Risk of Lung Carcinoma among Users of Nonsteroidal Antiinflammatory Drugs

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BACKGROUND. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the development of lung tumors in experimental animals. To the authors' knowledge there are little data regarding whether regular use of NSAIDs reduces the risk of developing lung carcinoma in humans.

METHODS. The association between lung carcinoma risk and regular use of NSAIDs, including aspirin, was evaluated in a hospital-based case–control study of 1038 patients and 1002 controls.

RESULTS. The relative risk estimate of lung carcinoma associated with using NSAIDs 3 times a week or more for 1 or more years demonstrated an odds ratio (OR) of 0.68 (95% confidence interval [95% CI], 0.53–0.89). Results were similar when separated by lung histologic type. The association varied by smoking status. The OR was1.28 (95% CI, 0.73–2.25) in never-smokers and 0.60 (95% CI 0.45–0.80) in ever-smokers. The smoking-specific risk estimates for aspirin were similar to those for all NSAIDs.

CONCLUSIONS. The results of the current study suggest a possible chemoprotective benefit with the use of NSAIDs among individuals who are former or current smokers. ***Cancer* 2003;97:1732–6.** *© 2003 American Cancer Society.*
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Nonsteroidal antiinflammatory drugs (NSAIDs) are common over-the-counter drugs that have antiproliferative effects in both in vivo and in vitro lung tumor cells.[1,2] The mechanism of this action is the inhibition of cyclooxygenase-2 (COX-2) enzymes.[3,4] The COX-2 enzyme stimulates lung tumor growth by mediating prostaglandin (PG) biosynthesis.[5] In addition to lung carcinoma, a number of human tumors contain higher levels of PGs than the adjacent tissues from which they arise. Both COX-1 and COX-2 are the rate-limiting enzymes in the metabolism of arachidonic acid and PG synthesis. Whereas COX-1 is constitutively expressed in most normal tissue and is necessary for normal physiologic functions, the inducible isoform, COX-2, is expressed in a variety of inflammatory and neoplastic conditions. Chemoprevention clinical trials have been initiated to determine whether selective COX-2 inhibitors affect patient response.[6]

Information concerning whether NSAID use might reduce the rate of lung carcinoma in healthy individuals is more limited. A significant benefit was found for aspirin users who were followed for up to 8 years after completing a baseline medication questionnaire in the National Health and Nutrition Examination Survey I (NHNES I).[7] Another cohort study, Cancer Prevention Study II (CPS II), found few

differences in lung carcinoma mortality rates after 6 years of follow-up.[8] In a California retirement community cohort, the incidence of lung carcinoma in daily aspirin users was reduced among women but not among men.[9] A British case–control study found a nonsignificant reduced risk associated with frequent aspirin prescriptions.[10] With the exception of the British study, the relation between lung carcinoma risk and duration of NSAID use has not been explored. Because relatively few new cases of lung carcinoma occurred in these cohort studies, with the exception of CPS II, the effects of aspirin use are unclear. The hypothesis that the risk of lung carcinoma is reduced with regular use of NSAIDs was tested in a large case–control study that obtained information regarding both the frequency and duration of NSAID use.

MATERIALS AND METHODS

Several large hospitals in New York and Washington, D.C., participated in the study between 1992 to 2000.[11] Eligible subjects were identified from thoracic surgical schedules and from oncology clinics for patients with inoperable tumors. The diagnoses were confirmed by review of the pathology reports. Controls were patients without cancer from the same hospital who were identified from general admission logs. They were matched to cases by month of interview, gender, and age (within 5 years). For the current study, controls with conditions related to regular aspirin use were excluded from the analysis. This included conditions associated with increased aspirin use including rheumatoid arthritis (RA), osteoarthritis (OA; International Classification of Disease [ICD] codes 714.0–716.9), and joint problems (ICD code v43.6), as well as for conditions for which NSAIDs are contraindicated including peptic ulcer (ICD code 533) and bleeding disorders (ICD codes 286, 7221–7229). Subjects were interviewed by trained personnel using a structured questionnaire that contained detailed habits on past and current lifestyle including smoking habits, demographics, and use of over-the-counter and prescription medications. For each medication, information on the brand, frequency, and duration of use was obtained. Each subject signed a consent form that was approved by their hospital's institutional review board.

