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# Pre-Diagnostic Non-steroidal Anti-inflammatory Drug Use and Lung Cancer Survival in the VITAL Study

**Theodore M. Brasky**[1,2], **Christina S. Baik**[1], **Christopher G. Slatore**[3], **Mariela Alvarado**[4], and **Emily White**[1]

[1]Fred Hutchinson Cancer Research Center, Cancer Prevention Program, Seattle, WA, USA

[2]The Ohio State University College of Medicine, Department of Internal Medicine, Division of Cancer Prevention and Control, Columbus, OH, USA

[3]Health Services Research and Development, Portland Veterans Affairs Medical Center, Portland, OR, USA; and Division of Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, USA

[4]Department of Natural Medicine, Bastyr University, Kenmore, WA, USA

## Abstract

**Introduction—**Inflammation is important for lung oncogenesis. Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to improve colorectal cancer survival; however, few have examined the association in lung cancer patients.

**Methods—**The VITamins And Lifestyle (VITAL) cohort includes Washington State residents, age 50 to 76 years who completed a baseline questionnaire between 2000 and 2002. Participants responded on the frequency and duration of use of individual NSAIDs in the previous 10 years. Subjects of this study were 785 members of the cohort who were identified with incident lung cancer from baseline through 2007 through linkage to a population-based cancer registry. Participants were followed for lung cancer death through linkage to state death records through 2009. Adjusted proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between NSAIDs and lung cancer death.

**Results—**522 (66%) participants died from lung cancer. Relative to non-use, high (≥4 days/week and ≥4 years) pre-diagnostic use of regular-strength or low-dose aspirin (HR 0.99, 95% CI: 0.74–1.33 and HR 0.89, 95% CI: 0.67–1.17, respectively) or total non-aspirin NSAIDs (HR 1.20, 95% CI: 0.79–1.83) did not reduce lung cancer death. However, high use of ibuprofen was associated with a 62% increased risk of lung cancer death (HR 1.62, 95% CI: 1.01–2.58).

**Conclusions—**Long-term, pre-diagnostic NSAID use does not improve lung cancer survival overall. Use of ibuprofen may reduce survival from lung cancer. Our results underscore the need for further study of the mechanisms of action for individual NSAIDs with regard to cancer survival.

### Keywords

Aspirin; Ibuprofen; NSAID; Lung Cancer; Histology; Survival

Address for Correspondence: Theodore M. Brasky, The Ohio State University Comprehensive Cancer Center, 1590 N. High St., Suite 525, Columbus, OH 43201, Phone: 614-293-3772, Fax: 614-366-5454, theodore.brasky@osumc.edu.

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## Introduction

Inflammation is important for lung cancer development and progression.[1] We,[2] and other prospective studies of non-steroidal anti-inflammatory drug (NSAID) use,[3] including one randomized trial of aspirin,[4] have demonstrated reductions in lung cancer risk, although findings have been inconsistent.[5–15] Recently, Rothwell et al.,[16] published findings from a pooled analysis of 3 randomized trials of aspirin and 20 year cancer mortality among men. The authors reported that allocation to aspirin versus a placebo was protective for lung cancer death (HR 0.71, 95% CI: 0.58–0.89).[16]

There is increasing evidence that use of NSAIDs improves survival from colorectal cancer;[17, 18] however relatively few studies have examined the association between use of NSAIDs and lung cancer survival.[19–24] The majority of such studies are randomized trials of NSAIDs in addition to chemotherapy in advanced disease; no survival benefit has been reported from these trials.[19–22, 24] The only observational study to examine the association between NSAID use and lung cancer survival reported that pre-operative, regular aspirin use was associated with a 16% reduction in the hazard of all-cause mortality (HR 0.84, *P* value=0.05).[23]

Existing studies of mortality or survival are limited. Findings from the pooled analysis are difficult to interpret because it is unclear as to whether they describe a reduction in lung cancer incidence or an improvement in survival after diagnosis.[16] Clinical trials involving lung cancer patients were limited in assessing the role of NSAIDs with survival due to small sample sizes ($n \leq 400$), scope (i.e., stages at diagnosis, histologic types), outcome (i.e., overall rather than cause-specific survival) and NSAID type (typically COX-2 inhibitors).[19–24] None have examined the use of commonly available non-aspirin NSAIDs (e.g., ibuprofen). Given that two studies of pre-diagnostic aspirin use reported improvements in lung cancer mortality[16] or survival[23], it remains a possibility that pre-diagnostic use of aspirin or other NSAIDs may improve survival from lung cancer.

Here we present our investigation of the association between long-term pre-diagnostic NSAID use and survival from lung cancer among members of the VITamins And Lifestyle (VITAL) cohort.

