II (CPS), and the Nurses' Health Study (NHS), which have reported HRs ranging from 0.69 to 1.10 (8–13). The inconsistent results may be due to heterogeneity in exposure definition such as dosage, frequency, duration of use, and adjusted covariates.

Inconsistencies between studies are further complicated by possible effect modification by gender with decreased risks primarily reported among men but not in women, suggesting either a real biologic difference or residual confounding by female-specific factors, such as postmenopausal hormone therapy. Preclinical studies show that female hormones may play a significant role in lung carcinogenesis (14, 15) and postmenopausal estrogen and progestin combination hormone use has been associated with increased lung cancer mortality in the Women's Health Initiative (WHI) hormone therapy (HT) trial (16). In the CPS cohort, long-term daily aspirin users were more likely to be HT users compared with non-aspirin users (41% vs. 30%; ref. 12), and similarly in the NHS, current

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aspirin users were more likely to be HT users (36% vs. 28%; ref. 13). This suggests that HT use may confound the association between NSAID use and lung cancer in studies that include postmenopausal women; thus, HT may be an important covariate which needs to be adjusted when evaluating aspirin and NSAID use in relation to lung cancer risk in women.

We report here on our investigation into the association between use of aspirin and non-aspirin NSAIDs and lung cancer risk in the WHI, a large multicenter prospective study of postmenopausal women in the United States. We recently reported the results of our investigation on the association between NSAID use and overall cancer risk in women within the WHI and this study included results in overall lung cancer (17). In the current study, we will expand on the reported results by further examining the associations by histologic subtypes and smoking status.

Materials and Methods

Study population

The WHI is a large study of postmenopausal women designed to investigate the determinants of major chronic diseases in women. Approximately 161,000 postmenopausal women, ages 50–79, were recruited at 40 clinical centers across the United States between September 1993 and December 1998 (18, 19). The study consisted of an observational study (OS) and clinical trials (CT) with aims to identify risk factors and develop prevention strategies for major causes of morbidity and mortality in postmenopausal women including cancer, cardiovascular disease, and osteoporotic fractures. The details of study design have been previously described (20, 21).

The WHI-CT ($n = 68,133$; trial registration: clinicaltrials.gov identifier, NCT00000611) included three overlapping components: two placebo-controlled hormone therapy trials [estrogen-alone ($n = 10,739$) and estrogen plus progestin ($n = 16,608$)]; a diet modification compared with usual diet trial ($n = 48,836$); and a calcium/vitamin D supplementation placebo controlled trial ($n = 36,282$). Participants in the WHI-OS were 93,676 women who were screened for participation in the CT but were ineligible or unwilling to participate, or who were directly recruited (21). Participants provided written informed consent and the WHI protocol was approved by institutional review boards at each participating institutions (19, 20). At baseline, women with history of any cancer except non–melanoma skin cancer ($n = 16,255$), women with missing baseline medication collection ($n = 2$), and missing baseline smoking status ($n = 2,126$) were excluded. After exclusions, there were 143,841 women available for inclusion in the analysis.

Data collection

WHI participants attended baseline screening visits, during which they completed self-administered questionnaires that collected detailed information on demographics, medical and reproductive history, family history of cancer, physical activity, and other risk factors. Women in the CT were followed regularly at annual clinic visits and exposure data were updated at 3, 6, and 9 years from randomization. Participants in the HT trial also had 6-month follow ups in their first 2 years. The participants in the OS were initially assessed at a baseline screening visit in which demographic, baseline biometric, and exposure data were collected. Participants were mailed annual forms for updated exposure data and medical history and they returned for a follow-up visit at 3 years after entry. Medication and supplement inventory was repeated at the year 3 visit (20).

