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Association of Non-Steroidal Anti-Inflammatory Drugs with Lung Cancer: Results from a Large Cohort Study

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Abstract

Background—Lung cancer is the most common cause of cancer-related mortality. Smoking cessation is crucial to decrease risk but additional prevention modalities are needed. Use of non-steroidal anti-inflammatory drugs (NSAIDs) may be promising.

Methods—The study was a prospective cohort of 77,125 men and women aged 50–76 years from Washington State recruited in 2000–2002 (the VITAL study). Lung cancer cases were identified through the Seattle-Puget Sound SEER cancer registry during 5 years of follow-up. Hazard ratios (HRs) associated with 10 year average use of total NSAIDs (excluding low-dose aspirin) and specific categories of NSAIDs were calculated for total incident lung cancer and specific morphologies.

Results—665 lung cancer cases were identified. After adjusting for smoking, age, gender, and acetaminophen use, there was a borderline-significant inverse trend with total NSAID use (>4.2 days/week over 10 years vs. none, HR 0.82, 95% CI, 0.64–1.04, P for trend 0.05). The association was strongest for adenocarcinoma (HR 0.59, 95% CI, 0.37–0.94, P for trend 0.01) and appeared to be limited to men (HR 0.66, 95% CI, 0.47–0.92, P for trend 0.01) and to long-term (≥ 10 years) former smokers (HR 0.65, 95% CI, 0.44–0.96, P for trend 0.04). There were no appreciable differences by NSAID type.

Conclusions—Total NSAID use was associated with a small reduced risk of lung cancer which was strongest for adenocarcinoma, men, and long-term former smokers. These findings are supported by known lung carcinogenesis mechanisms, and suggest that NSAIDS may be useful for chemoprevention.

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Keywords

lung cancer; adenocarcinoma; non-steroidal anti-inflammatory drugs; cyclooxygenase-2; chemoprevention

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the United States (US) (1). Smoking cessation is very important to reduce the risk of developing lung cancer but absolute risk remains elevated after cessation (2), emphasizing the importance of additional prevention modalities.

The cyclooxygenase 2 (COX-2) pathway is important in the pathogenesis of lung cancer, particularly adenocarcinoma (3–6). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX-2 enzyme and may reduce the incidence of lung cancer through several mechanisms (7–9). A meta-analysis indicated a lower risk of incident lung cancer in NSAID users with a relative risk of 0.79 (95% CI, 0.66–0.95) and dose-response analyses found longer term use seemed to be more strongly associated with a decreased risk (10).

We used data from a large prospective cohort, the VITamin And Lifestyle (VITAL) study (11) to evaluate associations of 10 year average use of NSAIDs with incident lung cancer.

METHODS

The methods employed in VITAL have been described (11). 77, 719 participants (21.3% of the total number of mailed questionnaires), aged 50–76 years, living in Western Washington State, were followed after baseline questionnaire administration for incident lung cancer occurring from baseline (October 2000–December 2002) through December 31, 2006, by linkage to the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) registry. The Institutional Review Board of the Fred Hutchinson Cancer Research Center approved the protocol.

Participants with a self-reported previous diagnosis of lung cancer or for whom this datum was missing (n= 588), with lung cancer identified on a death certificate only (n = 4), or lung cancer morphology of lymphoma (n=2) were excluded. The censored date was the earliest date of withdrawal from the study (0.03%), death (3.9%) (ascertained from Washington state death files), move out of the SEER catchment area (5.4%), or last date of linkage to SEER. If a subject had multiple diagnoses of lung cancer, we used the time to first diagnosis.

Assessment of NSAID use

Respondents reported their use of regular or extra-strength aspirin, low-dose aspirin, ibuprofen, naproxen, celecoxib or rofecoxib, and acetaminophen (listed as generic and brand names) during the ten years prior to baseline. Women also reported the use of indomethacin and piroxicam. Subjects reported how many years they used each medication in the previous ten years (1–3, 4–8 or 9–10 years) and the usual number of days per week. (1–3, 4–6 or 7). For the analysis, we estimated total average use over the 10 years by multiplying usual days per week by the number of years, using the midpoints of the categories, divided by 10. Total NSAID use was estimated by summing average weekly use of all NSAIDs, except low-dose aspirin. Secondary analyses evaluated total non-aspirin NSAID use (all NSAIDs as above except regular/extra strength and low-dose aspirin), total aspirin use (excluding low-dose aspirin), and each NSAID individually.

