Use of Glucosamine and Chondroitin and Lung Cancer Risk in the VITamins And Lifestyle (VITAL) Cohort

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Running Title: Glucosamine and Chondroitin and Lung Cancer Risk in VITAL

Keywords: Adenocarcinoma, Chondroitin, Glucosamine, Non-Small Cell Lung Cancer, Small-Cell Lung Cancer, Supplement

Abstract

Objective: Inflammation plays an important role in lung carcinogenesis. Epidemiologic studies have reported inverse associations of non-steroidal anti-inflammatory drug (NSAID) use and lung cancer risk. Previously, we found that ever use of glucosamine and chondroitin, which have anti-inflammatory properties, were inversely associated with lung cancer risk. After an additional year of follow-up, we further examined the association including frequency/duration of use, interaction with factors associated with inflammation, and lung cancer histology.

Methods: Participants were members of the VITamins And Lifestyle (VITAL) Cohort. Adults, ages 50-76 years, who were residents of western Washington State, completed a baseline questionnaire in 2000-2002 (n=76,904). Participants were queried on their use of glucosamine and chondroitin, over the 10 years prior to baseline, and categorized as nonuser, low use <4 days/week or <3 years, or high use ≥4 days/week and ≥3 years. Lung cancer cases (n=808) were ascertained through linkage to the Surveillance, Epidemiology, and End Results cancer registry.

Results: High 10-year use of glucosamine [Hazard Ratio (HR) 0.77, 95% CI: 0.56-1.07; *P*-trend=0.04] but not chondroitin was associated with a reduction in lung cancer risk. The association with glucosamine was limited to adenocarcinoma (HR 0.49, 95% CI: 0.27-0.90; *P*-trend<0.01), and was not modified by NSAID use or smoking status.

Conclusions: Our results for glucosamine use are similar to the prior human studies of NSAID use and lung cancer, both in magnitude and the limitation of the association to adenocarcinoma. Unlike NSAIDs, glucosamine has no known adverse-effects. Although confirmatory studies are needed, glucosamine is an attractive candidate for lung cancer chemoprevention.

Introduction

Inflammation plays an important role in cancer etiology and progression at several anatomic sites, including the lung (1). Studies of non-steroidal anti-inflammatory drug (NSAID) use and lung cancer incidence and death have generally reported inverse associations (2, 3). However use of NSAIDs for cancer prevention is not recommended due to their adverse effects (4-6).

Previously, in an exploratory study of 11 non-vitamin, non-mineral "specialty" supplements, we reported that ever use of glucosamine and chondroitin supplements over the 10 years before baseline were inversely associated with the risk of lung cancer in the VITamins And Lifestyle (VITAL) cohort study (7). These supplements exhibit anti-inflammatory and anti-cancer properties *in vitro* and *in vivo* (8-11). In Europe, they are approved prescription drugs for osteoarthritis; however, in the United States, they fall under the Dietary Supplements health and Education (DSHEA) Act, and are sold over-the-counter for "joint health". They are the most commonly used non-vitamin, non-mineral supplements in the United States (12) and have a very low risk of adverse effects (13). Here we comprehensively evaluate glucosamine and chondroitin use with the risk of lung cancer by examining use by frequency/duration, effect modification by factors associated with inflammation, and by histologic subtypes of lung cancer, after an additional year of follow-up.

Materials and Methods

Study population

Participants were members of the VITAL cohort, a study of men and women designed specifically to investigate the associations of vitamin, mineral, and specialty supplements with cancer risk. Details of the study design and cohort enumeration are given in White et al. (14).

Briefly, men and women, 50-76 years of age at baseline, who lived in the 13-county region in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry were eligible to participate. Between October 2000 and December 2002, we mailed baseline questionnaires and post-card reminders two weeks later to 364,418 names purchased from a commercial mailing list. Of 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 further excluded 214 participants who were missing baseline information on glucosamine and chondroitin. After exclusions there were 76,904 participants available for study.

