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# Non-steroidal anti-inflammatory drugs and small cell lung cancer risk in the VITAL study

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## Abstract

Few studies have examined the association between non-steroidal anti-inflammatory drug (NSAID) use and risk of small cell lung cancer (SCLC); among them, findings are mixed. Recently, we found that use of NSAIDs was differentially associated with lung cancer risk by histology. Here, we examine, more comprehensively, the association between individual NSAIDs and SCLC risk. 75,546 residents of western Washington State, ages 50–76, completed a baseline questionnaire in 2000–2002 and reported on their use of individual NSAIDs over the past 10 years. NSAID use was categorized as non-users, low (<4 days/week or <4 years), and high (≥4 days/week and ≥4 years). 111 SCLC were identified through linkage to a population-based cancer registry. Multivariable-adjusted Cox proportional hazards models including strong adjustment for smoking were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Compared to non-use, high use of regular-strength aspirin was associated with an elevated risk of SCLC (HR 1.78, 95% CI: 1.05–3.02; *P*-trend = 0.03). Findings for low-dose aspirin were elevated but did not reach statistical significance. Use of non-aspirin NSAIDs was not associated with SCLC risk. Our findings provide further indication of heterogeneity in the association between aspirin and lung cancer morphologies. Large, prospective studies with comprehensive assessments of NSAID use and smoking history and data on both men and women, are needed in order to better understand the association between use of aspirin and SCLC.

### Keywords

Aspirin; Ibuprofen; NSAID; Small cell lung cancer



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**Conflict of interest**
The authors declare no competing financial interests.

## 1. Introduction

Inflammation plays an important role in cancer development and progression at several sites, including the lung [1]. The association between non-steroidal anti-inflammatory drug (NSAID) use and lung cancer risk has been examined by several epidemiologic studies and meta-analyses [2–4] and one randomized clinical trial [5], but results remain equivocal. It may be that these differences in epidemiologic findings are explained by differences in the associations between NSAIDs and individual lung histologies. In a pooled analysis of randomized trials of aspirin versus a placebo, Rothwell et al. [6], reported strong reductions in lung adenocarcinoma deaths (HR 0.55, 95% CI: 0.33–0.94). Unlike non-small cell lung cancers, small cell lung cancers (SCLC) do not express COX-2, calling into question the preventive or therapeutic properties of NSAID use for this tumor subtype [7].

Nevertheless, few prospective studies have examined the association between NSAIDs and SCLC risk [5,8,9]. In a previous report, and consistent with Rothwell et al. [6], we found that use of any NSAID in the past 10 years was inversely associated with the risk of lung adenocarcinomas (HR 0.68, 95% CI: 0.51–0.92) but suggestive of perhaps an increased risk of SCLC (HR 1.43, 95% CI: 0.80–2.57) [9]. Recently, we found that NSAID use was associated with substantially poorer survival from SCLC (unpublished data).

Here we examine, more comprehensively, the use of individual NSAIDs in association with SCLC risk, including effect modification by sex and smoking, in the VITamins And Lifestyle (VITAL) cohort after an additional year of follow-up.

## 2. Methods

### 2.1. Study population

Participants were members of the VITAL cohort, a prospective study designed to investigate the associations of dietary supplements and other behaviors, including over-the-counter medication use, with cancer risk. Details of the study design and cohort enumeration are given in White et al. [10]. Briefly, men and women, ages 50–76 years at baseline, who lived in the 13-county region in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) registry were eligible to participate. Using names purchased from a commercial list, we mailed baseline questionnaires and post-card reminders two weeks later to 364,418 individuals between October 2000 and December 2002. Among these, 77,719 (21.3%) were returned and deemed eligible. We excluded participants with a positive or missing history of lung cancer at baseline ($n = 590$), participants for whom a lung cancer diagnosis was noted only on the death certificate ($n = 8$), as well as diagnoses of lung lymphoma histology ($n = 2$) or *in situ* lung cancer ($n = 1$). We additionally excluded 1572 participants who were missing baseline exposure data. After exclusions there were 75,546 participants available for study. In a sensitivity analysis, we excluded an additional 1953 participants with a positive history of other tobacco-related cancers [including cancers of the mouth, esophagus, stomach, pancreas, bladder, kidney, uterus, or leukemia]. All participants gave informed consent and study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