Covariates

Tobacco—We adjusted all the analyses for multiple smoking variables as previously described (12)

Additional covariates—Demographic, socioeconomic factors, previous history of cancer and self-report of physician-diagnosed emphysema or chronic obstructive pulmonary disease (COPD) were recorded. We categorized family history of lung cancer as none or at least one first degree relative with lung cancer. Indications for NSAID use included self-report of a physician diagnosis of arthritis (rheumatoid and/or osteoarthritis), coronary artery disease (computed as a history of coronary artery bypass graft, angioplasty, angina, and/or "heart attack"), chronic pain, and/or chronic headaches.

Statistical Analysis

All statistical analyses were performed using Stata SE-9 (StataCorp, College Station, TX). Cox regression was used to estimate the hazard ratios (HR) for associations of NSAID use categories with incident lung cancer, with robust standard errors to eliminate traditional proportional hazards assumptions. Age was the time variable, with left truncation for age at baseline and censoring. Subjects with missing data on NSAID use or other covariates in the model were excluded from analysis. NSAID use was analyzed by categories of use and as indicator variables, to estimate hazard ratios for lung cancer. We categorized the exposures into four groups: never use and tertiles of use based on the distribution in the entire cohort. Only 5.1% of subjects reported celecoxib/rofecoxib use so we created a dichotomous variable of use and no use. We treated the NSAID use categories as a continuous variable to assess for trends in lung cancer risk.

Based on previous work, we used a model to adjust for confounding by cigarette smoking that included years smoked, pack-years, and a squared pack-years term along with age and gender (12). We adjusted regular aspirin use for non-aspirin NSAID use and vice versa. We evaluated whether education, acetaminophen use (which shares NSAID indications), COPD, previous history of cancer, family history of lung cancer, arthritis, coronary artery disease, chronic pain, and/or chronic headaches confounded the association of total NSAID use with lung cancer. Except for acetaminophen use, no variables changed the point estimates by $\geq 10\%$ or level of statistical significance for total NSAID; thus, only acetaminophen use was added to the model.

We examined whether the associations for NSAID use differed by lung cancer morphology by treating each morphology as a separate outcome, exclusive of the other morphologies, compared to subjects who did not develop lung cancer. We also looked for differences of the NSAID-lung cancer associations defined by smoking status and sex. Likelihood ratio tests were conducted to assess the interaction between NSAID use, analyzed as trend variables, and the subgroups. P values for interaction were obtained to compare the fit of the models with the interaction terms and without them. P values less than 0.05 were considered statistically significant.

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RESULTS

77,125 subjects met inclusion criteria and were followed for a mean of 5.0 years (SD 1.01 years); 665 subjects developed lung cancer. Frequent use of total NSAIDs was associated with a borderline trend of reduced incidence of lung cancer (Table 1). Non-aspirin NSAIDs and regular aspirin use were each associated with a non-significant decreased lung cancer risk. Use of low-dose aspirin was not associated with lung cancer (> 3 days/week vs. none, HR 1.09, 95% CI, 0.87–1.37, P for trend 0.52), whereas specific types of non-aspirin NSAIDs were associated with a small, non-significant reductions: ibuprofen (>1.4 days/week vs. none, HR 0.87, 95% CI, 0.65–1.17, P for trend 0.18), naproxen (>1.2 days/week vs. none, HR 0.71, 95% CI, 0.44–1.13, P for trend 0.24), and selective COX-2 inhibitors (any use compared to no use, HR 0.91, 95% CI, 0.74–1.11, P 0.35).

The most frequent use of total NSAIDs was associated with a reduced incidence of NSCLC (Table 2). Results were similar for both the non-aspirin NSAID and regular aspirin use with NSCLC, but did not reach statistical significance (data not shown). When NSCLC was stratified into subtypes, the risk reduction associated with total NSAID use was strongest for adenocarcinoma and NSCLC, NOS (Table 2). Total NSAID use, non-aspirin NSAID use, and regular aspirin use were neither associated with small cell lung cancers nor with the “other” morphology category. Low-dose aspirin use and selective COX-2 inhibitor use were also not associated with any morphology of incident lung cancer (data not shown).

There was evidence of effect modification by sex for total NSAID use (P for interaction =0.05) (Table 3). For men, frequent total NSAID use was associated with a decreased risk of lung cancer that was not seen for women. Of note, there was no evidence for effect modification by sex for adenocarcinoma (P for interaction = 0.65). More frequent total NSAID use was associated with reduced risk for adenocarcinoma in both men and women: (men: 3rd tertile vs. none, HR 0.51, 95% CI, 0.26–1.00, P for trend 0.03; women: 3rd tertile vs. none, HR 0.68, 95% CI, 0.36–1.27, P for trend 0.12)..