Statistical Analysis

All statistical analyses were performed using SAS software (SAS Institute, Cary, NC). Regular NSAID use was defined as use of over-the-counter aspirin or any other NSAID (three tablets per week) for 1 or more years. Subjects who took NSAIDs for less than 1 year or who took them less frequently (fewer than 3 tablets per week) were included in the reference category. The reference group for analyses limited to aspirin only included subjects who used neither aspirin nor NSAIDs frequently. The odds ratio (OR) and 95% confidence intervals (95% CI) were calculated for short-term use (i.e., 12–59 months) and longer-term use. Because controls were selected from hospitals, the use of NSAIDs was first analyzed according to ICD diagnostic codes to determine the extent of possible selection bias. The use of NSAIDs among controls was analyzed further by subject characteristics such as age, gender, education, and smoking status to assess potential confounders. Unconditional logistic regression models were used to adjust risk estimates for known or potential confounders such as cigarette smoking (pack-years), age, and years of education. Analyses were performed for all subjects and men and women separately. The risk estimates were calculated for all lung carcinoma cell types, and separately for adenocarcinoma and all other types combined. For the histologic-specific analyses, each subgroup of cases was compared with all controls in logistic regression models. Because cigarette smoking is the major cause of lung carcinoma and it is correlated with other lifestyle habits associated with possible lung carcinoma risk,[11] separate analyses were performed among smokers.

RESULTS

The current data set included 1038 patients with lung carcinoma and 1002 control subjects. Twenty-one percent of controls used NSAIDs regularly. Controls were divided into 19 different diagnostic groups based on categories of ICD disease codes. There was little variation in use of NSAIDs between most of these groups (Table 1). Approximately 18% of the 28 controls with circulatory system illnesses used NSAIDs. Subjects admitted for injuries had the highest rate of NSAID use (25%).

Among controls, there were few differences in usage patterns by gender, age, education, and smoking status (Table 2). NSAIDs were taken slightly more frequently by men than women and by subjects with college degrees. Eighteen percent of current smokers, 23% of former smokers, and 20% of never smokers used NSAIDs regularly.

Seventeen percent of cases used NSAIDs regularly. The crude OR for lung carcinoma associated with regular NSAID use was 0.74 (95% CI, 0.59–0.93). In all analyses, there were little differences between the crude and adjusted ORs and therefore only adjusted ORs are reported. The overall OR was 0.68 (95% CI, 0.53–0.89; Table 3). The reduction in risk was somewhat greater for men (OR = 0.61; 95% CI, 0.42–0.87) than for women (OR = 0.82; 95% CI, 0.56–1.20). For all

TABLE 1
Regular Use of NSAIDs among 1002 Controls by Diagnostic Category[a]

Category	No.(%)
Infections	12 (16.7)
Benign neoplasms	27 (14.8)
Endocrine	18 (11.1)
Mental	34 (20.6)
Circulatory	28 (17.9)
Respiratory	34 (11.8)
Digestive	153 (19.6)
BPH/other genitourinary	270 (22.2)
Skin	36 (22.2)
Muskuloskeletal	70 (24.3)
III-defined conditions	52 (19.2)
Injuries	236 (25.0)
All others	32 (18.8)
Total	214 (21.4)

NSAID: nonsteroidal antiinflammatory drugs; BPH: benign prostatic hyperplasia.
[a] Use of over-the-counter prescription aspirin or any other NSAID (three tablets per week) for ≥ 1 year.