## Materials and Methods

### Study population

Because we were interested in case-fatality rather than mortality, we only considered the 851 lung cancer cases diagnosed in the VITAL cohort for our analysis. The VITAL cohort is a prospective study designed to investigate the associations of dietary supplements and medications with cancer risk. Details of the study design and cohort enumeration are given in White et al.[25] Briefly, 77,719 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) cancer registry, answered a baseline questionnaire between October 2000 and December 2002. All participants gave informed consent and study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Cohort members were followed for incident lung cancer diagnoses from baseline to December 31, 2007 through annual linkage to SEER, which ascertains all cancer cases diagnosed within western Washington State, along with data on stage and histology. After an average of 6 years of follow-up, 851 incident lung cancer cases were identified.

Exclusions were made for participants with a positive or missing history of lung cancer (n=32), diagnoses of lung lymphoma histology (n=2), *in situ* lung cancer (n=1), and lung cancers identified on their death certificate only (n=8). Participants were additionally excluded if they were missing data on NSAID use (n=14) or cause of death (n=9), leaving 785 lung cancer cases available for study.

### Follow-up for lung cancer death

The 785 members of the VITAL cohort diagnosed with incident lung cancer were followed prospectively for lung cancer death from the date of diagnosis to December 31, 2009, thus the range of follow-up time from diagnosis to end of follow-up was 2–9 years. Deaths were ascertained by linking to the Washington State death file, which includes deaths among Washington State residents who died out of state. Underlying causes of death were reported and coded using ICD-10.

### Censoring

The remaining participants were right-censored from the analysis at the earliest of date of the following events: death from other causes (n=91); emigration out of the Washington State catchment area (n=17), identified through the National Change of Address System and active follow-up; or December 31, 2009, the most recent date of linkage to the Washington State death file (n=155).

### Data collection

The baseline questionnaire included questions on 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 'non-aspirin NSAIDs', defined as the maximum of 10-year use of ibuprofen, naproxen, or celecoxib/rofecoxib, and 'regular-strength NSAIDs', defined as the maximum of 10-year use of regular or extra-strength aspirin, ibuprofen, naproxen, or celecoxib/rofecoxib. Both variables were categorized as none, low, and high use as for individual NSAIDs. Low-dose aspirin use was excluded from the 'regular-strength NSAIDs' variable as it is not thought to have strong anti-inflammatory activity.[26, 27]

Data were also collected at baseline on potential confounding factors. Participants reported on their demographic and health-related characteristics, including race, education, height and weight, physical activity, personal and family medical history, smoking history, and regular diet.

Lung cancer characteristics, including histology, SEER summary stage (all years), and American Joint Committee on Cancer (AJCC) stage (available for cancers diagnosed after 2003), were collected from SEER data.

### Statistical analysis

Cox proportional hazards regression models using follow-up time from the date of diagnosis as the time variable were used to calculate age and sex-adjusted or multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations of participant characteristics and NSAID use with lung cancer death. We selected *a priori* potential confounders for inclusion in multivariable models. Proportional hazards models were adjusted for known or suspected risk factors of lung cancer survival, indications/contraindications of NSAID use, and tumor characteristics (see Table footnotes). Multivariable models for any one NSAID variable were simultaneously adjusted for the

other NSAID variables. Because AJCC stage was only available for lung cancers diagnosed after 2003, models were adjusted for SEER summary stage for cancers diagnosed between 2000–2003 and AJCC stage for cancers diagnosed between 2004–2007. The spearman correlation coefficient between AJCC and SEER summary stage was 0.88, indicating strong agreement between the measures. Models were further adjusted for year of diagnosis (≤2003/>2003) to account for this difference. *P*-values for trend (*P*-trend) were calculated by treating categorical exposures as ordinal in proportional hazards models.

We stratified analyses to examine whether associations between the use of NSAIDs and lung cancer death were modified by gender, stage at diagnosis, and lung cancer histology. *P*-values for interaction (*P*-interaction) between NSAIDs and possible effect-modifiers were calculated by including a multiplicative term in multivariable models.

All analyses were performed using SAS 9.2 for the PC (Cary, NC, USA). All reported *P*-values are two-sided.

## Results

At the end of follow-up, 613 deaths were observed; among the deaths, 522 (85%) were due to lung cancer. The 91 deaths from causes other than lung cancer were due to a variety of causes, including: coronary heart disease (n=18), chronic lower respiratory disease (n=13), stroke (n=6), digestive system diseases (n=5), and ‘other cancers’ (n=26), defined as deaths from cancers other than breast (n=3), colorectal (n=2), prostate (n=1), pancreas (n=1), hematologic malignancies (n=5), or lung. Age and sex-adjusted associations of baseline participant characteristics and lung cancer survival status are given in Table 1. Among participants diagnosed with lung cancer in VITAL, increasing age and male sex were positively associated with lung cancer death. Increasing pack-years of smoking was associated with elevations in risk of lung cancer death and increasing fruit and vegetable consumption were inversely associated with lung cancer death. Correlates of NSAID use, including histories of heart disease, arthritis, or migraine headaches, were not associated with lung cancer death.