Data collection

The baseline questionnaire included a detailed assessment of dietary supplement use. Respondents were queried on their use of glucosamine and chondroitin during the 10-year period prior to baseline, in addition to use of individual vitamin, mineral, multivitamin, and other specialty or herbal supplements. Respondents answered questions about their current and past regular use, defined as ≥1 day/week for ≥1 year, of glucosamine and chondroitin. Questions included frequency (days/week) and duration (years) of use in the previous 10 years. Participants were not queried on dose because no standards exist for accurate dosing of these preparations. Although we did not evaluate the validity and reliability of our assessment of reported glucosamine or chondroitin use, we assessed the accuracy of 17 vitamin and mineral supplements in VITAL in a 3-month test-retest reliability sub-study of 220 randomly selected participants; intraclass-correlation coefficients ranged from 0.69 to 0.87 (15).

In addition to supplement use, we collected information at baseline on lung cancer risk factors and correlates of supplement use. Participants reported on personal characteristics, including height and weight at baseline and at 45 years of age [from which body mass index (BMI, kg/m^2) was computed], family history of lung cancer, medical history, and use of NSAIDs. A summary variable for NSAID use included aspirin and non-aspirin NSAIDs and excluded low-dose aspirin. Respondents also answered several questions regarding cigarette smoking behavior including the age at which they started smoking daily, whether they currently smoked at 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.

Case ascertainment

Cohort members were followed for incident lung cancer diagnoses from baseline to December 31, 2007, with a mean follow-up time of 6 years. Incident, primary, invasive lung cancers 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 diagnosed within the 13-county area of western Washington State (except non-melanoma skin cancer) are reported to SEER along with stage, histologic subtype, and other tumor characteristics (16). Cases were ascertained through all area hospitals, offices of pathologists, oncologists, and radiotherapists, and from state death certificates. Extensive quality-control procedures ensure that registry data are accurate and complete. Linkage to SEER is based on ranking of the agreement between characteristics common to VITAL and SEER including name, social security number, date of birth, etc.; matches with high concordance were

made automatically, while visual inspection was performed for matches in which some, but not all criteria matched. 808 incident, invasive lung cancer cases were diagnosed among eligible participants between baseline and December 2007.

Follow-up for censoring

Excluding the 1% of the cohort with incident lung cancer, the remaining participants were right-censored from the analysis at the earliest date of the following events: date of withdrawal from the study (0.02%), date of death (4.9%), date of emigration out of the SEER catchment region (5.5%), or December 31, 2007, the most recent date of linkage to the SEER registry (89.6%). Deaths that occurred in the cohort were ascertained by linkage to the Washington State death file, using procedures similar to the SEER linkage. The National Change of Address System and active follow-up by telephone calls and mailings were used to identify participants who moved out the study region.

Statistical analyses

Multivariable-adjusted Cox proportional hazards regression models, using participants' age as the time metric, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of glucosamine and chondroitin with lung cancer risk. We categorized glucosamine and chondroitin use in the past 10 years by ever use (nonuser; user: ≥1 day/week for ≥1 year) and 10-year use (nonuser; low: <4 days/week or <3 years; high: ≥4 days/week and ≥3 years). 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.

We selected *a priori* potential confounders for adjustment in multivariable models, including known or suspected risk factors for lung cancer: age (time variable), race (white, non-white), education (≤ high school graduate, some college, college or advanced degree), gender

(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), non-steroidal anti-inflammatory drug (NSAID) use (nonuser, low: <4 days/week or <4 years, high: ≥4 days/week and ≥4 years), a history of chronic-obstructive pulmonary disease and smoking. 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 (17). Our final model included years smoked, pack-years, and a squared pack-years term. BMI at baseline, rather than at age 45, was included in models as it was the stronger predictor of lung cancer risk. We further adjusted proportional hazards models for predictors of glucosamine or chondroitin use, including a history of osteoarthritis or chronic joint pain (no, yes), rheumatoid arthritis (no, yes), and use of multivitamin supplements (nonuser, former user, current user).