Case ascertainment

Incident lung cancers were identified through self-reports semiannually for CT participants and annually for OS participants, or by death certificates. Self-reported cases of lung cancer were confirmed with a pathology report. Reports of death were confirmed by medical record and death certificate review at the clinical coordinating center. National Death Index was used for participants who could not be contacted. The initial assignment of an outcome was assigned by the local clinical center physician adjudicator and this was further assessed by central review (22). All outcomes including lung cancers were centrally adjudicated by reviewers blinded to randomization assignments. Cancer stage, histology, and grade were coded per Surveillance, Epidemiology and End Results guidelines (16). At the end of September 2010, 1,902 incident lung cancer cases were identified after 11.4 years of follow up.

Exposure variable (NSAIDs)

The primary exposure variables were nonsteroidal anti-inflammatory drug (NSAID) use which included aspirin and non-aspirin NSAIDs. Non-aspirin NSAIDs included non-aspirin salicylates, ibuprofen, indomethacin, naproxen, piroxicam, celecoxib, and others. Details on medication usage were collected from baseline questionnaires and were updated at year 3 clinic visit for the OS and at years 1, 3, 6, and 9 for CT. Participants were asked to bring all prescription and over-the-counter medications that they used regularly. A regular NSAID user was defined as use of at least twice a week in each of the 2 weeks preceding the interview. Regular users were further asked for the type of medication, dosage, and duration of use (21).

Smoking exposure and other covariates

The adjusted smoking covariates were assessed at WHI enrollment and include smoking status (never, former, current), pack-years smoking, age at smoking initiation, years since quitting for former smokers, and environmental smoking exposure. Smoking status was obtained based on self-report on standard questionnaires. Participants were asked on their initial questionnaire whether they were current or former smokers. Former smokers were asked the age at which they discontinued smoking and both current and former smokers were asked to report their average number of cigarettes smoked per day, years of smoking, and the age at initiation. Never smokers were defined as smoking less than 100 cigarettes in their entire life. Participants with missing smoking status were excluded at baseline. Environment smoking (passive smoking) exposure data were collected only in the OS. Participants were asked if they had ever lived with someone who smoked cigarettes inside their homes, both when they were less than 18 years old and when they were 18 years or older. If so, the number of years lived with a smoker was assessed (21). Inclusion of this covariate in multivariate analysis did not change the risk estimates thus was not included in the final multivariate model.

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Covariates other than smoking included ethnicity, body mass index, alcohol intake, use of multivitamins, postmenopausal hormone use, reproductive history, fruit and vegetable intake, family history of lung cancer, personal history of heart, and respiratory diseases. Data on covariates were obtained by self-report on questionnaires and dietary intake was assessed by a semiquantitative food frequency questionnaire (21). Reproductive history including parity and age at menopause were initially included as covariates, however, these were removed from the final model as they did not significantly alter the point estimates in the multivariate models.

Special care was taken for HT adjustment as this was associated with increased lung cancer mortality and a nonstatistical increase in lung cancer incidence in a previously published analysis of WHI-HT trial (16). Prior use of HT was assessed at baseline via personal interviews in both the CT and OS. In the HT trial, the participants in the placebo arm were considered to be never/former users based on the baseline data. Participants in the intervention arm were considered to be current users.

Statistical analysis

Cox proportional hazards models were used, with time from enrollment as the basic time variable with stratification on baseline age, smoking status (never/former/current), and cohort (CT vs. OS), to estimate the HRs of lung cancer incidence in each exposure category compared with a reference category to evaluate the association between NSAID use and lung cancer incidence. For continuous variables, *P* values for linear trend were calculated using the Cochran–Mantel–Haenszel test. The multivariate models adjusted for the aforementioned covariates and also were adjusted for randomization in the trials. In regards to smoking adjustment, age at started smoking was modeled as a linear term using the median of the reported age category and years since quitting smoking was also modeled as a linear term subtracting the median of the age category at quitting from age at baseline. Pack-years smoking was modeled as a categorical term. Updated NSAID data were used in time-dependent models taking in account the updated medication information in follow up questionnaires. In the time-dependent models of various NSAID types (e.g., ASA only, non-ASA NSAID only), participants were censored if they started a different type of NSAIDs during follow up. Participants who initially reported to be a NSAID user who reported no use at a later time remained within the user category and their duration of use remained as reported at the time of last use. In the absence of updated information, participants remained in the analysis and their NSAID user status remained as last reported if their last medication status was a user. However, if their last status was nonuser and they had any prior use, they were retained in the models as a user. In regards to the duration of NSAID use, participants who reported regular NSAID use were asked about the duration of use at each follow up and the reported duration of use at each update was considered to represent cumulative use. Separate analyses were performed stratifying by smoking status (never, former, current) and histologic subtypes (adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma). Participants were right censored from analysis when any other cancer, with the exception of non–melanoma skin cancer, was reported or at the time of non–lung cancer death, withdrawal from the study or loss of contact. Statistical analyses were performed using SAS 9.2 and a two-sided $P < 0.05$ was considered statistically significant.

