Short Communication

Association of Nonsteroidal 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. The use of nonsteroidal anti-inflammatory drugs (NSAID) may be promising.**

Methods: **The study was a prospective cohort of 77,125 men and women, ages 50 to 76 years, from Washington state recruited in 2000 to 2002 (the VITamin And Lifestyle study). Lung cancer cases were identified through the Seattle-Puget Sound Surveillance, Epidemiology and End Results cancer registry during 5 years of follow-up. Hazard ratios (HR) 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: **A total of 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 d/wk for >10 years versus none: HR, 0.82; 95% confidence interval (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 seemed 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.** (Cancer Epidemiol Biomarkers Prev 2009;18(4):1203–7)

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States (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). Nonsteroidal anti-inflammatory drugs (NSAID) 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 study (11) to evaluate associations of 10-year average use of NSAIDs with incident lung cancer.

Materials and Methods

The methods used in the VITamin And Lifestyle study have been described (11). A total of 77, 719 participants (21.3% of the total number of mailed questionnaires), ages 50 to 76 y, 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

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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), the move out of the SEER catchment area (5.4%), or the 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 10 y before baseline. Women also reported the use of indomethacin and piroxicam. Subjects reported how many years they used each medication in the previous 10 y (1-3, 4-8, or 9-10 y) and the usual number of days per week (1-3, 4-6, or 7 d). For the analysis, we estimated the total average use over the 10 y by multiplying the 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 the 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 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 done with the use of Stata/SE 9 (StataCorp). Cox regression was used to estimate the hazard ratios (HR) for associations of NSAID use categories with incident lung cancer, with robust SE 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 HRs 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), chronic obstructive pulmonary disease, previous history of cancer, family

Table 1. HRs for lung cancer associated with 10-y average use of NSAIDs

NSAID use*	Non-lung cancer (n = 76,460), %	Lung cancer (n = 665), %	Adjusted HR†	Adjusted 95% CI†
Total NSAID use‡				
None	51.9%	50.9%	Reference	
1st tertile (0.4-1.4 d/wk)	18.1%	17.9%	0.94	(0.75-1.18)
2nd tertile (>1.4-4.2 d/wk)	17.1%	16.2%	0.83	(0.66-1.05)
3rd tertile (>4.2 d/wk)	13.0%	15.0%	0.82	(0.64-1.04)
P for trend§				0.05
Non-aspirin NSAID use‖				
None	67.8%	71.3%	Reference	
1st tertile (0.4-1.19 d/wk)	9.3%	8.8%	0.88	0.65-1.18
2nd tertile (1.2-2.2 d/wk)	12.9%	11.1%	0.89	0.68-1.16
3rd tertile (>2.2 d/wk)	10.0%	8.8%	0.81	0.60-1.09
P for trend§				0.12
Regular aspirin use¶				
None	75.4%	70.7%	Reference	
1st tertile (0.4-1.4 d/wk)	8.6%	10.1%	1.16	0.89-1.53
2nd tertile (>1.4-3.0 d/wk)	5.5%	4.3%	0.77	0.51-1.15
3rd tertile (>3.0 d/wk)	10.5%	14.9%	0.90	0.71-1.15
P for trend§				0.31

*Percentages are of nonmissing data but may not add up to 100% secondary to rounding. No subjects were missing age or gender information. A total of 769 (1.0%) and 916 (1.1%) of subjects were missing information on years smoked and pack-years, respectively; 4,000 subjects (5.2%) were missing information on acetaminophen use.

†All adjusted for age, sex, years smoked, pack-years, pack-years 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. Six percent 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). Subjects (7.4%) missing this datum.

¶Excludes low-dose aspirin use. Subjects (4.9%) missing this datum.

Table 2. HRs for different morphologies of lung cancer associated with 10-y average use of NSAIDs

Morphology	Adjusted HRs (95% CI)*			P for trend [†]
	Total NSAID use [‡]			
	1st tertile (0.4-1.4 d/wk)	2nd tertile (>1.4-4.2 d/wk)	3rd tertile (>4.2 d/wk)	
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 HRs use the ''No Use'' category as reference All HRs adjusted for age, sex, years smoked, pack-years, pack-years 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 does not sum to 501 secondary to 16 cases of large cell carcinoma not included in this analysis.

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 >10% or the 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 with 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 <0.05 were considered statistically significant.

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Results

A total of 77,125 subjects met the 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 nonsignificant decreased lung cancer risk. The use of low-dose aspirin was not associated with lung cancer (>3 d/wk versus 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 small, nonsignificant reductions: ibuprofen (>1.4 d/wk versus none: HR, 0.87; 95% CI, 0.65-1.17; P for trend = 0.18), naproxen (>1.2 d/wk versus none: HR, 0.71; 95% CI, 0.44-1.13; P for trend = 0.24), and selective COX-2 inhibitors (any use compared with 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 non–small cell lung cancer (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, not otherwise specified (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 in 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 versus none: HR, 0.51; 95% CI, 0.26-1.00; P for trend = 0.03 and women: 3rd tertile versus 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) although the only significant association was for subjects who had quit smoking 10 or more years before 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% to 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

Table 3. HRs for lung cancer for subgroups based on sex and smoking status associated with 10-y average use of NSAIDs

Subgroup	Adjusted HRs (95% CI)*			*P* for trend †
	Total NSAID use ‡			
	1st tertile (0.4-1.4 d/wk)	2nd tertile (>1.4-4.2 d/wk)	3rd tertile (>4.2 d/wk)	
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 ≥10 y	0.79 (0.55-1.14)	0.88 (0.62-1.25)	0.65 (0.44-0.96)	0.04
Former, quit <10 y	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 HRs use the ''No Use'' category as reference. All HRs adjusted for age, years smoked, pack-years, pack-years squared, and acetaminophen use. HRs 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.

