Association between Nonsteroidal Anti-inflammatory Drug Use and the Incidence of Lung Cancer in the Iowa Women's Health Study

Jennifer H. Hayes, Kristin E. Anderson, and Aaron R. Folsom

Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota

Abstract

Background: **Previous studies have suggested that use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with reduced risk of lung cancer, but the data are inconsistent and are limited particularly with respect to the effects of aspirin, separate from other NSAIDs.**
Methods: **The Iowa Women's Health Study is a prospective cohort of 41,836 Iowa women ages 55 to 69 years old at baseline in 1986. NSAID use was assessed in 1992. Over 10 years of follow-up, 403 incident cases of lung cancer were identified. The association of incident lung cancer with current use of aspirin or non-aspirin NSAIDs was analyzed after adjustment for lung cancer risk factors. Hazard ratios (HR) were estimated using multivariate COX proportional hazards regression.**
Results: **There were 27,162 women in the analytic cohort. After controlling for age, education, alcohol intake, pack-years, smoking status, body mass index, and total fruit intake, the RR of women taking six or more aspirin weekly was 1.21 (95% confidence interval, 0.92-1.59). The HR was 1.23 for women taking six or more non-aspirin NSAIDs weekly (95% confidence interval, 0.92-1.65). There was no statistically significant trend by frequency of use for either aspirin (P_{trend} = 0.22) or non-aspirin NSAIDs (P_{trend} = 0.53). Analyses by histologic type and smoking status yielded similar null results. Information on dosage and duration of use were not available for this analysis.**
Conclusion: **These findings do not suggest that aspirin or other NSAIDs reduce risk of lung cancer in this cohort of postmenopausal women.** (Cancer Epidemiol Biomarkers Prev 2006;15(11):2226–31)

Introduction

Lung cancer is the leading cause of cancer death in the United States with 163,510 deaths (90,490 males and 73,020 females) and 172,570 incident cases (93,010 males and 79,560 females) estimated in 2005 (1). The prognosis for lung cancer is dismal with a 15% five-year survival rate (1). The ideal strategies for preventing lung cancer are to prevent smoking initiation and promote smoking cessation; however, smoking is usually initiated in adolescence and continues through adult years and cessation programs have had limited success. Thus, other prevention strategies are also being pursued. Nonsteroidal anti-inflammatory drugs (NSAIDs) are possible chemoprotective agents for this cancer. Use of NSAIDs has been consistently related to decreased risk of colon cancer (2-5) and there is evidence of decreased risk for other cancers, such as esophageal (6, 7), ovarian (8, 9), female breast (10, 11), stomach (6, 12), and pancreatic cancers (13).

In experimental studies on animals, NSAIDs have been shown to have a chemoprotective effect on lung cancer (14, 15) and they are thought to act through targeting cyclooxygenase (COX), the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins (16). Prostaglandins are mediators of signal transduction pathways, which modulate cellular adhesion, growth, and differentiation (10). Prostaglandins may promote carcinogenesis through several mechanisms, including direct mutagenesis, increased cell proliferation, immune suppression, tumor promotion, and facilitation of metastasis (17-20).

Two COX genes have been identified. Although COX-1 has long been considered a housekeeping gene, recent data has shown that COX-1 can also be induced by certain carcinogens (21) or hormones (22). The pathophysiologic role of COX-2 has been connected to inflammation, ovulation, and carcinogenesis. Laboratory data suggest the presence of COX-2 in human lung carcinomas and precursor lesions that lead to malignancy. Wolff et al. (23) found COX-2 mRNA levels to be high in well-differentiated adenocarcinoma samples but low in poorly differentiated adenocarinoma, squamous cell carcinoma, and small cell carcinoma, as detected by Northern blot analysis. COX-2 was also detected in all the squamous cell tissue samples on which immunohistochemistry was done. The COX-2 protein was not detected in normal lung tissues.

Fifteen studies have been published to date on the association of aspirin or other NSAIDs with lung cancer in humans (4, 24-37). One of these studies was a randomized control trial of 5,139 British physicians, two thirds of whom were randomized to daily use of aspirin (500 mg ordinary, soluble, or effervescent aspirin or 300 mg enteric coated aspirin) and one third of whom were randomized to avoidance of aspirin from November 1978 (or November 1979) to November 1984 (24). Although there were fewer deaths reported per 100,000 person years for those taking aspirin versus those avoiding aspirin (7.4 versus 11.6), the difference was not statistically significant. The Women's Health Study, a second controlled trial, randomized 19,934 women to 100 mg aspirin daily and 19,942 women to placebo (34). Women were followed on average 10.1 years. Cook et al. (34) reported a trend toward reduction in risk for lung cancer [relative risk (RR), 0.78; 95% confidence interval (95% CI), 0.59-1.03; n = 205; P = 0.08] and a reduction in the aspirin-treated group in lung cancer mortality (RR, 0.70; 95% CI, 0.50-0.99; n = 140; P = 0.04).