Results

The characteristics of participants are shown in Table 1 by duration of NSAID use at baseline. Among the 161,808 participants in the CT and OS, 143,841 participants were included in the analysis after exclusions were made. Among the 143,841 participants, 1,902 centrally confirmed lung cancer cases were identified as of September 2010. The most frequent histologic subtypes were adenocarcinoma (46%), squamous cell carcinoma (14%), and small-cell carcinoma (10%). Less frequent subtypes included large cell carcinoma, carcinoid tumors, spindle cell carcinoma, and others.

Among the participants, 51% had no smoking history while 42% were former and 7% were current smokers. Any regular NSAID use was reported by 34.6% of the participants while 18.6% reported use of aspirin only and 12.3% reported non-aspirin NSAID use only.

After adjusting for age, women with greater than 10 years of NSAID use were more likely to have a history of cardiovascular disease, more likely to use multivitamins and have a history of HT use compared with non-NSAID users. They were also slightly more likely to be former or current smokers (Table 1).

Table 2 shows the association between lung cancer and NSAID use by type and duration. The initial model adjusted for various smoking variables including smoking status, pack-years of smoking, age started, and years since quitting smoking. The second model further adjusted for hormone therapy use and the final multivariate model included other covariates including body mass index, multivitamin use, history of cardiovascular disease, fruit and vegetable intake, and alcohol use (Table 2). After adjustment for the above covariates, no significant associations between overall lung cancer and NSAID use by type and duration were observed (NSAID use >10 years; HR 0.87; 95% CI, 0.71–1.08; $P_{trend} = 0.13$). The risk estimates were changed somewhat with smoking adjustment but they were little altered by adjustment for HT or other covariates in the multivariate models. For example, the risk estimate for NSAID use >10 years without any smoking adjustments was HR 0.96; 95% CI, 0.78–1.19; $P_{trend} = 0.45$.

We also examined associations between NSAID use and lung cancer risk defined by histologic subtype. Again, there were no statistically significant associations; however, there was a statistically nonsignificant trend of decreased HR with longer duration of all NSAID use ($P_{trend} = 0.07$) and aspirin use ($P_{trend} = 0.08$) for adenocarcinoma subtype (Table 3). No significant associations were observed for squamous cell and small-cell lung cancers although case numbers were small. Finally, in analyses stratified on smoking status, no significant interactions were observed (Table 4).

We performed several sensitivity analyses to ensure the robustness of our findings. As the participants in OS did not provide updated information on NSAID use at years 6 and 9, we performed an analysis without updates at years 6 and 9 and results were not significantly different from the primary analysis (NSAID use >10 years; HR 0.91; 95% CI, 0.73–1.13; $P_{trend} = 0.20$). In another analysis with all updates but which only included participants from CT, results were also not significantly altered from

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Table 1. Baseline characteristics and lung cancer risk factors by duration of NSAID exposure in the Women's Health Initiative (WHI) observational study and clinical trial ($n = 143,841$)