Associations between SEER-reported tumor characteristics and lung cancer death are additionally presented in Table 1. As expected, later stage at diagnosis was strongly predictive of poorer lung cancer survival. In addition, there were differences in survival by lung cancer histology, with non-small cell, NOS, small cell carcinomas, and other histologies each associated with increases in risk of lung cancer death relative to adenocarcinomas. Although surgical treatments were associated with reductions in risk of lung cancer death, and non-surgical treatments were associated with increases in risk of lung cancer death, these findings are reflective of mutual confounding and confounding by stage at diagnosis. Each was strongly protective for lung cancer death after being placed in a single regression model and further adjusted for stage at diagnosis (data not shown).

Table 2 gives age and sex-adjusted and multivariable-adjusted HRs and 95% CI for the associations between pre-diagnostic 10-year use of individual NSAIDs and lung cancer death. There were few differences between the minimally-adjusted and fully-adjusted models. Compared to non-use, high 10-year use of regular-strength NSAIDs was not associated with lung cancer death (HR 1.14, 95% CI: 0.87–1.51; *P*-trend=0.10). Use of low-dose or regular-strength aspirin, or non-aspirin NSAIDs overall was not associated with lung cancer death; however, high 10-year use of ibuprofen was associated with a borderline 62% increased risk of lung cancer death (HR 1.62, 95% CI: 1.01–2.58; *P*-trend=0.21). The associations did not differ by gender (data not shown).

We hypothesized that NSAIDs may be associated with some survival benefit for those diagnosed at earlier stages in particular. Therefore, we stratified our analysis on SEER summary stage (Table 3). Relative to non-use, high 10-year use of regular-strength NSAIDs was not associated with improved lung cancer survival for participants whose cancers were diagnosed at local/regional (HR 1.12, 95% CI: 0.62–2.03) or distant stage (HR 1.11, 95% CI: 0.78–1.59). High use of non-aspirin NSAIDs was suggestive of an increased risk of lung cancer death among those diagnosed at late stage (HR 1.70, 95% CI: 1.00–2.90; *P*-trend <0.01). The *P*-value for interaction was <0.01. Although the non-aspirin NSAIDs variable is a combination of several NSAIDs, 17 of 22 participants classified as 'high' non-aspirin NSAID users among those diagnosed as distant stage took ibuprofen.

In an exploratory analysis with limited statistical power, we additionally stratified analyses on the most common lung cancer histologic types (Table 4): SCLC (n=111), adenocarcinoma (n=275), squamous cell carcinoma (n=133), and NSCLC, NOS (n=173). Compared to non-use, high 10-year use of regular-strength NSAIDs was associated with a more than three-fold increase in the risk of death from SCLC (HR 3.33, 95% CI: 1.05–10.52; *P*-trend=0.03) and not associated with survival from the other histologic types. The increase in SCLC deaths was due to positive associations with both regular-strength aspirin (HR 4.13, 95% CI: 1.28–13.30; *P*-trend<0.01) and non-aspirin NSAIDs (HR 3.24, 95% CI: 0.49–21.57; *P*-trend=0.42). Six of seven participants classified as 'high' non-aspirin NSAID users among the SCLC group used ibuprofen. Use of low-dose aspirin was not associated with survival among those diagnosed with SCLC. We additionally observed a positive, albeit statistically non-significant association between high use of non-aspirin NSAIDs and risk of death from NSCLC, NOS (HR 2.00, 95% CI: 0.77–5.17; *P*-trend=0.10). Use of low-dose, but not regular-strength aspirin, was associated with an increased risk of death from squamous cell carcinoma (HR 3.69, 95% CI: 1.04–13.17; *P*-trend=0.34) and a reduced risk of death from NSCLC, NOS (HR 0.45, 95% CI: 0.23–0.85; *P*-trend=0.03). *P* values for interaction did not achieve statistical significance.

## Discussion

In this study of 785 VITAL cohort members diagnosed with incident lung cancer, we found little evidence to support the hypothesis that long-term pre-diagnostic use of aspirin or non-aspirin NSAIDs improves lung cancer survival. Rather, our findings suggest that use of non-aspirin NSAIDs increase the risk of lung cancer death among those diagnosed with distant stage disease, and use of aspirin and non-aspirin NSAIDs increase the risk of lung cancer death among those diagnosed with SCLC.

Our finding of no association between the use of low-dose or regular-strength aspirin and lung cancer survival differs from the literature. In the only previous observational study, Fontaine et al.,[23] examined the association between regular aspirin use prior to surgical resection and overall survival among 1,765 patients with primarily early-stage (89% stages I-IIb) NSCLC. The authors reported that aspirin use was associated with a 16% reduction in death from all causes (HR 0.84, *P*-value=0.05). Fontaine et al.,[23] did not examine cause-specific survival and the authors suggest that their findings may be due to reductions in cardiovascular disease deaths.[23] In contrast, in a trial of 303 SCLC patients randomized to aspirin (1g/d) plus chemotherapy vs. chemotherapy alone, Lebeau et al.,[24] reported no effect on overall survival.