Received 3/6/06; revised 8/6/06; accepted 8/16/06.

Grant support: National Cancer Institute.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Kristin E. Anderson, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Suite 300, 1300 South Second Street, Minneapolis, MN 55454-1015. Phone: 612-626-8568; Fax: 612-624-0315.
E-mail: anderson_k@epi.umn.edu

doi:10.1158/1055-9965.EPI-06-0172

The remaining 13 studies consisted of 7 cohort studies (4, 25-27, 35-37) and 6 case-control studies (28-33) and the results were inconsistent: no significant risk reduction (25, 26, 30, 31, 35-37), significant risk reduction for both males and females (28, 29), significant risk reduction for females only (4, 33), significant risk reduction for males only (27, 32), and significant risk reduction for non–small cell carcinoma, but not overall (33). Some of these studies have been limited in their ability to separate the effects of aspirin from other NSAIDs or to account for lung cancer risk factors.

The findings reported here are from the Iowa Women's Health Study (IWHS), a prospective cohort involving 41,836 postmenopausal women. The use of aspirin and other NSAIDs was assessed in separate questions allowing for analysis of separate and combined use. There is limited information on lung cancer in relation to the separate use of these agents despite differences in their mechanism of action. In addition, although aspirin is a single agent, non-aspirin NSAIDs describe a broad category that may have differential effects between individuals and between studies. Previous research has also been limited in assessing the association of aspirin or other NSAIDs with specific histologic types of cancer.

Materials and Methods

The IWHS Cohort and Data Collection. The IWHS is a prospective cohort study investigating cancer and chronic disease incidence in women ages 55 to 69 years old at baseline. Questionnaires were sent to 99,826 randomly selected women with a valid Iowa driver's license in 1986. Of these 99,826 women, the response rate was 42.7%, which resulted in a study cohort of 41,836 (38). The cohort comprises 98% Caucasians and 65% residents of towns with populations <10,000 people. Respondents to the initial invitation have been shown to have lower mortality rates from smoking-related illnesses than nonrespondents (39). In addition, respondents were shown to be 3 months older and have a 0.4 kg/m^2 lower body mass than nonrespondents (40).

At baseline, women were asked to respond to questions on marital status, cigarette smoking, alcohol intake within the past year, hormone-replacement therapy use, physical activity, height and weight, reproductive history, and personal and family medical history. Information collected on cigarette smoking history included age at initiation, average packs daily, and smoking cessation history. A Willett food frequency questionnaire (41) was also included. Follow-up surveys were sent in 1987 (91% response rate of the original cohort), 1989 (89% response), 1992 (83% response), and 1997 (79% response).

Lung cancer incidence was obtained through linkage to the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER). Name, address, maiden name, birth date, and social security number were linked. Mortality was tracked through follow-up mailings, linkage to Iowa death certificates, and the National Death Index.

Exposure Assessment. Aspirin and other NSAID use was obtained in 1992. Participants were asked how often they took aspirin and were given the following examples: Bufferin, Anacin, enteric-coated aspirin, Ecotrin, and Excedrin. Choices of frequency were never, less than one weekly, once weekly, two to five times weekly, and six or more times weekly. Respondents were directed to not include acetaminophen, Tylenol, ibuprofen, and Advil. The question was similar for non-aspirin NSAID use with examples given as ibuprofen, Advil, Nuprin, Motrin, Naprosyn, Feldene, and Clinoril. For this question, respondents were instructed not to include aspirin, acetaminophen, Tylenol, prednisone, cortisone, and Deltasone. There were no questions asked about the duration or dose of aspirin or other NSAID use.

Current smoking status, history of migraines, and current alcohol use were obtained from the 1992 survey. Body mass index (BMI), waist-to-hip ratio (WHR), family history of cancer in female relatives, pack-years of cigarette smoking, multivitamin use, education level, vegetable and fruit intake, and personal histories of arthritis and high blood pressure were obtained from the baseline 1986 survey. History of heart attack, angina, or other heart disease was obtained from surveys in 1992, 1989, 1987, and 1986.

Data Analysis. Starting with a study cohort of 41,836, women were excluded from analysis if they reported cancer other than nonmelanoma skin cancer before 1986 (n = 3,830) or had an incident cancer before the exposure assessment in 1992 (n = 1,629). Women were also excluded if they did not respond to the 1992 questionnaire (n = 7,796) or did not respond to the aspirin or NSAID questions (n = 539). In addition, women who moved out of Iowa before 1992 were excluded (n = 865) as were women who were <55 years old at baseline (n = 15). Thus, the cohort used for this analysis consisted of 27,162 women.