	Nonuser ($N = 94,051$) *N* (%)	<5 year ($N = 30,199$) *N* (%)	5–10 years ($N = 12,171$) *N* (%)	>10 years ($N = 7,420$) *N* (%)
Age group at screening, mean (SD)	62.6 (7.2)	64.0 (7.1)	64.1 (7.2)	63.5 (7.2)
50–59	34,590 (36.78)	8,517 (28.2)	3,433 (28.21)	2,342 (31.56)
60–69	41,573 (44.20)	14,238 (47.15)	5,535 (45.48)	3,360 (45.28)
70–79	17,888 (19.02)	7,444 (24.65)	3,203 (26.32)	1,718 (23.15)
Race/ethnicity				
White	75,066 (79.81)	25,746 (85.25)	10,858 (89.21)	6,759 (91.09)
Black	9,496 (10.10)	2,490 (8.25)	708 (5.82)	332 (4.47)
Hispanic	4,406 (4.68)	1,014 (3.36)	297 (2.44)	151 (2.04)
American Indian	415 (0.44)	122 (0.4)	46 (0.38)	33 (0.44)
Asian/Pacific Islander	3,249 (3.45)	454 (1.5)	126 (1.04)	61 (0.82)
Unknown	1,419 (1.51)	373 (1.24)	136 (1.12)	84 (1.13)
Smoking status				
Never	48,983 (52.08)	15,300 (50.66)	5,872 (48.25)	3,689 (49.72)
Past	38,403 (40.83)	12,988 (43.01)	5,472 (44.96)	3,131 (42.2)
Current	6,665 (7.09)	1,911 (6.33)	827 (6.79)	600 (8.09)
History of emphysema				
No	85,451 (96.58)	27,495 (96.34)	11,129 (96.11)	6,767 (96.31)
Yes	3,026 (3.42)	1,045 (3.66)	451 (3.89)	259 (3.69)
History of CVD				
No	86,858 (92.35)	25,707 (85.13)	10,071 (82.75)	6,567 (88.5)
Yes	7,193 (7.65)	4,492 (14.87)	2,100 (17.25)	853 (11.5)
Family history of cancer				
No	31,126 (34.54)	9,565 (33.15)	3,764 (32.35)	2,361 (33.01)
Yes	58,985 (65.46)	19,290 (66.85)	7,873 (67.65)	4,792 (66.99)
BMI (kg/m^2)				
<25	34,280 (36.78)	9,091 (30.34)	3,950 (32.73)	2,606 (35.42)
≥25	58,931 (63.22)	20,875 (69.66)	8,120 (67.27)	4,752 (64.58)
Multivitamin use				
No	60,327 (64.14)	17,039 (56.42)	6,566 (53.95)	4,137 (55.75)
Yes	33,722 (35.86)	13,160 (43.58)	5,605 (46.05)	3,283 (44.25)
Fruit/vegetable servings per day				
0–2	14,255 (15.65)	4,350 (14.8)	1,614 (13.63)	1,086 (14.94)
>2–4	35,893 (39.42)	11,637 (39.6)	4,607 (38.90)	2,869 (39.46)
>4–6	25,274 (27.76)	8,298 (28.24)	3,443 (29.07)	2,158 (29.68)
>6	15,638 (17.17)	5,098 (17.35)	2,178 (18.39)	1,158 (15.93)
Postmenopausal HT use[a]				
Never	36,750 (39.11)	10,627 (35.22)	3,928 (32.31)	2,473 (33.34)
Past E-alone	7,419 (7.89)	2,720 (9.01)	1,055 (8.68)	645 (8.7)
Past E+P	5,139 (5.47)	1,677 (5.56)	740 (6.09)	454 (6.12)
Current E-alone	22,533 (23.98)	8,197 (27.16)	3,498 (28.77)	2,035 (27.44)
Current E+P	22,131 (23.55)	6,955 (23.05)	2,938 (24.16)	1,810 (24.4)

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; E, unopposed estrogen; E+P, estrogen and progestin combination.