To our knowledge, no prior study has examined the association between ibuprofen or other over-the-counter non-aspirin NSAIDs and lung cancer survival. The association between other non-aspirin NSAIDs, celecoxib (800mg/d) or rofecoxib (50mg/d) in addition to chemotherapy (e.g., irinotecan, docetaxel, and gemcitabine), and lung cancer survival have

been examined in a few small randomized trials among patients diagnosed with late-stage NSCLC;[20–22] in contrast to our observations of increased risks of lung cancer death, none observed an association with survival. In light of the many differences between these studies and ours, particularly differences in scope (i.e., stages at diagnosis and histologic type), and NSAID type, timing, and dose, replication of our finding is warranted.

Although limited by statistical power, we additionally examined the association between NSAID use and lung cancer death by lung cancer histology. Our finding that use of regular-strength aspirin and non-aspirin NSAIDs (primarily ibuprofen) was associated with 3 to 4-fold increases in risk of lung cancer death among those diagnosed with SCLC is not supported by the trial by Lebeau et al.[24] described above, the only survival study to examine the association between an NSAID (aspirin) and survival in SCLC. With the exception of NSCLC, NOS, for which we observed an inverse association between low-dose aspirin use and lung cancer death, our finding of no benefit of NSAID use for NSCLC subtypes is largely supported by the clinical trials described above which reported no association in NSCLC patients.[19–22] However, in the only other observational study of aspirin and overall survival in NSCLC patients an inverse association was reported with no difference by histologic subtypes.[23]

Chronic inflammation is thought to be important for the development and progression of cancer,[28, 29] and there is evidence that it is associated specifically with lung oncogenesis.[1] Cyclooxygenase (COX) enzymes are responsible for the synthesis of prostaglandins as a result of cytokine signaling. The inducible COX isoform, COX-2 has been associated with cell invasion, angiogenesis, and metastasis *in vitro* [1] and its expression in human lung cancers has been associated with poorer survival among NSCLC patients.[30] NSAIDs are thought to inhibit inflammation by binding to COX-2. In humans, increasing blood concentrations of inflammatory biomarkers have been associated with poorer lung cancer survival.[31–36] Given this evidence, it is unclear why long-term pre-diagnostic use of NSAIDs was not associated with a reduction in lung cancer death in this study. It is also unclear why some NSAIDs would be associated with significant increases in SCLC or late-stage lung cancer deaths. Recently we reported that NSAID use was inversely associated with risk of adenocarcinoma[2] and positively associated with SCLC risk.[37] One possible mechanism may be via modulation of cellular epithelial-mesenchymal transition (EMT). The COX-2 pathway has been implicated to play a role in EMT, which has been associated with increased cellular migration and tumor metastasis.[1] While there is *in vitro* evidence that NSAIDs may reverse EMT in lung cancer,[1, 38] there is also data suggesting that certain NSAIDs can promote EMT in lung cancer cell lines, thus enhancing cellular migration.[39] This suggests that NSAIDs may alter tumor behavior, although the exact mechanism needs to be further elucidated.

This study has some pertinent limitations that should be considered in the evaluation of our results. Foremost, NSAID data was collected at baseline, up to 7 years prior to lung cancer diagnosis. Should NSAIDs reduce lung cancer death, proper timing and dose is not well understood; however if we assume that use closer to time to diagnosis is more important than earlier time periods,[17] non-differential measurement error would be introduced. Depending on its strength, such error may explain the mostly null results we observed, however subgroup findings would be *in spite of* this error. Because we were not able to adjust for AJCC stage at diagnosis for cancers diagnosed between 2000 and 2003, we are additionally limited by incomplete adjustment in regression models. We attempted to minimize any residual effect by including SEER summary stage as a surrogate for AJCC staging for those years and adjusting for AJCC stage among cancers diagnosed after 2003. In general, point estimates were not appreciably changed, suggesting that stage at diagnosis and other tumor characteristics likely do not lie on the pathway between pre-diagnostic

NSAID use and lung cancer death. In addition, NSAID users in this study were generally less healthy at baseline and possibly more likely to die from causes other than lung cancer than non-users. These competing risks would have minimal effects on our results for two reasons: 1) there were relatively few deaths from causes other than lung cancer; and 2) it is unlikely that those who died from other causes differed in their risks of lung cancer death independent of their shared risk factors, for which we made every effort to adjust. Lastly, given the large number of exploratory subgroup analyses, it is possible that these findings in particular are the result of chance.

This study has several strengths. It is the first study to examine the association between several commonly available NSAIDs and lung cancer survival, and the first to examine these associations by histologic type, stage, and treatment. Our study is the largest in scope, in that we were able to examine associations in patients with a range of histologies and stages at diagnosis. Although limited by the timing of NSAID assessment, our baseline questionnaire was comprehensive with regard to NSAID type and characterization of long-term use. In addition, we were able to adjust for many potential confounding factors as well as indications/contraindications of NSAID use.