TABLE 2
Regular Use of Nonsteroidal Antiinflammatory Drugs among 1002 Controls by Gender Age, Education, and Smoking Status

Characteristics	No.(%)
Gender	
Male	518 (22.8)
Female	484 (19.8)
Age (yrs)	
< 45	77 (20.8)
45–54	184 (23.5)
55–64	273 (19.0)
≥ 65	468 (23.7)
Education (yrs)	
< 12	126 (16.7)
12	272 (19.9)
13–15	183 (23.0)
≥ 16	421 (23.0)
Smoking	
Never	446 (20.0)
Current	133 (18.0)
Former	423 (23.9)

subjects combined, there were no differences in the risk reduction between short-term and long-term users. The OR associated with aspirin use only was 0.84 (95% CI, 0.62–1.14). The association with aspirin use was found only in men (OR = 0.70; 95% CI, 0.47–1.04) and not in women (OR = 1.11; 95% CI, 0.69–1.80). There was no evidence of a dose-response effect, either when medication use was classified by duration (12–59 months, ≥ 60 months) or by cumulative tablet exposure.

After stratification by smoking status, regular use of NSAIDs or aspirin was not found to be associated with lung carcinoma risk in never-smokers (Table 4). An inverse association was observed in ever-smokers. When further stratified by both smoking status (never, current, and former) and by gender, the OR for regular use of NSAIDs was 0.37 (95% CI, 0.18–0.76) in male current smokers and 1.77 (95% CI, 0.68–4.52) in female current smokers. In former smokers, a protective effect was found for both men (OR = 0.60; 95% CI, 0.39–0.94) and women (OR = 0.56; 95% CI, 0.31–1.04).

Table 5 demonstates that the association with NSAID use or aspirin did not vary substantially by lung histologic type. The risks were similar among adenocarcinoma, small cell, and all other histologic types combined.

DISCUSSION

The results of the current study showed that the risk of lung carcinoma was reduced in smokers who regularly used NSAIDs and that the association was consistent for all lung histologic types. No benefit was found among nonsmokers. The findings were similar for all NSAIDs and for aspirin separately. These results provide what we believe to be the strongest evidence to date for a chemoprotective effect of NSAIDs, yet the findings from all studies are contradictory. For example, studies of arthritic patients have not found a benefit of aspirin use on lung carcinoma risk. The incidence of colon carcinoma,[12] but not lung carcinoma,[12,13] was reduced among a cohort of patients with RA. Cigarette smoking is associated with RA[14,15] and high smoking rates would offset any possible benefit of aspirin use. A reduced incidence of both lung and colon carcinoma was reported for OA patients,[12] although the protective effect against lung carcinoma might be due to lower smoking rates among the OA group.

The incidence rate of lung carcinoma among aspirin users in 12,668 adults participating in the NHNES I was 0.68 (95% CI, 0.49–0.94) after 12.4 years of follow-up.[7] However, there was no information regarding the amount and duration of aspirin use. In the California Leisure World cohort of 13,987 retirees, no significant differences in lung carcinoma rates were found by aspirin use.[9] In this study, 111 cases of lung carcinoma were found after 6.5 years of follow-up. The relative risk was 1.35 (95% CI, 0.73, 2.32[1]) in men and 0.29 (95% CI, 0.07, 1.14) in women. Among 635, 031 adults who were followed for 6 years in the CPS II, there was no reduction in lung carcinoma mortality rates among aspirin users, except for a subgroup of women who took 1–15 tablets a month.[8] Although the

[1]The CI was estimated by the authors based on unadjusted data. Published relative risks are adjusted for age.

TABLE 3
OR for Lung Carcinoma by Regular Use of NSAIDs and Aspirin

	NSAIDs			Aspirin		
Characteristics	**Cases**	**Controls**	**OR (95% CI)**	**Cases**	**Controls**	**OR (95% CI)**
NSAIDs						
No/infrequent use	864	788	1.0	864	788	1.0
Regular use	174	214	0.68 (0.53–0.89)	133	130	0.84 (0.62–1.14)
No/infrequent use	864	788	1.0	864	788	1.0
12–59 mos	78	110	0.62 (0.44–0.89)	53	65	0.72 (0.47–1.11)
≥ 60 mos	96	104	0.75 (0.53–1.06)	80	65	0.96 (0.64–1.43)
Tablets/day (yrs)[a]						
< 1	819	704	1.0	834	730	1.0
1–5	98	146	0.61 (0.45–0.83)	70	99	0.65 (0.45–0.93)
5 +	121	152	0.58 (0.43–0.78)	93	89	0.73 (0.51–1.05)

OR: odds ratio; NSAID: nonsteroidal antiinflammatory drugs; CI: confidence interval.
[a] Adjusted for age, gender, years of education, and pack-years of smoking.