[a]Current use includes participants randomized to the active arms of the hormone trial, or current use reported at baseline for participants not in the hormone trial. Past use includes participants randomized to the placebo arms of the hormone trial who reported either past or current use at baseline and past use reported at baseline for participants not in the hormone trial.

the primary analysis (NSAID use >10 years; HR 0.86; 95% CI, 0.42–1.18; $P_{trend} = 0.33$).

Discussion

In this analysis of lung cancer incidence, no significant associations between overall NSAID use and lung cancer were observed. However, there was a statistically nonsignificant trend of decreased risk of adenocarcinoma with longer duration of NSAID use.

The effect of NSAID use in lung adenocarcinoma has been inconsistent in the literature with reports of both protective and null findings. The VITAL cohort, a prospective study of approximately 77,000 participants, reported a decreased lung cancer incidence with NSAID use (>4.2 days/week use for >10 years) and the association was strongest for adenocarcinoma (HR 0.59; 95% CI, 0.37–0.94), whereas no significant association was seen in squamous cell carcinoma (HR 0.97; 95% CI, 0.57–1.64; ref. 8). In contrast, in the IWHS in which 27,000 women were assessed, there were no significant associations in overall lung cancer or in the adenocarcinoma subtype (9). Of note, this study assessed the role of current NSAID use and did not report the association by duration of use. Other prospective observational studies including the Cancer Prevention Study, National Health and Nutrition Examination Study, the NHS, and HPFS study did not report risk estimates by histologic subtypes (10–13).

There have been a few randomized studies that aimed to assess the effect of aspirin in cancer. One of these studies is the Women's Health Study in which approximately 40,000 women were randomized to receive either aspirin 100 mg every other day or placebo and the primary outcome was newly

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Table 2. HRs of lung cancer by type and duration of NSAID use in the WHI clinical trial and observational study

	Participants, *n*	Cases[a], *n*	Smoking-adjusted[b] HR (95% CI)	Smoking and HT-adjusted[c] HR (95% CI)	Multivariate-adjusted[d] HR (95% CI)
All NSAID					
Nonuser	94,051	1,176	1 (reference)	1 (reference)	1 (reference)
<5 years	30,199	439	1.01 (0.90–1.12)	1.00 (0.90–1.11)	0.98 (0.87–1.11)
5–10 years	12,171	188	1.07 (0.93–1.23)	1.06 (0.92–1.22)	1.03 (0.89–1.20)
>10 years	7,420	99	0.90 (0.74–1.11)	0.90 (0.73–1.10)	0.87 (0.71–1.08)
P_{trend}[e]			*0.10*	*0.10*	*0.13*
ASA only: <100 mg					
Nonuser	94,051	848	1 (reference)	1 (reference)	1 (reference)
<5 year	4,901	61	1.06 (0.86–1.31)	1.06 (0.85–1.31)	1.02 (0.82–1.28)
≥5 years	1,239	14	1.19 (0.86–1.63)	1.18 (0.86–1.62)	1.16 (0.83–1.62)
P_{trend}[e]			*0.61*	*0.63*	*0.50*
ASA only: >100 mg					
Nonuser	94,051	870	1 (reference)	1 (reference)	1 (reference)
<5 years	10,974	116	1.05 (0.88–1.26)	1.04 (0.87–1.24)	1.00 (0.83–1.22)
≥5 years	9,704	111	1.05 (0.87–1.28)	1.05 (0.86–1.28)	1.02 (0.83–1.26)
P_{trend}[e]			*0.09*	*0.10*	*0.15*
ASA only (all)					
Nonuser	94,051	955	1 (reference)	1 (reference)	1 (reference)
<5 years	15,875	203	1.01 (0.88–1.17)	1.01 (0.87–1.16)	0.97 (0.84–1.13)
5–10 years	6,002	81	1.12 (0.93–1.35)	1.12 (0.93–1.34)	1.03 (0.84–1.26)
>10 years	4,941	58	0.85 (0.65–1.11)	0.85 (0.65–1.11)	0.82 (0.62–1.08)
P_{trend}[e]			*0.12*	*0.12*	*0.15*
Non-ASA NSAID only					
Nonuser	94,051	880	1 (reference)	1 (reference)	1 (reference)
<5 years	12,257	124	1.02 (0.86–1.20)	1.01 (0.85–1.19)	1.02 (0.85–1.22)
5–10 years	4,506	41	0.92 (0.68–1.25)	0.91 (0.67–1.23)	0.90 (0.66–1.24)
>10 years	958	9	0.91 (0.51–1.61)	0.89 (0.50–1.58)	0.78 (0.42–1.47)
P_{trend}[e]			*0.81*	*0.77*	*0.46*