In conclusion, among 785 members of the VITAL cohort diagnosed with lung cancer, we found little evidence to support the hypothesis that long-term pre-diagnostic NSAID use is associated with an improvement in lung cancer survival. Contrary to our hypothesis and current knowledge on mechanisms of action, we found that long-term pre-diagnostic use of non-aspirin NSAIDs was associated with a reduction in lung cancer survival (i.e., increases in death) among those diagnosed as late stage. In addition, use of regular-strength NSAIDs was associated with substantial reductions in lung cancer survival among those diagnosed with SCLC. Our results underscore the need for further study of the timing of use and mechanisms of action for individual NSAIDs with regard to cancer survival. Because these findings are novel, replication is warranted before a clinical recommendation can be made.

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## Table 1

Age, sex, and follow-up time-adjusted associations between lifestyle and tumor characteristics and lung cancer survival among 785 VITAL participants diagnosed with lung cancer.

| | Lung Cancer Death | | |
|---|---|---|---|
| **Characteristic** | **Yes *n* = 522, N (%)** | **No *n* = 263, N (%)** | **Age & Sex-Adjusted HR (95% CI) of lung cancer death** |
| Age at diagnosis (years) | | | |
| 50 to 55.0 | 16 (72.73) | 6 (27.27) | 1.00 (reference) |
| 55.1 to 60.0 | 36 (64.29) | 20 (35.71) | 0.94 (0.52–1.69) |
| 60.1 to 65.0 | 64 (65.31) | 34 (34.69) | 0.91 (0.52–1.57) |
| 65.1 to 70.0 | 102 (68.00) | 48 (32.00) | 1.11 (0.65–1.88) |
| 70.1 to 75.0 | 141 (65.28) | 75 (34.72) | 1.00 (0.60–1.69) |
| 75.1 to 82.4 | 163 (67.08) | 80 (32.92) | 1.25 (0.74–2.09) |
| Sex | | | |
| Female | 322 (73.52) | 116 (26.48) | 1.00 (reference) |
| Male | 200 (57.64) | 147 (42.36) | 1.51 (1.26–1.81) |
| Race | | | |
| White | 481 (66.99) | 237 (33.01) | 1.00 (reference) |
| Non-white | 31 (68.89) | 14 (31.11) | 1.20 (0.82–1.74) |
| Education | | | |
| ≤ High school | 177 (66.29) | 90 (33.71) | 1.00 (reference) |
| Some college | 215 (67.61) | 103 (32.39) | 1.05 (0.86–1.29) |
| ≥ College graduate | 121 (67.60) | 58 (32.40) | 0.99 (0.78–1.25) |
| Body mass index ($kg/m^2$) | | | |
| <25.0 | 178 (63.35) | 103 (36.65) | 1.00 (reference) |
| 25.0 to 29.9 | 220 (70.29) | 93 (29.71) | 1.06 (0.87–1.30) |
| ≥ 30.0 | 98 (66.22) | 50 (33.78) | 1.01 (0.79–1.29) |
| Pack-years | | | |
| None | 30 (51.72) | 28 (48.28) | 1.00 (reference) |
| >0 to 35.0 | 155 (63.01) | 91 (36.99) | 1.37 (0.93–2.04) |
| 35.1 to 52.5 | 178 (68.46) | 82 (31.54) | 1.65 (1.11–2.44) |
| 52.6 to 135 | 147 (71.36) | 59 (28.64) | 1.75 (1.17–2.61) |
| Self-perceived health | | | |
| Excellent | 29 (65.91) | 15 (34.09) | 1.00 (reference) |
| Very good | 146 (67.91) | 69 (32.09) | 1.08 (0.72–1.61) |
| Good | 201 (67.22) | 98 (32.78) | 1.13 (0.76–1.66) |
| Fair | 111 (66.07) | 57 (33.93) | 1.23 (0.82–1.86) |
| Poor | 23 (60.53) | 15 (39.47) | 1.31 (0.75–2.28) |
| Physical activity (MET-hrs/wk) | | | |
| None | 125 (63.45) | 72 (36.55) | 1.00 (reference) |
| >0 to 3.4 | 129 (68.62) | 59 (31.38) | 1.14 (0.89–1.46) |
| 3.5 to 11.1 | 124 (65.26) | 66 (34.74) | 0.96 (0.75–1.24) |
| 11.1 to 89.0 | 132 (69.11) | 59 (30.89) | 1.04 (0.81–1.33) |