There was no appreciable effect modification by smoking status for total NSAID use (P for interaction = 0.22) though the only significant association was for subjects who had quit smoking ten or more years prior to baseline (Table 3).

Discussion

In this study, frequency of total long-term NSAID use (excluding low-dose aspirin) was associated with a borderline inverse association with incident lung cancer. Frequent use of total NSAIDs was associated with a significant 30–40% decreased incidence of NSCLC and adenocarcinoma. There was no clear difference by type of NSAID. There was evidence for effect modification by sex, as total NSAID use was significantly associated with a decreased risk for total lung cancer for men but not for women.

Our results are consistent with the meta-analysis of the association between NSAIDs and lung cancer that was strongest for 36 months or more of use (10). Our analysis has several advantages in that it is a large, prospective cohort of both sexes. We extensively evaluated smoking behaviors and other potential confounding factors, including indications for NSAID use, and modeled long-term NSAID use in a dose-response fashion. We evaluated the association of NSAID use with specific lung cancer morphologies to explore the underlying biologic mechanisms.

Lung adenocarcinoma may be the predominant morphology affected by NSAIDs. COX-2 is expressed at greater levels in lung adenocarcinoma compared to other histologies (3,4,13) and it is overexpressed in pre-malignant atypical adenomatous hyperplasia (14). COX-2

overexpression has been found to be associated with expression of the proliferation marker Ki-67 in adenocarcinoma but not squamous cell carcinoma (15) and a trial of subjects at risk of lung cancer given the selective COX-2 inhibitor celecoxib showed decreased levels of this same proliferation marker in bronchial biopsies (16). The observed association between total NSAID use and a decreased risk of adenocarcinoma adds to this evidence.

There was no clear evidence of effect modification by smoking status but there was evidence for a gender difference. A meta-analysis did not show a gender difference though the combined odds ratio was not significant for women (10). Recent studies limited to women have had conflicting results; the Iowa Women's Health Study did not show an association with either aspirin or non-aspirin NSAIDs with incident lung cancer (17) though a recent case-control analysis found a protective association (18). A lung cancer pathogenesis model showed that estradiol increased COX-2 production (19), which could lead to a potentiation of NSAIDs inhibitory effect on COX-2. In addition, given that COX-2 is associated with the production of aromatase (20,21), which is critical for estrogen production, it may be that the effects of COX-2 inhibition may differ according to background estrogen production.

Despite the biologic plausibility of our results, there are several potential limitations. First, residual confounding may be a factor. We were unable to adjust for environmental tobacco exposure or occupational exposures. Second, the measurement of long-term use of NSAIDs is based on recall and did not include pills per day; each of these issues may attenuate our results. Third, the VITAL cohort was predominantly white and includes fewer current smokers than the overall proportion of the U.S. as whole, limiting generalizability.

In conclusion, we found that long-term, frequent use of total non-steroidal anti-inflammatory drugs was associated with a decreased incidence of lung cancer with the strongest evidence for a protective association with adenocarcinoma. While we cannot exclude the possibility of residual confounding, our study was able to adjust for many confounders, most importantly smoking variables and health conditions associated with NSAID use. Importantly, the results are in agreement with underlying biological mechanisms of the COX-2 pathway and lung adenocarcinoma. While our results are promising, the known risks and benefits for current and former smokers of the various COX-2 inhibitor NSAIDs must be evaluated before they should be recommended as chemoprevention agents for lung cancer.

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Table 1

Hazard Ratios for Lung Cancer Associated with Ten Year Average Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAID Use*	Non-Lung Cancer (N=76,460) %	Lung Cancer (N=665) %	Adjusted hazard ratio†	Adjusted 95% Confidence Interval†
Total NSAID Use‡				
None	51.9%	50.9%	Referent	
1st Tertile (0.4–1.4 days/week)	18.1%	17.9%	0.94	(0.75–1.18)
2nd Tertile (>1.4–4.2 days/week)	17.1%	16.2%	0.83	(0.66–1.05)
3rd Tertile (>4.2 days/week)	13.0%	15.0%	0.82	(0.64–1.04)
P for trend§				0.05
Non-Aspirin NSAID Use‖				
None	67.8%	71.3%	Referent	
1st Tertile (0.4–1.19 days/week)	9.3%	8.8%	0.88	0.65–1.18
2nd Tertile (1.2–2.2 days/week)	12.9%	11.1%	0.89	0.68–1.16
3rd Tertile (> 2.2 days/week)	10.0%	8.8%	0.81	0.60–1.09
P for trend§				0.12
Regular Aspirin Use**				
None	75.4%	70.7%	Referent	
1st Tertile (0.4–1.4 days/week)	8.6%	10.1%	1.16	0.89–1.53
2nd Tertile (>1.4–3.0 days/week)	5.5%	4.3%	0.77	0.51–1.15
3rd Tertile (> 3.0 days/week)	10.5%	14.9%	0.90	0.71–1.15
P for trend§				0.31

* Percentages are of non-missing data though may not add to 100% secondary to rounding. No subjects were missing age or gender information. 769 (1.0%) and 916 (1.1%) of subjects were missing information on years smoked and packyears, respectively. 4000 subjects (5.2%) of subjects were missing information on acetaminophen use.