### 2.2. Data collection

The baseline questionnaire included a detailed assessment of participants regular use of NSAIDs, defined as ≥1 day/week for ≥1 year, including frequency (days/week) and duration of use (years) in the past 10 years of low-dose aspirin, regular or extra-strength aspirin, ibuprofen, naproxen, and celecoxib/rofecoxib. Use of each drug over the 10 years prior to baseline was categorized as none; low, <4 days/week or <4 years; and high, ≥4 days/week and ≥4 years. Additional variables included: ‘total aspirin’, defined as the maximum of 10-

year use of low-dose or regular/extra-strength aspirin; 'non-aspirin NSAIDs', defined as the maximum of 10-year use of ibuprofen, naproxen, and celecoxib/rofecoxib, and 'any NSAIDs', defined as the maximum of 10-year use of each of the NSAIDs assessed. Each variable was categorized as none, low, and high use as for individual NSAIDs. Although assessed at baseline, use of acetaminophen was not analyzed as it has little anti-inflammatory capacity [11].

In addition to data on NSAID use, we collected information at baseline on lung cancer risk factors and indications/contraindications of NSAID use. Participants reported their demographic and health-related characteristics, including height and weight [from which body mass index (BMI, $kg/m^2$) was computed], education, family history of lung cancer, and medical history. Participants who reported having had a heart attack, angina, angioplasty, or bypass surgery were considered to have a positive history of coronary artery disease. Participants also answered several questions regarding cigarette smoking behavior including the age at which they started smoking daily, whether they currently smoked as baseline, the number of cigarettes smoked each day, and the cumulative years of smoking. From these data, we computed pack-years of smoking and number of years since quitting. A summary smoking status variable was also calculated and categorized as never-smoker, former smoker (quit ≥10 years), recent smoker (quit <10 years), and current smoker.

### 2.3. Case ascertainment

Cohort members were followed for incident SCLC diagnoses from baseline to December 31, 2007, with a median follow-up time of 6 years. Incident, primary, invasive SCLCs were ascertained by linking the study cohort to the western Washington SEER cancer registry, which is maintained by the Fred Hutchinson Cancer Research Center. All incident cancer cases (except non-melanoma skin cancer) diagnosed within the 13-county area of western Wash-ington State are reported to SEER along with stage, histologic subtype, and other tumor characteristics [12]. One-hundred eleven incident, invasive SCLC cases were diagnosed among eligible participants between baseline and December 2007.

### 2.4. Follow-up for censoring

Excluding the 111 incident cases of SCLC, participants were right-censored from the analysis at the earliest date of the following events: diagnosis for non-small cell lung cancer ($n = 683$), withdrawal from the study ($n = 22$), death ($n = 3670$), emigration out of the SEER catchment region ($n = 4107$), or December 31, 2007, the end of follow-up ($n = 66,953$).

### 2.5. Statistical analysis

Multivariable-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between use of NSAIDs and SCLC risk. Participants' ages were used as the time metric in regression models, with left truncation at age at baseline. All reported *P*-values are two-sided. *P*-values for trend (*P*-trend) were calculated by treating categorical variables as ordinal in Cox regression models. SAS v9.2 (Cary, NC) was used for all statistical analyses.

We selected potential confounders, *a priori*, for adjustment in multivariable models, including known or suspected risk factors for lung cancer. To accurately control for smoking, we used a step-wise procedure to select the smoking variables [among pack-years, pack-years squared, years of smoking, years of smoking squared, smoking status (4 categories as above), and age when started smoking] that were associated with lung cancer risk at the $P < 0.05$ level [13]. Our final model included years smoked, pack-years, and a squared pack-years term in addition to adjustments for the following characteristics: age (time variable), race (white/non-white), education (≤high school graduate, some college,

college or advanced degree), sex (male, female), BMI at baseline (<25.0, 25.0–29.9, ≥30.0 kg/m$^2$), number of first-degree relatives with a history of lung cancer (none, 1, ≥2), and a history of chronic-obstructive pulmonary disease (yes, no).

To address the issue of confounding by indication, we additionally adjusted models for indications/contraindications of NSAID use, including (yes/no for each of the following): histories of ulcers; migraine or chronic headaches; osteoarthritis or chronic joint pain; rheumatoid arthritis; or coronary artery disease. Regression analyses for any one exposure were further adjusted for use of other NSAIDs.

Due to sex differences in NSAID metabolism [14,15] and the risks of SCLC due to smoking [16], we hypothesized, *a priori*, that the association between NSAIDs and SCLC risk would be modified by sex and smoking status. We therefore stratified multivariable models on these factors. *P*-values for multiplicative interaction (*p*-interaction) between NSAIDs and potential effect-modifiers were computed by including a multiplicative term using the ordinal 10-year NSAID variables in multivariable models.