Abbreviations: ASA, aspirin; CI, confidence interval; CVD, cardiovascular disease.

[a]Case numbers for nonusers differ in the various categories due to time-dependent censoring. Follow-up time was censored if participants started a NSAID that is different from the defined NSAID in the category. For example, in the ASA only analysis, if nonusers started taking a non-ASA during follow up, they were censored from analysis.

[b]From a Cox proportional hazards regression model stratified by 5-year age intervals, CT versus OS, extension study enrollment, and smoking status (never/former/current); adjusted for linear age, pack years of smoking, age started, and years since quitting smoking.

[c]Stratified and adjusted as in Model 1, with additional adjustment for postmenopausal hormone use (never, past/E-alone, past/E+P, current/E-alone, current/E+P).

[d]Stratified and adjusted as in Model 2, with additional adjustment for BMI, race/ethnicity, history of emphysema, history of CVD, family history of cancer, alcohol intake, multivitamin use, fruit/vegetable intake, and randomization arm of the DM trial.

[e]Tested using a linear form of years of use.

diagnosed invasive cancers. After 10 years of active intervention, the study reported that there was no reduction in risk of incident cancers [relative risk (RR) 1.01; 95% CI, 0.94–1.08] except for lung cancer in which there was a trend of reduced risk (RR 0.78; 95% CI, 0.59–1.03; ref. 23). There was no reduction in cancer mortality overall or by site, except for lung cancer mortality (RR 0.70; 95% CI, 0.50–0.99). However, this was not confirmed in a subsequent follow-up analysis after 18 years of follow up (lung cancer incidence HR 1.04; 95% CI, 0.86–1.26) and no significant outcomes were observed in adenocarcinoma versus non-adenocarcinoma metastases in all cancer (24).

Although we did not examine the associations in lung cancer mortality, studies indicate that aspirin may decrease the risk of lung cancer mortality, particularly in adenocarcinoma. An inverse association for adenocarcinoma was observed in the study by Rothwell and colleagues in which the associations between daily aspirin for 5 years or longer and mortality from various cancer sites were evaluated in a pooled analysis of individual patient data from randomized trials (25). This study showed that for lung cancer, the lower risk was confined to adenocarcinoma. For instance, the HR at 20-year follow up was 0.55 (95% CI, 0.33–0.94) for adenocarcinoma, whereas the HR in squamous cell was 1.26 (95% CI, 0.73–2.18).

A potential reason for the inconsistent results across various studies of NSAID use in lung cancer is that the effect of aspirin on lung cancer may vary by the driver molecular pathway of each tumor. The past decade has been marked by significant advances in our understanding of lung cancer biology and it is now known that lung adenocarcinoma is not a homogeneous disease but is comprised of various molecular subtypes with distinct oncogenic drivers such as an EGFR mutation and anaplastic lymphoma kinase (ALK) rearrangement (26). There is evidence from the literature that the role of aspirin in colorectal cancer risk differs by BRAF (V-Raf murine sarcoma viral oncogene homolog B) mutational status in which the protective effect is observed in BRAF wild-type but not in BRAF-mutated cancers (27). This is thought to be due to the upregulation of COX2 by Raf kinases whose activity is upregulated in BRAF mutation–positive colorectal cancers (28, 29). Similarly, the effect of aspirin on lung cancer may differ in the various molecular subtypes and the inconsistent risk estimates may be due to differing prevalence of the various molecular subtypes. Therefore, further molecular epidemiologic studies are needed to clarify the role of aspirin and other NSAIDs in the various molecular subtypes of lung cancer.