| | Lung Cancer Death | | |
|---|---|---|---|
| **Characteristic** | **Yes *n* = 522, N (%)** | **No *n* = 263, N (%)** | **Age & Sex-Adjusted HR (95% CI) of lung cancer death** |
| Fruit and vegetable consumption (servings/day) | | | |
| 0 to 1.9 | 162 (71.05) | 66 (28.95) | 1.00 (reference) |
| 2.0 to 3.4 | 158 (68.70) | 72 (31.30) | 0.88 (0.70–1.09) |
| 3.5 to 12.7 | 142 (62.01) | 87 (37.99) | 0.76 (0.60–0.96) |
| History of chronic-obstructive pulmonary disease | | | |
| No | 428 (65.95) | 221 (34.05) | 1.00 (reference) |
| Yes | 94 (69.12) | 42 (30.88) | 1.19 (0.95–1.49) |
| Number of first-degree relatives with lung cancer | | | |
| None | 417 (66.51) | 210 (33.49) | 1.00 (reference) |
| 1 | 93 (66.91) | 46 (33.09) | 0.89 (0.71–1.12) |
| ≥2 | 10 (71.43) | 4 (28.57) | 1.38 (0.74–2.60) |
| History of coronary artery disease | | | |
| No | 427 (66.41) | 216 (33.59) | 1.00 (reference) |
| Yes | 95 (66.90) | 47 (33.10) | 1.02 (0.81–1.28) |
| History of osteoarthritis or chronic joint pain | | | |
| No | 258 (68.07) | 121 (31.93) | 1.00 (reference) |
| Yes | 264 (65.02) | 142 (34.98) | 0.99 (0.83–1.17) |
| History of rheumatoid arthritis | | | |
| No | 486 (66.30) | 247 (33.70) | 1.00 (reference) |
| Yes | 36 (69.23) | 16 (30.77) | 1.20 (0.85–1.68) |
| History of migraine or chronic headaches | | | |
| No | 469 (67.00) | 231 (33.00) | 1.00 (reference) |
| Yes | 53 (62.35) | 32 (37.65) | 1.12 (0.84–1.50) |
| History of gastric ulcers | | | |
| No | 463 (66.52) | 233 (33.48) | 1.00 (reference) |
| Yes | 59 (66.29) | 30 (33.71) | 1.04 (0.79–1.36) |
| Tumor histology | | | |
| Adenocarcinoma | 157 (57.72) | 115 (42.28) | 1.00 (reference) |
| Squamous cell carcinoma | 78 (58.65) | 55 (41.35) | 0.98 (0.75–1.29) |
| Large cell carcinoma | 13 (76.47) | 4 (23.53) | 1.54 (0.87–2.71) |
| Non-small cell carcinoma, NOS | 134 (79.29) | 35 (20.71) | 2.01 (1.59–2.54) |
| Small cell carcinoma | 90 (82.57) | 19 (17.43) | 2.29 (1.75–2.99) |
| Other | 50 (58.82) | 35 (41.18) | 1.39 (1.01–1.91) |
| SEER summary stage (2000–2003) | | | |
| Local | 17 (30.91) | 38 (69.09) | 1.00 (reference) |
| Regional | 43 (64.18) | 24 (35.82) | 3.14 (1.78–5.56) |
| Distant | 119 (90.84) | 12 (9.16) | 8.73 (5.14–14.82) |
| AJCC stage (2004–2007) | | | |
| I | 23 (21.70) | 83 (78.30) | 1.00 reference |
| II | 12 (52.17) | 11 (47.83) | 3.38 (1.68–6.82) |
| III | 83 (66.94) | 41 (33.06) | 5.17 (3.24–8.23) |

| | Lung Cancer Death | | |
|---|---|---|---|
| **Characteristic** | **Yes *n* = 522, N (%)** | **No *n* = 263, N (%)** | **Age & Sex-Adjusted HR (95% CI) of lung cancer death** |
| IV | 184 (85.58) | 31 (14.42) | 11.51 (7.39–17.92) |
| Surgical treatment | | | |
| No | 463 (81.37) | 106 (18.63) | 1.00 (reference) |
| Yes | 59 (27.31) | 157 (72.69) | 0.14 (0.10–0.18) |
| Lymph node resection or aspiration | | | |
| No | 423 (79.81) | 107 (20.19) | 1.00 (reference) |
| Yes | 98 (38.74) | 155 (61.26) | 0.22 (0.18–0.28) |
| Radiation therapy | | | |
| No | 264 (58.15) | 190 (41.85) | 1.00 (reference) |
| Yes | 253 (78.82) | 68 (21.18) | 1.61 (1.35–1.93) |
| Chemotherapy | | | |
| No | 189 (52.65) | 170 (47.35) | 1.00 (reference) |
| Yes | 324 (78.26) | 90 (21.74) | 1.60 (1.33–1.92) |

Abbreviations: HR, hazard ratio; CI, confidence interval

**Table 2**

Associations between NSAID use and lung cancer death in VITAL (n=785).