Follow-up time was calculated as the length of time from the completion of the 1992 questionnaire to one of the following events: (a) the date of diagnosis of lung cancer, (b) the date of death (if death occurred in Iowa), (c) the date the woman moved out of Iowa (if known), (d) the midpoint of the interval between the last follow-up contact in Iowa and the first known date out of Iowa or December 31, 2002 (if the emigration date from Iowa was unknown), or (e) the midpoint of the date of last contact in Iowa and the date of death (for deaths in women who emigrated from Iowa). Women who did not fall into any of these categories were assumed to be living in Iowa and follow-up time was to December 31, 2002. Out-migration was estimated to be ~1% yearly (42).

Comparisons of characteristics based on lung cancer status were done using ANOVA. Incidence of lung cancer was calculated by dividing the number of new cases by the number of person-years of follow-up for each exposure category. Initial analyses were done to assess the association between any NSAID use in each of two categories (aspirin or other NSAIDs) and lung cancer, relative to nonusers of each. Multivariate COX proportional hazards regression was used for subsequent analyses to calculate hazard ratios (HR) of lung cancer and 95% CIs. Analyses were done to test the independent effects of any aspirin use or any NSAID use relative to nonusers of each. Analyses were also done to test the association between any NSAID use (aspirin and/or other NSAIDs) and lung cancer, relative to nonusers of either. The trend test option in the proportional hazards regression was used to test for trends in HRs using ordinal categories of increasing NSAID use. Potential interaction of the combined use of aspirin and other NSAIDs on risk of lung cancer was done by forming nine categories of aspirin and NSAID use ranging from no reported current use (reference category) to high frequency of reported use. Results were also stratified by smoking category (current, past, and never), pack-years smoked (0, 1-19, 20-39, and 40+), and lung cancer histology (adenocarcinoma, squamous, small, and other).

Results

This analysis included 27,162 women with a total of 266,086 person years. Lung cancer was defined as codes 34.0 to 34.3 and 34.8 to 34.9 by WHO *International Classification of Oncology, Second Edition*. A total of 403 lung cancer cases were identified from 1992 to December 31, 2002. This number approximately equals the national SEER data age-adjusted incidence for age 55 to 64 Caucasian females, which for the same period averages 136 per 100,000 yearly (43). Subsite analyses of these cases were divided as follows: 142 cases of adenocarcinoma,

Table 1. Characteristics of women who developed lung cancer and noncases in the IWHS

Characteristics	All lung cancer cases, N = 403, n (%)	Noncases, N = 26,759, n (%)	HR (95% CI)	P
Age				
61-65	148 (36.7)	9,974 (37.3)	1.00 (reference)	
66-70	142 (35.2)	9,392 (35.1)	1.02 (0.81-1.28)	
71+	113 (28.0)	7,383 (27.6)	1.03 (0.80-1.32)	0.97
Pack-years				
0	73 (18.8)	18,174 (69.4)	1.00 (reference)	
1-19	23 (5.9)	3,537 (13.5)	1.62 (1.01-2.59)	
20-39	122 (31.4)	2,665 (10.2)	11.4 (8.50-15.3)	
40+	170 (43.8)	1,808 (6.9)	23.4 (17.7-30.9)	<0.0001
Smoking status				
Never	73 (18.5)	18,174 (69.0)	1.00 (reference)	
Past	148 (37.5)	6,008 (22.8)	6.13 (4.63-8.13)	
Current	174 (44.0)	2,178 (8.3)	19.9 (15.1-26.2)	<0.0001
Alcohol (g/d)				
0	175 (43.4)	14,963 (55.9)	1.00 (reference)	
0.9-1.9	54 (13.4)	3,974 (14.8)	1.16 (0.85-1.56)	
≥2	174 (43.2)	7,822 (29.2)	1.90 (1.52-2.32)	<0.0001
Education				
<High school graduate	91 (22.6)	4,603 (17.2)	1.00 (reference)	
High school graduate	164 (40.7)	11,308 (42.4)	0.73 (0.57-0.95)	
Post-high school	148 (36.7)	10,791 (40.4)	0.69 (0.53-0.90)	0.02
BMI				
≥30 kg/m^2	57 (14.1)	6,085 (22.7)	0.56 (0.42-0.74)	<0.0001
WHR				
≥0.8274 (median)	203 (50.6)	13,338 (50.0)	1.03 (0.84-1.25)	0.80
Total fruit servings weekly				
≥17 (median)	149 (37.0)	13,486 (50.4)	0.58 (0.47-0.71)	<0.0001
Total vegetable servings weekly				
≥22.5 (median)	194 (48.1)	13,764 (51.4)	0.88 (0.72-1.07)	0.19
Energy intake (kcal/d)				
≥1707 (median)	205 (50.9)	13,383 (50.0)	1.03 (0.85-1.26)	0.73
Current vitamin use	117 (29.1)	8,763 (33.2)	0.84 (0.68-1.04)	0.03
History of arthritis	206 (51.8)	12,749 (48.2)	0.87 (0.71-1.06)	0.16
History of high blood pressure	136 (34.4)	9,450 (36.1)	1.16 (0.87-1.54)	0.49
History of migraines	40 (10.0)	2,544 (9.6)	1.04 (0.75-1.45)	0.95
Family history of cancer	159 (39.4)	10,013 (37.5)	1.09 (0.89-1.33)	0.40
History of heart disease/heart attack	75 (21.1)	3,297,(14.1)	1.74 (1.35-2.25)	0.0002