## 3. Results

Fourteen percent of lung cancers diagnosed in VITAL were SCLC. High users of NSAIDs in the VITAL study were older, heavier, smoked more, and were more likely to have a positive history of coronary artery disease, diabetes, osteoarthritis/joint pain, or migraine/chronic headaches [17]. Multivariable-adjusted associations between NSAID use and SCLC risk are given in Table 1. Relative to non-use, high use of regular-strength aspirin was linearly associated with SCLC risk (HR 1.78, 95% CI: 1.05–3.02; *P*-trend = 0.03). Although HRs were elevated for low-dose aspirin (HR 1.34, 95% CI: 0.77–2.32; *P*-trend = 0.29), confidence intervals were wide and included the null. Use of non-aspirin NSAIDs was not associated with SCLC risk. High use of any NSAID was suggestive of an increased SCLC risk (HR 1.64, 95% CI: 0.94–2.86; *P*-trend = 0.07; data not shown), although this finding was driven almost exclusively by aspirin use. In a sensitivity analysis in which participants with a positive history of tobacco-related cancers were excluded, findings were essentially unchanged (regular-strength aspirin, high vs. non-use: HR 1.65, 95% CI: 0.94–2.91; *P*-trend = 0.06).

Because only regular-strength aspirin was associated with SCLC risk overall, we give findings for aspirin stratified on sex and smoking status in Table 2. Among men, high use of regular-strength aspirin (HR 1.40, 95% CI: 0.70–2.78; *P*-trend = 0.32) was associated with a statistically non-significant increased risk of SCLC compared to non-use (Table 2, top). In women, we observed strong, linear increases in the risk of SCLC for regular-strength aspirin (HR 2.72, 95% CI: 1.18–6.25; *P*-trend = 0.02), however the *P*-interaction (*P* = 0.15) did not achieve statistical significance. Among former smokers at baseline (≥10 years since quitting), hazard ratios of regular-strength aspirin were above but not statistically different from 1.0 (Table 2, bottom). Associations were stronger among current or recent smokers (<10 years since quitting) at baseline: relative to non-use, high use of regular-strength aspirin was associated with a more than doubling of SCLC risk (HR 2.11, 95% CI: 1.13–3.96; *P*-trend = 0.02; *P*-interaction = 0.15), although again the *P*-interaction was statistically non-significant. There were no differences for the associations between low-dose aspirin or non-aspirin NSAIDs and SCLC risk by sex or smoking status (data not shown).

## 4. Discussion

In this prospective cohort of 75,546 men and women living in western Washington State, we found no support for the hypothesis that long-term use of NSAIDs reduces SCLC risk. In contrast, use of regular-strength aspirin was associated with elevated SCLC risk.

Few prior studies have examined the association between NSAID use and SCLC risk, among these, findings were inconsistent [8,18–21]. Whereas, in this cohort, we observed an increased risk for aspirin but not non-aspirin NSAIDs, two of three hospital-based case-control studies reported strong, inverse associations between NSAID use and SCLC risk. In an analysis including 109 SCLC cases from Boston and Washington, D.C., Muscat et al. [21], found that regular use of aspirin (OR 0.68, 95% CI: 0.34–1.35) or any NSAID (OR 0.64, 95% CI: 0.35–1.15) reduced SCLC risk. Moysich et al. [20], observed strong reductions in risk for aspirin use (OR 0.32, 95% CI: 0.16–0.63) in 157 SCLC cases from Buffalo. The remaining case-control study reported no association between aspirin or non-aspirin NSAIDs [18]. In support of our results, Hayes et al. [8], observed a statistically non-significant elevated risk of SCLC with aspirin (≥6 days/week vs. never: HR 1.46, 95% CI: 0.68–3.13) but not NSAID use (≥6 days/week vs. never: HR 0.94, 95% CI: 0.41–2.12) in the Iowa Women's Health Study (IWHS), a prospective cohort of 41,836 women in which 65 SCLC cases developed. Because the primary focus of these studies was the association between NSAID use and overall lung cancer risk, none examined whether the association with SCLC differed by sex (excluding the IWHS which involved only women) or smoking status. Authors from the International Lung Cancer Consortium (ILCCO) recently published a pooled analysis of NSAID use and lung cancer risk using data from 7 case-control studies and 1 prospective cohort; from these data 410 cases of SCLC were examined [19]. Comparing NSAID ever use to never-use, the authors found no clear association in men (OR 0.78, 95% CI: 0.55–1.09) or women (OR 1.18, 95% CI: 0.84–1.66), although use of individual NSAIDs was not examined.