† All adjusted for age, sex, years smoked, packyears, packyears squared, and acetaminophen use; non-aspirin NSAID use also adjusted for regular aspirin use and regular aspirin use also adjusted for total non-aspirin NSAID use

‡ Includes aspirin, ibuprofen, naproxen, celecoxib, rofecoxib, and other pain relievers such as indomethacin and piroxicam (last category for women only) but excludes low-dose aspirin use. 6.0% of subjects missing this datum.

§ P values for trend across ordered categories

‖ Includes ibuprofen, naproxen, celecoxib, rofecoxib, and other pain relievers such as indomethacin and piroxicam (last category for women only). 7.4% of subjects missing this datum.

** Excludes low-dose aspirin use. 4.9% of subjects missing this datum.

Table 2

Hazard Ratios for Different Morphologies of Lung Cancer Associated with Ten Year Average Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Morphology	Adjusted Hazard Ratios (95% CI)*			P for trend‡
	Total NSAID Use†			
	1st Tertile 0.4–1.4 days/week	2nd Tertile >1.4–4.2 days/week	3rd Tertile >4.2 days/ week	
NSCLC (501 cases)§	0.89 (0.68–1.15)	0.85 (0.65–1.10)	0.68 (0.51–0.92)	0.01
Adenocarcinoma 226 cases	1.03 (0.72–1.47)	0.69 (0.45–1.05)	0.59 (0.37–0.94)	0.01
Squamous Cell 116 cases	0.62 (0.33–1.16)	1.01 (0.60–1.70)	0.97 (0.57–1.64)	0.95
NSCLC, NOS 143 cases	0.89 (0.55–1.45)	0.88 (0.55–1.43)	0.57 (0.32–1.01)	0.06
SCLC (90 cases)	1.51 (0.84–2.69)	0.66 (0.30–1.44)	1.43 (0.80–2.57)	0.57

Abbreviations: NSCLC: Non-small cell lung cancer; SCLC: Small Cell Lung Cancer; NOS: not otherwise specified

*All HR's use the "No Use" category as the referent. All HR's adjusted for age, sex, years smoked, packyears, packyears squared, and acetaminophen use

†Includes aspirin, ibuprofen, naproxen, celecoxib, rofecoxib, and other pain relievers such as indomethacin and piroxicam (last category for women only) but excludes low-dose aspirin use

‡P values for trend measured ordered categorically

§Subset of NSCLC cases do not sum to 501 secondary to 16 cases of large cell carcinoma not included in this analysis

Table 3

Hazard Ratios for Lung Cancer for Subgroups based on Sex and Smoking Status Associated with Ten Year Average Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Subgroup	Adjusted Hazard Ratios (95% CI)*			P for trend‡
	Total NSAID Use†			
	1st Tertile 0.4–1.4 days/ week	2nd Tertile >1.4–4.2 days/week	3rd Tertile >4.2 days/ week	
Sex				
Women	0.90 (0.64–1.27)	0.92 (0.66–1.30)	1.07 (0.75–1.51)	0.91
Men	0.98 (0.73–1.32)	0.76 (0.55–1.06)	0.66 (0.47–0.92)	0.01
P for Interaction	0.05			
Smoking Status				
Former, quit ≥ 10yrs	0.79 (0.55–1.14)	0.88 (0.62–1.25)	0.65 (0.44–0.96)	0.04
Former, quit <10 yrs	1.40 (0.88–2.21)	0.61 (0.33–1.13)	0.97 (0.56–1.68)	0.46
Current	0.76 (0.49–1.17)	0.79 (0.51–1.22)	1.02 (0.68–1.52)	0.74
P for Interaction	0.22			

*All HR's use the "No Use" category as the referent. All HR's adjusted for age, years smoked, packyears, packyears squared, and acetaminophen use. HR's for smoking status also adjusted for sex.

†Includes ibuprofen, naproxen, celecoxib, rofecoxib, and other pain relievers such as indomethacin and piroxicam (last category for women only)

‡P values for trend measured ordered categorically