NOTE: Baseline (1986) variables: BMI, WHR, family history of lung cancer, family history of cancer, pack-years, high blood pressure, multivitamin use, fruit and vegetable intake, education, and energy intake. Follow-up (1992) variables: age, history of arthritis, smoking status, history of heart disease/heart attack, history of migraines, and alcohol.

65 cases of small cell, 73 cases of squamous cell, and 106 cases of other or unspecified types of lung cancer. Subsite analyses excluded cases that did not fall strictly into these four categories.

Women who developed lung cancer were similar to noncases for several characteristics, which included age, family history of cancer, history of migraines, history of high blood pressure, history of arthritis, average weekly vegetable intake, average energy intake daily, and WHR (Table 1). As expected, incident cases had greater pack-years smoked (P < 0.0001) and higher proportion of current smokers (P < 0.0001) than noncases. The HR was especially pronounced for current smokers (HR, 19.9; 95% CI, 15.1-26.2). The mean BMI (kg/m^2; P < 0.0001), median fruit intake

Table 2. Prevalence (%) of participant characteristics by frequency of aspirin or other NSAID use

Characteristics	Aspirin*					NSAIDS*				
	0	<1	1	2-5	6+	0	<1	1	2-5	6+
	n = 7,628	n = 7,524	n = 1,492	n = 4,799	n = 5,719	n = 16,429	n = 4,158	n = 836	n = 2,182	n = 3,557
Age, >65 y [†]	65	59	64	62	66	64	58	63	60	63
BMI, ≥30 kg/m^2 [‡]	25	19	20	21	25	20	21	24	26	34
WHR, ≥0.8274 [‡]	52	46	50	48	54	49	47	51	50	56
Multivitamin use [‡]	31	30	34	34	37	31	33	36	37	37
Currently smoking [†]	9	8	8	9	10	9	8	8	9	10
History of migraines [†]	9	7	8	11	13	8	10	10	13	14
History of arthritis [‡]	53	44	46	52	63	44	51	58	64	79
History of high blood pressure [‡]	36	30	33	36	44	34	33	37	37	43
History of heart disease/heart attack [†]	13	8	9	12	27	14	12	14	14	18
High school graduate or higher education [‡]	82	86	82	82	82	83	85	80	81	82
Alcohol, ≥2 g/d [†]	26	30	32	33	29	28	33	35	32	28

NOTE: Tests of overall difference in characteristics among NSAID categories were all significant, except BMI by aspirin (P = 0.51) and alcohol by both aspirin (P = 0.16) and NSAID use (P = 0.16).

*Frequency of use (weekly).

[†] 1992.

[‡] 1986.

Table 3. Association of aspirin or non-aspirin NSAID use with lung cancer incidence, IWHS, 1992-2002

	No. cases	Total person-years	Age-adjusted HR* (95% CI)	Multivariate-adjusted HR*,† (95% CI)	Multivariate-adjusted HR*,‡ (95% CI)
Aspirin use					
Never	110	73,658	1.00	1.00	1.00 (1.00)
≤1 weekly	126	89,767	0.96 (0.74-1.25)	1.10 (0.84-1.43)	1.01 (0.77-1.35)
2-5 weekly	58	47,615	0.83 (0.60-1.14)	0.87 (0.63-1.21)	0.85 (0.60-1.19)
6+ weekly	109	55,046	1.34 (1.02-1.74)	1.21 (0.92-1.59)	1.08 (0.81-1.45)
P_{trend}			0.01	0.22	0.58
NSAID use					
Never	241	160,623	1.00	1.00	1.00
≤1 weekly	68	49,652	0.93 (0.71-1.22)	0.99 (0.75-1.30)	0.92 (0.68-1.24)
2-5 weekly	33	21,503	1.04 (0.72-1.50)	1.10 (0.76-1.60)	1.16 (0.79-1.70)
6+ weekly	61	34,308	1.16 (0.88-1.54)	1.23 (0.92-1.65)	1.10 (0.80-1.51)
P_{trend}			0.64	0.53	0.71