Evidence from randomized trials is sparse. In contrast to our findings of an increased risk in women, Cook et al. [5], reported a borderline protective effect of aspirin versus placebo and SCLC risk (RR 0.54, 95% CI: 0.27–1.10) in the Women's Health Study, a randomized trial of very low-dose aspirin (100 mg) taken every other day; however, the number of SCLC cases was very low ($n = 35$). In a recent pooled analysis of eight randomized trials of aspirin, Roth-well et al. [6], found no effect of aspirin on SCLC deaths (HR 0.85, 95% CI: 0.52–1.39). Because these results were for mortality rather than incidence and were based upon three trials comprised almost entirely (91%) of men [22], meaningful comparisons to our findings are quite limited.

In our study, aspirin use was associated with elevated SCLC risks overall and especially among women and current or recent smokers. One explanation for our subgroup findings is chance. Alternatively, these results are consistent with evidence from studies in animals [15] and humans [14] that aspirin is metabolized differently between the sexes, due in part to differences in the activity of metabolizing enzymes including the Cytochrome P450 and UDP-Glucuronosyltransferase enzyme families, leading to greater bioavailability of aspirin in women [23]. Several of the same metabolizing enzymes for which effects differ by sex are also responsible for the metabolism of polycyclic aromatic hydrocarbons (PAH) found in cigarette smoke [24–26].

Although there is ample evidence indicating that the COX pathway plays an important role in non-small cell lung cancers, SCLC may not depend on the COX pathway for tumorigenesis. For instance, in a study by Hida et al. [7], COX-2 expression was found to occur in 70% adenocarcinomas but no COX-2 expression was observed in SCLC. This suggests that the potential chemopreventive effect of NSAIDS may be limited to non-small cell lung cancers.

A major strength of the VITAL study is its size and prospective design. Ours is the largest prospective study to examine the association between NSAIDs and SCLC risk. Additional strengths include: (a) detailed data on individual NSAIDs and on a wide range of potential

confounding factors, including the capacity to control for indications/contraindications for NSAID use; and (b) near complete follow-up. Although our study has the largest number of cases among prospective studies, we were nevertheless underpowered to examine effect modification by sex or smoking status. An additional limitation is that we did not collect data on the specific timing of NSAID use in the 10 years prior to baseline, and in relation to the timing of cigarette smoking in particular.

In sum, in this large prospective study, we found that use of aspirin was associated with increases in risk of SCLC overall and among women and current/recent smokers in particular. Our findings provide further indication of heterogeneity in the association between aspirin and lung cancer morphologies. Additional large, prospective studies, with comprehensive assessments of NSAID use and smoking history and data on both men and women, are needed in order to better understand the association between use of aspirin and SCLC.

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## Table 1

Association between 10-year NSAID use and small cell lung cancer risk in the VITAL cohort ($n$ = 75,546).