In this study, one of the objectives was to evaluate whether the associations of NSAID use is confounded by HT use and other

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Table 3. HRs of lung cancer histology subtypes by type and duration of NSAID use in the WHI clinical trial and observational study

	Adenocarcinoma		Squamous cell		Small cell	
	Cases, *n*	HR (95% CI)[a]	Cases, *n*	HR (95% CI)[a]	Cases, *n*	HR (95% CI)[a]
All NSAID						
Nonuser	538	1 (reference)	162	1 (reference)	119	1 (reference)
<5 years	212	0.98 (0.83–1.16)	63	1.03 (0.77–1.39)	36	0.80 (0.54–1.18)
5–10 years	85	0.86 (0.68–1.09)	22	0.85 (0.55–1.30)	23	1.29 (0.83–2.00)
>10 years	39	0.80 (0.58–1.10)	17	0.80 (0.45–1.42)	13	0.89 (0.46–2.73)
P_{trend}[b]		*0.07*		*0.26*		*0.51*
ASA only (all)						
Nonuser	443	1 (reference)	130	1 (reference)	93	1 (reference)
<5 years	102	0.96 (0.77–1.19)	27	1.03 (0.70–1.51)	15	0.86 (0.51–1.44)
≥5 years	61	0.80 (0.61–1.05)	17	0.59 (0.34–1.01)	17	1.25 (0.75–2.07)
P_{trend}[b]		*0.08*		*0.22*		*0.63*
Non-ASA NSAID only						
Nonuser	414	1 (reference)	125	1 (reference)	89	1 (reference)
<5 years	62	1.16 (0.91–1.49)	19	1.31 (0.72–1.80)	8	0.69 (0.34–1.35)
≥5 years	23	0.78 (0.50–1.21)	11	1.68 (0.91–3.08)	4	0.44 (0.14–1.40)
P_{trend}[b]		*0.12*		*0.65*		*0.26*

[a]From a Cox proportional hazards regression model stratified by 5-year age intervals, CT versus OS, extension study enrollment, and smoking status (never/former/current); adjusted for linear age, pack years of smoking, age started and years since quitting smoking, postmenopausal hormone use (never, past/E-alone, past/E+P, current/E-alone, current/E+P), BMI, race/ethnicity, history of emphysema, history of CVD, family history of cancer, alcohol intake, multivitamin use, fruit/vegetable intake, and randomization arm of the DM trial.
[b]Tested using a linear form of years of use.

reproductive factors. Literature has reported that there appears to be a gender-specific chemopreventive effect of NSAID use. For instance, the VITAL study reported a decreased risk in men (HR 0.66; 95% CI, 0.47–0.92) but not in women (HR 1.07; 95% CI, 0.75–1.51) although there was no significant effect modification by gender when the analysis was limited to adenocarcinoma subtype (8). A gender difference was also observed in the National Health and Nutrition Examination Study where there was a decrease in risk of lung cancer mortality in men (RR 0.69; 95% CI, 0.49–0.96) but not in women (RR 1.10; 95% CI, 0.67–1.81; ref. 11). Given the previous report from the WHI-HT trial which reported increased lung cancer mortality with HT use (16), we hypothesized that the observed null effect in the above studies may have been due to inadequate adjustment for HT use and reproductive factors. However, the adjustment for these covariates in our analysis did not alter the HR estimates in overall lung cancer. The apparent null association in women may be due to an interaction between the COX and estrogen pathways. Studies indicate that there may be a cross-talk between COX and estrogen pathways; for example, an analysis of NHS participants showed that women who were regular NSAID users had lower levels of estradiol (30) and increased proinflammatory prostaglandin E2 production was associated with increased aromatase activity (31).