| NSAID | 10-year Use | | | |
|---|---|---|---|---|
| | Non-user | Low (<4d/wk or <4y) | High (≥4d/wk and ≥4y) | *P*-trend |
| Regular-strength NSAIDs[c] | | | | |
| Lung cancer deaths, *n*, Yes/No | 245/136 | 131/60 | 105/50 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.19 (0.95–1.48) | 1.10 (0.87–1.39) | 0.27 |
| HR (95% CI) for lung cancer death[b] | 1.00 (reference) | 1.54 (1.20–1.96) | 1.14 (0.87–1.51) | 0.10 |
| Regular-strength aspirin | | | | |
| Lung cancer deaths, *n*, Yes/No | 351/189 | 69/31 | 83/38 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.14 (0.87–1.50) | 1.05 (0.81–1.35) | 0.53 |
| HR (95% CI) for lung cancer death[b] | 1.00 (reference) | 1.49 (1.10–2.01) | 0.99 (0.74–1.33) | 0.51 |
| Non-aspirin NSAIDs[d] | | | | |
| Lung cancer deaths, *n*, Yes/No | 356/186 | 106/50 | 33/15 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.08 (0.86–1.35) | 1.15 (0.79–1.67) | 0.37 |
| HR (95% CI) for lung cancer death[b] | 1.00 (reference) | 1.22 (0.94–1.59) | 1.20 (0.79–1.83) | 0.14 |
| Ibuprofen | | | | |
| Lung cancer deaths, *n*, Yes/No | 402/209 | 73/41 | 29/6 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.94 (0.72–1.24) | 1.65 (1.10–2.47) | 0.13 |
| HR (95% CI) for lung cancer death[b] | 1.00 (reference) | 0.96 (0.71–1.30) | 1.62 (1.01–2.58) | 0.21 |
| Low-dose aspirin | | | | |
| Lung cancer deaths, *n*, Yes/No | 323/158 | 78/50 | 89/37 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.88 (0.68–1.14) | 1.05 (0.82–1.35) | 0.94 |
| HR (95% CI) for lung cancer death[b] | 1.00 (reference) | 0.92 (0.68–1.23) | 0.89 (0.67–1.17) | 0.36 |

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; CI, confidence interval

[a]Adjusted for age at diagnosis and sex

[b]Adjusted for age at diagnosis, sex, race, pack-years of smoking, self-perceived health, fruit and vegetable consumption, chronic-obstructive pulmonary disease, family history of lung cancer, ulcer, migraine or chronic headaches, osteoarthritis or chronic joint pain, rheumatoid arthritis, coronary artery disease, stage at diagnosis, year of diagnosis, histology, surgical treatment, lymph node resection, radiation, chemotherapy, and other NSAIDs

[c] Includes regular-strength aspirin, ibuprofen, naproxen, and COX-2 inhibitors

[d] Includes ibuprofen, naproxen, and COX-2 inhibitors

## Table 3

Multivariable-adjusted associations between NSAID use and lung cancer death, stratified on SEER summary stage at diagnosis (n=785).

| NSAID | 10-year Use | | | |
|---|---|---|---|---|
| | Non-user | Low (<4d/wk or <4y) | High (≥4d/wk and ≥4y) | *P*-trend |
| **Regular-strength NSAIDs**[b] | | | | |
| *Local/Regional stage* (n=353) | | | | |
| Lung cancer deaths, *n*, Yes/No | 70/96 | 40/50 | 32/37 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.79 (1.06–3.03) | 1.12 (0.62–2.03) | 0.45 |
| *Distant stage* (n=419) | | | | |
| Lung cancer deaths, *n*, Yes/No | 167/38 | 90/6 | 69/13 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.81 (1.34–2.45) | 1.11 (0.78–1.59)<br>*P*-interaction = 0.08 | 0.10 |
| **Regular-strength aspirin** | | | | |
| *Local/Regional stage* (n=353) | | | | |
| Lung cancer deaths, *n*, Yes/No | 103/139 | 21/26 | 22/26 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.04 (0.57–1.88) | 0.89 (0.47–1.69) | 0.79 |
| *Distant stage* (n=419) | | | | |
| Lung cancer deaths, *n*, Yes/No | 239/46 | 48/3 | 57/12 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.71 (1.17–2.51) | 0.89 (0.61–1.30)<br>*P*-interaction = 0.29 | 0.79 |
| **Non-aspirin NSAIDs**[c] | | | | |
| *Local/Regional stage* (n=353) | | | | |
| Lung cancer deaths, *n*, Yes/No | 101/131 | 34/42 | 14/12 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.42 (0.86–2.35) | 0.79 (0.36–1.74) | 0.80 |
| *Distant stage* (n=419) | | | | |
| Lung cancer deaths, *n*, Yes/No | 242/51 | 71/5 | 19/3 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.50 (1.07–2.11) | 1.70 (1.00–2.90)<br>*P*-interaction < 0.01 | <0.01 |
| **Low-dose aspirin** | | | | |
| *Local/Regional stage* (n=353) | | | | |
| Lung cancer deaths, *n*, Yes/No | 94/121 | 26/36 | 24/26 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.49 (0.27–0.89) | 0.95 (0.53–1.71) | 0.45 |
| *Distant stage* (n=419) | | | | |
| Lung cancer deaths, *n*, Yes/No | 219/34 | 52/12 | 61/10 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.12 (0.78–1.62) | 0.80 (0.57–1.13)<br>*P*-interaction = 0.35 | 0.32 |