| NSAID | SCLC cases ($n$ = 111), $n$ (%) | Non-cases ($n$ = 75,435), $n$ (%) | Minimally-adjusted HR (95% CI)[a] | Multivariable-adjusted HR (95% CI)[b] |
|---|---|---|---|---|
| Aspirin | | | | |
| Non-user | 38 (38.00) | 37,657 (53.94) | 1.00 (reference) | 1.00 (reference) |
| Low (<4 d/wk or <4 y) | 22 (22.00) | 16,812 (24.08) | 1.16 (0.66–2.04) | 1.18 (0.66–2.09) |
| High (≥4 d/wk and ≥4 y) | 40 (40.00) | 15,350 (21.99) | 1.66 (1.01–2.72) *P*-trend = 0.05 | 1.71 (1.01–2.87) *P*-trend = 0.05 |
| Low-dose aspirin | | | | |
| Non-user | 66 (63.46) | 50,960 (71.36) | 1.00 (reference) | 1.00 (reference) |
| Low (<4 d/wk or <4 y) | 17 (16.35) | 11,673 (16.35) | 1.13 (0.63–2.02) | 1.13 (0.63–2.04) |
| High (≥4 d/wk and ≥4 y) | 21 (20.19) | 8779 (12.29) | 1.33 (0.78–2.29) *P*-trend = 0.29 | 1.34 (0.77–2.32) *P*-trend = 0.29 |
| Regular-strength aspirin | | | | |
| Non-user | 67 (63.21) | 55,191 (75.40) | 1.00 (reference) | 1.00 (reference) |
| Low (<4 d/wk or <4 y) | 15 (14.15) | 9439 (12.90) | 1.32 (0.71–2.45) | 1.32 (0.71–2.44) |
| High (≥4 d/wk and ≥4 y) | 24 (22.64) | 8568 (11.71) | 1.75 (1.05–2.92) *P*-trend = 0.03 | 1.78 (1.05–3.02) *P*-trend = 0.03 |
| Non-aspirin NSAIDs[c] | | | | |
| Non-user | 71 (70.30) | 49,748 (68.97) | 1.00 (reference) | 1.00 (reference) |
| Low (<4 d/wk or <4 y) | 23 (22.77) | 17,210 (23.86) | 0.98 (0.59–1.64) | 0.98 (0.58–1.67) |
| High (≥4 d/wk and ≥4 y) | 7 (6.93) | 5171 (7.17) | 1.04 (0.47–2.29) *P*-trend = 0.97 | 0.98 (0.43–2.21) *P*-trend = 0.94 |
| Ibuprofen | | | | |
| Non-user | 81 (77.88) | 55,145 (75.46) | 1.00 (reference) | 1.00 (reference) |
| Low (<4 d/wk or <4 y) | 17 (16.35) | 13,890 (19.01) | 0.97 (0.54–1.73) | 0.97 (0.54–1.75) |
| High (≥4 d/wk and ≥4 y) | 6 (5.77) | 4044 (5.53) | 1.20 (0.51–2.79) *P*-trend = 0.80 | 1.13 (0.47–2.68) *P*-trend = 0.88 |

Abbreviations: HR: hazards ratio; CI: confidence interval; NSAID: non-steroidal anti-inflammatory drug; SCLC: small cell lung cancer.

[a]Adjusted for age, sex, pack-years, pack-years squared, years smoked, and use of other NSAIDs.

[b]Adjusted for age, sex, race, education, body mass index, pack-years, pack-years squared, years smoked, family history of lung cancer, history of chronic-obstructive pulmonary disease, history of ulcer, migraine or chronic headache, osteoarthritis or chronic joint pain, rheumatoid arthritis, coronary artery disease, and use of other NSAIDs.

[c]Includes ibuprofen, naproxen, and COX-2 inhibitors.

## Table 2

Associations between 10-year regular-strength aspirin use and small cell lung cancer risk in the VITAL cohort, stratified on sex and smoking status ($n$ = 75,546).

| **Regular-strength aspirin** | **10-year Use** | | | ***P*-trend** |
|---|---|---|---|---|
| | **Non-user** | **Low (<4 d/wk or <4 y)** | **High (≥4 d/wk and ≥4 y)** | |
| Males | | | | |
| SCLC cases/non-cases | 38/24,410 | 10/4777 | 15/5483 | |
| HR (95% CI)[a] | 1.00 (reference) | 1.23 (0.56–2.71) | 1.40 (0.70–2.78) | 0.32 |
| Females | | | | |
| SCLC cases/non-cases | 29/3085 | 5/4662 | 9/30,781 | |
| HR (95% CI)[a] | 1.00 (reference) | 1.39 (0.51–3.80) | 2.72 (1.18–6.25)<br>*P*-interaction = 0.15 | 0.02 |
| Former smokers (≥10 y since quit) | | | | |
| SCLC cases/non-cases | 21/19,611 | 2/3543 | 5/3779 | |
| HR (95% CI)[a] | 1.00 (reference) | 0.65 (0.15–2.86) | 1.43 (0.50–4.12) | 0.66 |
| Current/recent smokers (<10 y since quit) | | | | |
| SCLC cases/non-cases | 41/7884 | 11/1503 | 17/1414 | |
| HR (95% CI)[a] | 1.00 (reference) | 1.53 (0.74–3.17) | 2.11 (1.13–3.96)<br>*P*-interaction = 0.15 | 0.02 |

Abbreviations: HR: hazards ratio; CI: confidence interval; NSAID: non-steroidal anti-inflammatory drug; SCLC: small cell lung cancer.

[a]Adjusted for age, sex, race, education, body mass index, pack-years, pack-years squared, years smoked, family history of lung cancer, history of chronic-obstructive pulmonary disease, history of ulcer, migraine or chronic headache, osteoarthritis or chronic joint pain, rheumatoid arthritis, coronary artery disease, and use of other NSAIDs.