The strengths of this study are that this is a large study with a long follow-up period and well annotated exposure data including updated exposure information on dose and duration, and

Table 4. HRs of lung cancer by baseline smoking status and type and duration of NSAID use in the WHI clinical trial and observational study

	Never smokers		Former smokers		Current smokers	
	Cases, *n*	HR (95% CI)[a]	Cases, *n*	HR (95% CI)[a]	Cases, *n*	HR (95% CI)[a]
All NSAIDs						
Nonuser	203	1 (reference)	612	1 (reference)	361	1 (reference)
<5 years	70	1.02 (0.78–1.35)	259	1.00 (0.86–1.17)	110	0.91 (0.74–1.13)
5–10 years	20	0.93 (0.63–1.39)	109	0.99 (0.80–1.22)	59	1.19 (0.91–1.56)
>10 years	11	0.60 (0.32–1.14)	53	1.02 (0.77–1.34)	35	0.76 (0.50–1.14)
P_{trend}[b]		*0.16*		*0.64*		*0.24*
Test of heterogeneity[c]						*P = 0.80*
ASA only (all)						
Nonuser	178	1 (reference)	458	1 (reference)	319	1 (reference)
<5 years	41	1.08 (0.76–1.51)	106	0.92 (0.74–1.13)	56	1.02 (0.78–1.33)
≥5 years	14	0.80 (0.50–1.26)	77	1.00 (0.79–1.26)	48	0.92 (0.67–1.25)
P_{trend}[b]		*0.20*		*0.93*		*0.08*
Test of heterogeneity[c]						*P = 0.54*
Non-ASA NSAID only						
Nonuser	161	1 (reference)	441	1 (reference)	278	1 (reference)
<5 years	18	1.02 (0.66–1.57)	73	1.31 (0.90–1.43)	33	0.78 (0.54–1.14)
≥5 years	7	0.77 (0.36–1.64)	29	0.84 (0.57–1.24)	14	1.04 (0.63–1.71)
P_{trend}[b]		*0.81*		*0.33*		*0.77*
Test of heterogeneity[c]						*P = 0.72*

[a]From a Cox proportional hazards regression model stratified by 5-year age intervals, CT versus OS, and extension study enrollment; adjusted for linear age, for smokers: pack years of smoking, age started and years since quitting smoking if former, postmenopausal hormone use (never, past/E-alone, past/E+P, current/E-alone, current/E+P), BMI, race/ethnicity, history of emphysema, history of CVD, family history of cancer, alcohol intake, multivitamin use, fruit/vegetable intake, and randomization arm of the DM trial.
[b]Tested using a linear from of years of use.
[c]Tested for an interaction of duration of use (linear) and smoking status (never/former/current).

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detailed data on covariates such as smoking history, reproductive history and HT use, and centrally confirmed cancer diagnosis. Despite this, this analysis was still limited by small numbers when stratified by histologic subgroups. Also, the analysis may have been affected by misclassification of NSAID use, particularly in the OS, where NSAID use was updated twice (baseline and year 3), whereas in the CT, the use was updated at multiple time points. In addition, the role of frequency of use could not be fully addressed in this study as participants were asked whether they used NSAIDs at least twice a week but no additional data on frequency (e.g., daily versus alternate day use) were collected. The exposure data were based on self-reported use thus studies incorporating biomarker measurements of anti-inflammatory effect would strengthen future studies investigating the role of NSAIDs.

Lung cancer continues to be the leading cause of cancer mortality globally and there is a need to continue to develop prevention strategies to reduce its disease burden. Smoking cessation is imperative in a successful lung cancer prevention program but there is a need for additional prevention strategies for the growing number of former smokers who have successfully quit smoking. Therefore, ongoing research in identifying potential chemopreventive agents is warranted. Future studies of NSAIDS in lung cancer will need to take in account the various molecular subtypes in addition to the histologic subtypes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.S. Baik, J. Wactawski-Wende
Development of methodology: C.S. Baik, T.M. Brasky, M. Pettinger
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Wactawski-Wende, R.L. Prentice
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.S. Baik, T.M. Brasky, M. Pettinger, R.L. Prentice
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