We hypothesized *a priori* that the associations of glucosamine and chondroitin with lung cancer risk would be modified by factors associated with inflammation. Therefore, we stratified multivariable models on several such factors including NSAID use, BMI at baseline, history of osteoarthritis or chronic joint pain, history of chronic-obstructive pulmonary disease, and smoking status. We additionally performed stratified analyses on gender, due to gender differences in lung cancer incidence rates, and BMI at 45 years of age, a time point that would predate the measured use of glucosamine or chondroitin for most participants in the study. *P*-values for interaction (*P*-interaction) were calculated by including a multiplicative term between the effect modifier and the dichotomous variable for glucosamine or chondroitin use in the unstratified multivariable models.

In order to assess whether differences in etiology exist for glucosamine or chondroitin exposures in association with biologically defined subsets of lung cancer, we stratified our analyses by the most common histologic types: small cell lung cancer (SCLC, n=112), non-small cell lung cancer (NSCLC, n=608), including adenocarcinoma (n=280), squamous cell carcinoma (n=134), non-small cell lung cancer, not otherwise specified (NSCLC, NOS; n=176), and large cell lung cancer (n=18). We further analyzed NSCLC stratified into its major subsets: adenocarcinoma, squamous cell carcinoma, and NSCLC, NOS. Excluded from these analyses were 88 cases with lung cancers of other histologies.

Results

Characteristics of VITAL participants stratified by glucosamine and chondroitin status are given in Table 1. There were only small differences between users and nonusers of glucosamine and chondroitin in terms of age, education level, race, BMI, family history of lung cancer, and a personal history of chronic-obstructive pulmonary disease. However, glucosamine and chondroitin users were substantially more likely to be female, users of NSAIDs and multivitamins, and have personal histories of osteoarthritis or chronic joint pain, or rheumatoid arthritis. Users of glucosamine and chondroitin were less likely to be current or recent smokers, however among ever smokers there were only small differences in mean duration or pack-years smoked by glucosamine or chondroitin status.

Age and gender-adjusted and multivariable-adjusted associations between glucosamine and chondroitin use and lung cancer risk are given in Table 2. Compared to nonuse, use of glucosamine was associated with a 20% reduction in lung cancer risk (HR 0.80, 95% CI: 0.65-0.99) after multivariable adjustment. High 10-year use of glucosamine was associated with a linear 23% reduction in risk (HR 0.77, 95% CI: 0.56-1.07; *P*-trend = 0.04). Use of chondroitin

was similarly associated with a 21% reduction in lung cancer risk (HR 0.79, 95% CI: 0.62-1.02); however there was no clear trend with 10-year use (*P*-trend = 0.21). A large proportion of glucosamine users were also users of chondroitin. When the analysis of glucosamine was restricted to nonusers of chondroitin, glucosamine use was suggestive of an inverse association with lung cancer (HR 0.84, 95% CI: 0.61-1.17; data not shown) and high 10-year use of glucosamine alone was associated with a 61% reduction in lung cancer risk (HR 0.39, 95% CI: 0.17-0.86; data not shown); however, the finding was not linear (*P*-trend = 0.08).

There was no effect-modification of the association of glucosamine or chondroitin with lung cancer risk, by factors associated with inflammation (Table 3). Although not statistically different, the associations appeared stronger among women, participants with a BMI <25.0 at 45 years of age, a history of osteoarthritis/joint pain, no history of chronic-obstructive pulmonary disease, and among long-term (>10 years) quitters rather than current or recent smokers.