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 with other histologies (3, 4, 13), and it is overexpressed in premalignant 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 although 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) although 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 VITamin and Lifestyle study cohort was predominantly Caucasian and includes fewer current smokers than the overall proportion of the United States as a whole, limiting generalizability.

In conclusion, we found that long-term frequent use of total nonsteroidal anti-inflammatory drugs was associated with a decreased incidence of lung cancer, with the strongest evidence for a protective association with adenocarcinoma. Although 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. Although 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Ries LAGMD, Krapcho M, Mariotto A, et al., editors. SEER Cancer Statistics Review, 1975-2004, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008. Bethesda, MD: National Cancer Institute; 2008.

2. Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. J Natl Cancer Inst 1993;85:457–64.
3. Lee JM, Yanagawa J, Peebles KA, Sharma S, Mao JT, Dubinett SM. Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. Crit Rev Oncol Hematol 2008;66:208–17.
4. Hida T, Yatabe Y, Achiwa H, et al. Increased expression of cyclooxygenase 2 occurs frequently in human lung cancers, specifically in adenocarcinomas. Cancer Res 1998;58:3761–4.
5. Harris RE, Beebe-Donk J, Doss H, Burr Doss D. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). Oncol Rep 2005;13:559–83.
6. Harris RE. Cyclooxygenase-2 (cox-2) and the inflammogenesis of cancer. Subcell Biochem 2007;42:93–126.
7. Winterhalder RC, Hirsch FR, Kotantoulas GK, Franklin WA, Bunn PA, Jr. Chemoprevention of lung cancer-from biology to clinical reality. Ann Oncol 2004;15:185–96.
8. Sandler AB, Dubinett SM. COX-2 inhibition and lung cancer. Semin Oncol 2004;31:45–52.
9. Riedl K, Krysan K, Pold M, et al. Multifaceted roles of cyclooxygenase-2 in lung cancer. Drug Resist Updat 2004;7:169–84.
10. Khuder SA, Herial NA, Mutgi AB, Federman DJ. Nonsteroidal antiinflammatory drug use and lung cancer: a metaanalysis. Chest 2005;127:748–54.
11. White E, Patterson RE, Kristal AR, et al. VITamins And Lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol 2004;159:83–93.
12. Slatore CG, Littman AJ, Au DH, Satia JA, White E. Long-term use of supplemental multivitamins, vitamin C, vitamin E, folate does not reduce the risk of lung cancer. Am J Respir Crit Care Med 2008;177:524–30.
13. Xing L, Zhang Z, Xu Y, Zhang H, Liu J. Expression and significance of cyclooxygenase 2 gene in lung cancer. J Huazhong Univ Sci Technolog Med Sci 2004;24:326–8.
14. Hosomi Y, Yokose T, Hirose Y, et al. Increased cyclooxygenase 2 (COX-2) expression occurs frequently in precursor lesions of human adenocarcinoma of the lung. Lung Cancer 2000;30:73–81.
15. Tsubochi H, Sato N, Hiyama M, et al. Combined analysis of cyclooxygenase-2 expression with p53 and Ki-67 in nonsmall cell lung cancer. Ann Thorac Surg 2006;82:1198–204.
16. Mao JT, Fishbein MC, Adams B, et al. Celecoxib decreases Ki-67 proliferative index in active smokers. Clin Cancer Res 2006;12:314–20.
17. Hayes JH, Anderson KE, Folsom AR. Association between nonsteroidal anti-inflammatory drug use and the incidence of lung cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2006;15:2226–31.
18. Van Dyke AL, Cote ML, Prysak G, Claeys GB, Wenzlaff AS, Schwartz AG. Regular adult aspirin use decreases the risk of non-small cell lung cancer among women. Cancer Epidemiol Biomarkers Prev 2008;17:148–57.
19. Ho CC, Ling YC, Chang LW, Tsai HT, Tsai MH, Lin P. 17-β estradiol and hydroxyestradiols interact via the NF-κB pathway to elevate cyclooxygenase 2 expression and prostaglandin E2 secretion in human bronchial epithelial cells. Toxicol Sci 2008;104:294–302.
20. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. Endocrinology 1996;137:5739–42.
21. Brueggemeier RW, Quinn AL, Parrett ML, Joarder FS, Harris RE, Robertson FM. Correlation of aromatase and cyclooxygenase gene expression in human breast cancer specimens. Cancer Lett 1999;140:27–35.