TABLE 4
OR for Lung Carcinoma and Regular Use of NSAIDs and Aspirin by Smoking Status

	NSAIDs			Aspirin		
Smoking status	**Cases**	**Controls**	**OR (95% CI)**	**Cases**	**Controls**	**OR (95% CI)**
Never-smokers						
No/infrequent use	63	357	1.0	63	357	1.0
Regular use	21	89	1.28 (0.73–2.25)	19	51	2.03 (1.08–3.81)
Ever-smokers						
No/infrequent use	801	431	1.0	801	431	1.0
Regular use	153	125	0.60 (0.45–0.80)	114	79	0.68 (0.49–0.96)
Current smokers						
No/infrequent use	410	109	1.0	410	109	1.0
Regular use	72	24	0.71 (0.41–1.22)	51	16	0.72 (0.38–1.36)
Former smokers						
No/infrequent use	391	322	1.0	391	322	1.0
Regular use	81	101	0.58 (0.41–0.83)	63	63	0.69 (0.46–1.04)

OR: odds ratio; NSAID: nonsteroidal antiinflammatory drug; CI: confidence interval.

number of lung carcinoma deaths was not reported, a crude estimate is approximately 1500. In a British case–control study of 2560 lung carcinoma patients, there was no trend in risk with the number of aspirin prescriptions in the 3 years preceding the diagnosis.[10] However, among persons who had the highest number of prescriptions (7 or more), the OR was 0.84 (95% CI, 0.69–1.02). In the U.K., over-the-counter purchases of pain medication are relatively uncommon because prescription drugs are obtained without cost.

The largest discrepancy among these studies is between the current protective findings and the lack of an effect in the large CPS II cohort. It is possible that the current study is biased because controls were hospital patients and more likely to have been NSAID users than the general population. This potential bias was minimized somewhat by the inclusion of a variety of control diagnoses. There was relatively little variability between groups. Other studies of NSAID use and colorectal carcinoma risk that used hospital-based controls had similar results to population-based studies.[16] Nevertheless, the use of hospital controls is often problematic in case–control studies and bias cannot be ruled out when interpreting the current findings. The use of NSAIDs was not associated with a reduced risk of lung carcinoma in female current smokers. We did note that the percentage of NSAID users in this subgroup was substantially lower than in other subgroups (10.7% vs. ≥ 18%). However, whether this finding simply reflects the variability that arises from multiple subgroup analysis remains to be determined. Alternatively, if there is a benefit of NSAID use

TABLE 5
OR for Lung Carcinoma Histology by Regular Use of NSAIDs and Aspirin

	NSAIDs			Aspirin		
Histologic type	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Adenocarcinoma						
No/infrequent use	362	788	1.0	362	788	1.0
Regular use	73	214	0.66 (0.47–0.91)	56	130	0.82 (0.56–1.20)
Small cell						
No/infrequent use	85	788	1.0	85	788	1.0
Regular use	19	214	0.64 (0.35–1.15)	14	130	0.68 (0.34–1.35)
Squamous/other						
No/infrequent use	417	788	1.0	417	788	1.0
Regular use	82	214	0.70 (0.51–0.96)	63	130	0.80 (0.55–1.17)

OR: odds ratio; NSAID: nonsteroidal antiinflammatory drug; CI: confidence interval.

only in smokers, it is possible that an effect might have been missed in the CPS II study because the rates were determined for both smokers and nonsmokers combined.

If the current findings do reflect a chemoprotective effect, it is uncertain why the inverse association was limited to smokers. It is possible that smoking might induce COX-2 expression. In 101 lung carcinoma samples, a greater percent of COX-2 expression was reported for smokers than for nonsmokers (32% vs. 10%).[17] Similarly, cigarette tar extracts increased COX activity in rat pulmonary alveolar macrophages.[18] Because lung carcinoma is the leading cause of cancer deaths, the possibility that commonly used pain medication can reduce the rates should be explored further.

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