*Aspirin analyses adjusted for NSAID use and NSAID analyses adjusted for aspirin use.
† Adjusted for age (61-65, 66-70, and 71+), education (<high school, high school, and >high school), alcohol intake (continuous), smoking status (never, past, and current), pack-years (0, 1-19, 20-39, and 40+), BMI (continuous), and total fruit servings weekly (continuous).
‡ Adjusted for age (61-65, 66-70, and 71+), education (<high school, high school, and >high school), alcohol intake (continuous), smoking status (never, past, and current), pack-years (0, 1-19, 20-39, and 40+), BMI (continuous), total fruit servings weekly (continuous), and history of heart disease/heart attack (yes and no).

weekly ($P < 0.0001$), and current vitamin consumption ($P = 0.03$) among cases were statistically significantly lower than among noncases. Personal history of heart disease was significantly higher in cases compared with noncases ($P = 0.0002$). Cases also were more likely than noncases to consume >2 g alcohol daily (43.2% versus 29.2%, respectively) and less likely to have a post-high school education (36.7% versus 40.4%, respectively).

Compared with nonusers, women who reported use of aspirin and other NSAIDs had higher multivitamin use (Table 2). Women who reported higher usage of non-aspirin NSAIDs had a higher BMI compared with nonusers of non-aspirin NSAIDs. Women who reported aspirin or other NSAID use were more likely to report a history of arthritis, heart disease, high blood pressure, or migraines e.g., 44% of women taking no NSAIDs reported having arthritis compared with 79% of women taking six or more NSAIDs weekly.

Two models were used to assess the relation between incident lung cancer and aspirin or NSAID use (Table 3). The first model was adjusted for age and the second was adjusted for age, education, total fruit intake, alcohol intake, smoking status, pack-years smoked, and BMI. In addition, NSAID use was adjusted for aspirin use and ''vice versa.'' Personal history of heart attack and heart disease was also investigated as a confounder because people with a history of heart disease may routinely take lower versus higher doses of aspirin and heart disease is positively associated with smoking. This addition to the model brought the HRs closer to the null.

There was a small statistically significant positive association ($P = 0.01$) between lung cancer incidence and aspirin use in the age-adjusted model; however, after adjusting for pack-years smoked as well as the other variables in the multivariate model, the association was no longer statistically significant ($P = 0.2$). Including the variable ''any heart disease'' or ''heart attack'' further attenuated the association ($P = 0.6$). There was no statistically significant association between lung cancer and NSAID use in the age-adjusted or multivariate models. Stratifying on aspirin and other NSAID use simultaneously (Table 4) showed no statistically significant associations with lung cancer risk.

We postulated that NSAIDs would have a stronger preventive effect in lung cancer incidence in never smokers. However, there was no statistically significant association found between frequency of aspirin or other NSAID use and lung cancer incidence among women who had never smoked. In the never smokers, there was a consistent decrease in HR with increased frequency of aspirin use, but this trend was not statistically significant. Similar results were found when smoking status (never, current, past, and ever) was examined. There was also no difference in the association among women who had smoked <40 pack-years versus those who had smoked ≥40 pack-years (Table 5).

In past epidemiological studies, squamous and small cell lung cancers have been linked more strongly to smoking status than other histologic types (44, 45). We hypothesized that aspirin or other NSAIDs may reduce risk of lung cancer in adenocarcinoma and other types less strongly influenced by smoking. We found no statistically significant associations between aspirin or NSAID use and lung cancer by histologic type (Table 6).

Discussion

After adjusting for pack-years as well as other covariates included in the multivariate model, lung cancer incidence was not statistically significantly associated with frequency of aspirin or non-aspirin NSAID use. Although, the trends and the HRs were not significant, on examination of the association of lung cancer with aspirin and NSAID use by pack-years, there was a suggestion that never smokers had an inverse association between lung cancer and use of aspirin (but not other NSAIDs). Apparently, the positive association between

Table 4. Joint association of aspirin and NSAID use with lung cancer incidence, IWHS, 1992-2002

		Aspirin use*		
Other NSAID use	HR (95% CI)	Nonusers	<1-5 weekly	6+ weekly
	Nonusers	1 (referent)	1.03 (0.74-1.44)	1.19 (0.82-1.73)
	<1-5 weekly	1.09 (0.65-1.82)	1.02 (0.69-1.51)	1.14 (0.67-1.92)
	6+ weekly	1.36 (0.82-2.26)	1.00 (0.54-1.83)	1.23 (0.67-2.26)

NOTE: Adjusted for age (61-65, 66-70, and 71+ years), education (<high school, high school, and >high school), alcohol intake (continuous), smoking status (never, past, and current), pack-years (0, 1-19, 20-39, and 40+), BMI (continuous), total fruit servings weekly (continuous), and any heart disease/heart attack.
*Aspirin analyses adjusted for NSAID use and NSAID analyses adjusted for aspirin use.