We observed differences in the association of glucosamine and chondroitin use by subsets of lung cancer classified by histology (Table 4). Use of glucosamine and chondroitin were associated with a reduced risk of NSCLC; this was due to associations limited to adenocarcinoma. Glucosamine use was associated with a 36% (HR 0.64, 95% CI: 0.44-0.90) risk reduction of adenocarcinoma and chondroitin with a 45% reduction (HR 0.55, 95% CI: 0.35-0.86). High 10-year average use of glucosamine was associated with a 51% reduction in risk of adenocarcinoma (HR 0.49, 95% CI: 0.27-0.90; *P*-trend<0.01). The *p*-value for trend of 10-year use of chondroitin was 0.03; however the point-estimates show there was no clear trend with increasing use. There were no associations of use of these supplements with the other subtypes of NSCLC nor with small cell lung cancers.

Discussion

In this prospective cohort study of 76,904 men and women living in western Washington State, we further evaluated our previous findings that use of glucosamine and chondroitin during the 10 years prior to baseline was inversely associated with the risk of lung cancer (7). In this analysis, we found that the association was limited to adenocarcinomas. While it is difficult to separate any associations with glucosamine from those with chondroitin because they are often taken together in one pill, the trends with frequency/duration of use were stronger for glucosamine than chondroitin overall and for adenocarcinoma, and users of glucosamine only had the lowest risk of lung cancer. Factors associated with inflammation did not significantly modify the associations.

Glucosamine and chondroitin are thought to have anti-inflammatory properties, which may explain any protective association with lung cancer. While these supplements have not been studied for their relationship to lung cancer except in the VITAL cohort, the association of NSAIDs with lung cancer incidence has been studied in this and other prospective studies (18-29) and one randomized trial (30). Among those that adjusted for smoking, findings have been mixed. Similar in magnitude to our findings for glucosamine and chondroitin, we (28) and others have reported that use of NSAIDs was associated with 20-40% reductions in lung cancer risk (19, 26, 29). In the Women's Health Study, the only randomized, placebo-controlled trial of aspirin that reported on lung cancer risk, Cook et al., (30) reported that women assigned to low-dose aspirin (100mg), taken every other day, had a borderline statistically significant reduction in lung cancer risk (RR 0.78, 95% CI: 0.59-1.03) compared to a placebo. In addition, in a recent pooled analysis of 3 randomized trials of aspirin use and risk of cancer *death*, daily treatment

with aspirin for ≥5 years compared to a placebo was associated with a significant reduction in lung cancer death after 20 years of follow-up (HR 0.71, 95% CI: 0.58-0.89) (3).

We found that use of glucosamine and chondroitin was associated with an approximate 35-45% reduction in risk of adenocarcinoma, with the greatest reduction (51%) associated with high use of glucosamine. Five prospective studies reported on the association of NSAIDs with lung cancer stratified by histologic subtypes (19, 21, 23, 24, 28). Because histologic subtypes were differently defined between studies, comparisons are somewhat limited. In two studies, differences by subtype were reported for NSAIDs that were consistent with our findings for glucosamine and chondroitin (19, 28). Akhmedkhanov et al., (19) found that ever use of aspirin was associated with a stronger reduction in risk of NSCLC (OR 0.39, 95% CI: 0.16-0.96) than lung cancer risk overall (OR 0.66, 95% CI: 0.34-1.28). Slatore et al., (28) reported that NSAID use was associated with strong reductions in risk of NSCLC overall (10-year average use >4.2 days/week vs. non-use: HR 0.68, 95% CI: 0.51-0.92; *P* trend=0.01) and adenocarcinoma in particular (HR 0.59, 95% CI: 0.37-0.94; *P*-trend=0.01), but not squamous or small cell lung cancers in the VITAL cohort, similar to our results for glucosamine and chondroitin. In two other studies, NSAIDs were not associated with lung cancer risk and no differences were reported by lung cancer subtype (21, 24). In the remaining study, NSAIDs were positively associated with lung cancer risk, with no differences by subtype; however, the authors did not adjust for smoking (23). Finally, in the recent pooled analysis of randomized trials mentioned above, the effect of ≥5 years of aspirin use on lung cancer death was restricted to adenocarcinomas (HR 0.55, 95% CI: 0.33-0.94) (3), highly consistent with our result for high use of glucosamine. Biomarkers of inflammation are expressed at greater levels in lung adenocarcinomas than other histologies (1, 31), suggesting that inhibiting inflammation may differentially reduce adenocarcinoma incidence.