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; CI, confidence interval

[a]Adjusted for age at diagnosis, sex, race, pack-years of smoking, self-perceived health, fruit and vegetable consumption, chronic-obstructive pulmonary disease, family history of lung cancer, ulcer, migraine or chronic headaches, osteoarthritis or chronic joint pain, rheumatoid arthritis, coronary artery disease, AJCC stage at diagnosis, year of diagnosis, histology, surgical treatment, lymph node resection, radiation, chemotherapy, and other NSAIDs

[b]Includes regular-strength aspirin, ibuprofen, naproxen, and COX-2 inhibitors

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

## Table 4

Multivariable-adjusted associations between NSAID use and lung cancer death, stratified on lung cancer histologic type (n=785).

| NSAID | 10-year Use | | | |
|---|---|---|---|---|
| | Non-user | Low (<4d/wk or <4y) | High (≥4d/wk and ≥4y) | *P*-trend |
| **Regular-strength NSAIDs**[b] | | | | |
| *Small cell lung cancer (n=111)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 36/8 | 20/4 | 23/6 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 2.27 (0.82–6.29) | 3.33 (1.05–10.52) | 0.03 |
| *Adenocarcinoma (n=275)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 77/56 | 46/36 | 22/15 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.93 (1.21–3.08) | 0.80 (0.42–1.52) | 0.78 |
| *Squamous cell carcinoma (n=133)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 38/29 | 16/7 | 18/18 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.61 (0.19–1.91) | 0.88 (0.30–2.58) | 0.65 |
| *Non-small cell lung cancer, not otherwise specified (n=173)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 64/21 | 34/6 | 28/4 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.22 (0.68–2.22) | 1.24 (0.69–2.23)<br>*P*-interaction = 0.89 | 0.42 |
| **Regular-strength aspirin** | | | | |
| *Small cell lung cancer (n=111)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 53/12 | 13/2 | 19/5 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 2.90 (1.06–7.97) | 4.13 (1.28–13.30) | <0.01 |
| *Adenocarcinoma (n=275)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 111/88 | 24/14 | 17/12 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.85 (0.97–3.51) | 0.73 (0.35–1.54) | 0.89 |
| *Squamous cell carcinoma (n=133)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 51/34 | 11/6 | 13/14 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.51 (0.13–1.95) | 0.62 (0.19–2.07) | 0.37 |
| *Non-small cell lung cancer, not otherwise specified (n=173)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 93/26 | 15/5 | 24/2 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.86 (0.38–1.90) | 0.94 (0.51–1.76)<br>*P*-interaction = 0.93 | 0.80 |
| **Non-aspirin NSAIDs**[c] | | | | |
| *Small cell lung cancer (n=111)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 57/13 | 19/4 | 6/1 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.87 (0.26–2.87) | 3.24 (0.49–21.57) | 0.42 |
| *Adenocarcinoma (n=275)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 106/74 | 38/31 | 5/3 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.35 (0.81–2.23) | 0.75 (0.24–2.31) | 0.64 |
| *Squamous cell carcinoma (n=133)* | | | | |

| NSAID | 10-year Use | | | |
|---|---|---|---|---|
| | Non-user | Low (<4d/wk or <4y) | High (≥4d/wk and ≥4y) | *P*-trend |
| Lung cancer deaths, *n*, Yes/No | 54/44 | 11/6 | 8/5 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.81 (0.24–2.69) | 1.42 (0.39–5.19) | 0.75 |
| *Non-small cell lung cancer, not otherwise specified (n=173)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 93/29 | 25/2 | 10/2 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.40 (0.74–2.63) | 2.00 (0.77–5.17)<br>*P*-interaction = 0.65 | 0.10 |
| **Low-dose aspirin** | | | | |
| *Small cell lung cancer (n=111)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 53/11 | 14/3 | 17/4 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.01 (0.33–3.04) | 1.23 (0.47–3.22) | 0.68 |
| *Adenocarcinoma (n=275)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 97/68 | 27/29 | 25/13 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.64 (0.35–1.17) | 1.08 (0.61–1.93) | 0.70 |
| *Squamous cell carcinoma (n=133)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 51/34 | 8/7 | 13/9 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 0.20 (0.05–0.84) | 3.69 (1.04–13.17) | 0.34 |
| *Non-small cell lung cancer, not otherwise specified (n=173)* | | | | |
| Lung cancer deaths, *n*, Yes/No | 84/17 | 21/7 | 21/8 | |
| HR (95% CI) for lung cancer death[a] | 1.00 (reference) | 1.08 (0.53–2.19) | 0.45 (0.23–0.85)<br>*P*-interaction = 0.33 | 0.03 |

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; CI, confidence interval

[a]Adjusted for age at diagnosis, sex, race, pack-years of smoking, self-perceived health, fruit and vegetable consumption, chronic-obstructive pulmonary disease, family history of lung cancer, ulcer, migraine or chronic headaches, osteoarthritis or chronic joint pain, rheumatoid arthritis, coronary artery disease, stage at diagnosis, year of diagnosis, surgical treatment, lymph node resection, radiation, chemotherapy, and other NSAIDs

[b]Includes regular-strength aspirin, ibuprofen, naproxen, and COX-2 inhibitors

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