Table 5. Association of aspirin and NSAID use and incident lung cancer by pack-years of smoking, IWHS, 1992-2002

	Pack-years		
	0	<40	40+
	n = 73 cases; n = 18,134 noncases	n = 144 cases; n = 6,161 noncases	n = 169 cases; n = 1,798 noncases
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Aspirin use			
Never	1.00	1.00	1.00
≤1 weekly	1.06 (0.58-1.95)	0.87 (0.55-1.35)	1.14 (0.73-1.80)
2-5 weekly	0.97 (0.47-2.02)	0.76 (0.44-1.32)	0.89 (0.51-1.54)
6+ weekly	0.71 (0.33-1.54)	1.06 (0.66-1.68)	1.34 (0.86-2.08)
P_{trend}	0.77	0.66	0.41
NSAID use			
Never	1.00	1.00	1.00
≤1 weekly	0.85 (0.42-1.72)	0.96 (0.61-1.52)	0.92 (0.57-1.47)
2-5 weekly	1.57 (0.70-3.52)	0.83 (0.42-1.66)	1.25 (0.70-2.22)
6+ weekly	1.28 (0.61-2.66)	0.91 (0.53-1.56)	1.18 (0.73-1.88)
P_{trend}	0.59	0.95	0.74

NOTE: Adjusted for age (61-65, 66-70, and 71+ years), education (<high school, high school, and >high school), alcohol intake (continuous), BMI (continuous), total fruit servings weekly (continuous), and any heart disease/heart attack (yes and no). Aspirin analyses adjusted for NSAID use and NSAID analyses adjusted for aspirin use.

aspirin use and lung cancer seen in smokers may be due to residual confounding from smoking because aspirin use was positively associated with smoking in this cohort. Non-aspirin NSAIDs showed no protective effect.

We thought it plausible that aspirin and non-aspirin NSAIDs may have different effects on lung cancer risk because of differences in their mechanistic properties. For example, aspirin is the only compound that permanently disables COX. All other NSAIDs bind tightly but reversibly to COX (46). The results do not support this hypothesis.

Cigarette smokers were at the highest risk of lung cancer. Compared with never smokers, those who had smoked 40+ pack-years had a HR of 23.4. Those currently smoking had a HR of 19.9. Only 0.4% of women who reported that they had never smoked developed lung cancer, whereas 2% of those who smoked <40 pack-years developed lung cancer, and 9% of those who smoked 40+ pack-years developed lung cancer, yet again, a clear demonstration of the increased likelihood of developing lung cancer in smokers.

Previous studies have reported inconsistent results by histology. Holick et al. (25) as part of the Health Professionals Follow-up study found no significant effect of regular aspirin use overall or by histologic type. By contrast, Akhmedkhanov et al. (odds ratio, 0.39; 95% CI, 0.16-0.96; ref. 33) and Moysich (odds ratio, 0.62; 95% CI, 0.45-0.86; ref. 31) found an inverse association between non–small cell carcinomas and NSAID use of once weekly for a year. Moysich (31) also found an inverse association for small cell carcinoma (odds ratio, 0.32; 95% CI, 0.16-0.63).

Akhmedkhanov et al. (33) noted that those who had taken aspirin for a period of at least 6 months showed an overall inverse association between aspirin use and risk of lung cancer. However, when looking at aspirin use by histologic type, they noticed a stronger inverse association with non–small cell carcinoma in women who had taken aspirin for at least 5 years compared with those who had taken aspirin for <5 years; there was no effect in those that had reported taking aspirin only during the 4 weeks before enrollment in the study.

Limitations of our study warrant consideration. Duration of use and dosage of NSAIDs were not ascertained and thus subjects may have been misclassified by exposure status. Apparently, those who were taking NSAIDs at a higher

Table 6. Association of aspirin or NSAID use with incident lung cancer by histologic type, IWHS, 1992-2002

	Histologic type			
	Small cell	Squamous	Adenocarcinoma	Other
	n = 65 cases; n = 26,414 noncases	n = 73 cases; n = 26,406 noncases	n = 142 cases; n = 26,357 noncases	n = 106 cases; n = 26,353 noncases
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (CI 95%)
Aspirin use				
Never	1.00	1.00	1.00	1.00
≤1 weekly	1.46 (0.70-3.06)	0.60 (0.28-1.29)	1.24 (0.77-2.01)	1.049 (0.68-1.61)
2-5 weekly	1.34 (0.58-3.13)	1.18 (0.57-2.45)	0.80 (0.43-1.50)	0.68 (0.38-1.19)
6+ weekly	1.46 (0.68-3.13)	1.31 (0.68-2.51)	1.50 (0.92-2.45)	0.64 (0.38-1.07)
P_{trend}	0.74	0.21	0.16	0.14
NSAID use				
Never	1.00	1.00	1.00	1.00
≤1 weekly	0.92 (0.45-1.85)	1.24 (0.64-2.40)	1.05 (0.66-1.60)	0.62 (0.36-1.08)
2-5 weekly	0.63 (0.19-2.06)	1.80 (0.83-3.91)	1.26 (0.66-2.39)	1.00 (0.52-1.93)
6+ weekly	0.94 (0.41-2.12)	0.91 (0.40-2.06)	1.13 (0.65-1.95)	1.32 (0.82-2.14)
P_{trend}	0.90	0.45	0.89	0.17

NOTE: Adjusted for age (61-65, 66-70, and 71+ years), education (<high school, high school, and >high school), alcohol intake (continuous), smoking status (never, past, and current), pack-years (0, 1-19, 20-39, and 40+), BMI (continuous), total fruit servings weekly (continuous), and any heart disease/heart attack (yes and no). Aspirin analyses adjusted for NSAID use and NSAID analyses adjusted for aspirin use.

frequency were actually taking a lower dosage each time, although including history of heart attack and heart disease in the model addressed this issue. We had limited power in these analyses to examine aspirin use by smoking status and by histologic type. Another important limitation is the brief assessment of exposure to aspirin and other NSAIDs. Aspirin and non-aspirin NSAIDs are often taken sporadically, resulting in possible recall bias and possible misclassification.

This study also had several strengths. The IWHS is a prospective population-based study. The response rate to the questionnaires was excellent and we were able to control for multiple potential confounders. In addition, because we ascertained aspirin use and other NSAID use with separate questions, we were able to analyze them independently and together with respect to their association with lung cancer risk.

Our data suggest that aspirin or other NSAIDs do not offer protection from lung cancer in postmenopausal women who actively smoke (current or former). Smoking avoidance is paramount for prevention of lung cancer risk.

References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. Collet JP, Sharpe C, Belzile E, Boivin JF, Hanley J, Abenhaim L. Colorectal cancer prevention by non-steroidal anti-inflammatory drugs: effects of dosage and timing. Br J Cancer 1999;81:62–8.
3. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. J Natl Cancer Inst 1991;83:355–8.
4. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heathe CW, Jr. Aspirin use and risk of fatal cancer. Cancer Res 1993;53:1322–7.
5. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne colorectal cancer study. Cancer Res 1988;48:4399–404.
6. Thun MJ. Aspirin and gastrointestinal cancer. Adv Exp Med Biol 1997;400A: 395–402.
7. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102.
8. Rosenberg L, Palmer JR, Rao RS, et al. A case-control study of analgesic use and ovarian cancer. Cancer Epidemiol Biomarkers Prev 2000;9:933–7.
9. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, Kato I, Koenig KL, Shore RE. Aspirin and epithelial ovarian cancer. Prev Med 2001;33:682–7.
10. Johnson TW, Anderson KE, Lazovich D, Folsom A. Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11:1586–91.
11. Harris R, Kasbari S, Farrar W. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. Oncol Rep 1999;6:71–3.
12. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. Int J Cancer 1999;82:473–6.
13. Anderson KE, Johnson TW, Lazovich D, Folsom A. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. J Natl Cancer Inst 2002;94:1168–71.
14. Jalbert G, Castonguay A. Effect of NSAIDs on NNK-induced pulmonary and gastric tumorigenesis in A/J mice. Cancer Lett 1992;66:21–8.
15. Castonguay A, Rioux N, Duperron C, Jalbert G. Inhibition of lung tumorigenesis by NSAIDs: a working hypothesis. Exp Lung Res 1998;24: 605–15.
16. Kisley LR, Barrett BS, Dwyer-Nield LD, Bauer AK, Thompson DC, Malkinson AM. Celecoxib reduces pulmonary inflammation but not lung tumorigenesis in mice. Carcinogenesis 2002;23:1653–60.
17. Marnett LJ. Aspirin and the potential role of prostaglandins in colon cancer. Cancer Res 1992;52:5575–89.
18. Harris R, Namboodiri K, Farrar W. Epidemiologic study of nonsteroidal anti-inflammatory drugs and breast cancer. Oncol Rep 1995;2:591–2.
19. Thompson HJ, Briggs S, Pasranka NS, et al. Inhibition of mammary carcinogenesis in rats by sulfone metabolite of sulindac. J Natl Cancer Inst (Bethesda) 1995;87:1259–60.
20. Vainio H, Morgan G. Cyclo-oxygenase 2 and breast cancer prevention. BMJ 1998;317:828–30.
21. Rioux N, Castonguay A. The induction of cyclooxygenase-1 by a tobacco carcinogen in U937 human macrophages is correlated to the activation of NF-κB. Carcinogenesis 2000;21:1745–51.
22. Kim HS, Song M, Kim E, Ryu SH, Suh P-G. Dexamethasone differentiates NG108-15 cells through cyclooxygenase 1 induction. Exp Mol Med 2003;35: 203–10.
23. Wolff H, Saukkonen K, Anttila S, Karjalainen A, Vainio H, Ristimäki A. Expression of cyclooxygenase-2 in human lung carcinoma. Cancer Res 1998; 58:4997–5001.
24. Peto R, Gray R, Collins R, Wheatley K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988;296:313–6.
25. Holick CN, Michaud DS, Leitzmann MF, Willett WC, Giovannucci E. Aspirin use and lung cancer in men. Br J Cancer 2003;89:1705–8.
26. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. BMJ 1989;299:1247–50.
27. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5:138–46.
28. Harris RE, Beebe-Donk J, Schuller HM. Chemoprevention of lung cancer by non-steroidal anti-inflammatory drugs among cigarette smokers. Oncol Rep 2002;9:693–5.
29. Muscat JE, Chen S, Richie JP, et al. Risk of lung carcinoma among users of nonsteroidal anti-inflammatory drugs. Cancer 2003;97:1732–6.
30. Rosenberg L. Nonsteroidal anti-inflammatory drugs and cancer. Prev Med 1995;24:107–9.
31. Langman MJS, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ 2000;320:1642–6.
32. Moysich KB, Menezes RJ, Ronsani A, et al. Regular aspirin use and lung cancer risk. BMC Cancer 2002;2:31.
33. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, Koenig KL, Shore RE. Aspirin and lung cancer in women. Br J Cancer 2002;87:49–53.
34. Cook NR, Lee I-M, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:47–55.
35. Sørenson HT, Friis S, Nørgård B, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer 2003;88: 1687–92.
36. Skriver MV, Nørgaard M, Poulson AH, et al. Use of nonaspirin NSAIDs and risk of lung cancer. Int J Cancer 2005;117:873–6.
37. Ratnasinghe LD, Graubard BI, Kahle L, Tangrea JA, Taylor PR, Hawke E. Aspirin use and mortality from cancer in a prospective study. Anticancer Res 2004;24:3177–84.
38. Ebbert JO, Yang P, Vachan CM, et al. Lung cancer risk reduction after smoking cessation: observations from a prospective cohort of women. J Clin Oncol 2003;21:921–6.
39. Bisgard KM, Folsom AR, Hong CP, Sellers TA. Mortality and cancer rates in nonrespondents to a prospective study of older women: 5-year follow-up. Am J Epidemiol 1994;52:2447–55.
40. Folsom AR, Zhang S, Sellers TA, Zheng W, Kushi LH, Cerhan JR. Cancer incidence among women living on farms: findings from the Iowa Women's Health Study. J Occup Environ Med 1996;38:1171–6.
41. Willett WC, Sampson L, Stampfer MJ. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1986;124: 17–27.
42. Cerhan JR, Anderson KE, Janney CA, Vachon CM, Witzig TE, Habermann TM. Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma. Int J Cancer 2003;106:784–8.
43. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 9 Regs Public-Use, Nov 2004 Sub (1973-2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission. Available from: www.seer.cancer.gov.
44. Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment, and survival. Population-based study of 20561 cases. Ann Oncol 2002;13:1087–93.
45. Ferguson MK, Skosey C, Hoffman PC, Golomb HM. Sex-associated differences in presentation and survival in patients with lung cancer. J Clin Oncol 1990;8:1402–7.
46. IARC. Handbooks of cancer prevention I. Non-steroidal anti-inflammatory drugs. Lyon (France): IARC; 1997.

Association between Nonsteroidal Anti-inflammatory Drug Use and the Incidence of Lung Cancer in the Iowa Women's Health Study

Jennifer H. Hayes, Kristin E. Anderson and Aaron R. Folsom

Cancer Epidemiol Biomarkers Prev 2006;15:2226-2231.