Glucosamine and chondroitin have been shown to reduce the expression of inflammatory genes and inhibit cell proliferation through inhibition of the transcription factor NFκB *in vitro* and *in vivo* (8-11); these effects are associated with lower cancer risk (32). Glucosamine inhibits synthesis of pro-inflammatory mediators including IL-1 beta in human osteoarthritic chondrocytes (9), and chondroitin reduces expression of pro-inflammatory cytokines (e.g., IL-1, TNF-α) and enzymes with pro-inflammatory activity (e.g., COX2, VCAM-1) (8). There is indirect evidence from randomized trials that support the efficacy of glucosamine and chondroitin in reducing pain and improving function in osteoarthritis patients (13, 33-37); however we are unaware of any studies which demonstrate direct anti-inflammatory effects of glucosamine and chondroitin in humans.

This study has several strengths. The VITAL study is the first prospective study designed to investigate the association of specialty supplements with cancer risk. Supplement users were targeted for recruitment, and we had detailed assessment of glucosamine and chondroitin use over a sufficiently long time period (10 years before baseline) that could plausibly influence cancer risk. In addition, we collected extensive information on cancer risk factors, and we were able to carefully control for the confounding effect of smoking history. We were also able to adjust for correlates of supplement use, thereby correcting for potential confounding by indication. Another strength of this study was our ability to report associations with lung cancer histologies beyond comparisons of small cell and non-small cell tumors. Lastly, follow-up on the cohort was 95% complete; therefore, selection bias due to loss to follow-up is not likely to explain our findings.

This study also has several limitations. Foremost, we did not ascertain information on the dose of glucosamine or chondroitin that was taken, which would contribute to measurement

error. The recommended daily dose on the bottle labels is in the range of 500-1500mg glucosamine sulfate or hydrochloride typically with 400-1200mg chondroitin sulfate. ConsumerLab.com, which independently tests supplements for manufacturers and consumers, found that among 37 glucosamine and chondroitin supplements tested only 2 products (5%) contained <94% of the stated dose of chondroitin and all contained at least the stated dose of glucosamine (38). Other limitations of this study are that the supplement exposure data were ascertained by self-report and we were not able to update exposure information prospectively. Due to the prospective nature of the study, we expect that any exposure measurement error would be non-differential and would result in attenuated point-estimates.

In summary, we found that use of glucosamine and chondroitin was associated with reduced risk of lung cancer overall, and lung adenocarcinomas in particular; with long-term use of glucosamine conferring the greatest benefit. The association with glucosamine was of similar or stronger magnitude as those reported for NSAIDs. Furthermore, our result for glucosamine was limited to lung adenocarcinomas, the lung cancer histology that has been shown to be reduced in randomized trials of aspirin (3). Unlike NSAIDs (4-6, 39), glucosamine is considered safe and has no known side-effects (13). Although more research is needed on mechanisms of action, should these findings be replicated, they would suggest glucosamine would make an attractive candidate for chemoprevention.

Acknowledgements

This work is supported in part by grants, R25-CA94880, R01-CA142545, and K05-CA154337 from the National Institutes of Health, National Cancer Institute. Dr. Slatore's work on this project was supported with resources and the use of facilities at the Portland VA Medical Center.

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Table 1. Baseline characteristics of VITAL participants by glucosamine and chondroitin status (*n*=76,904).

Characteristic	**Glucosamine**		**Chondroitin**	
	User (*n*=15,546),%	**Nonuser (*n*=61,302), %**	**User (*n*=10,423), %**	**Nonuser (*n*=66,481), %**
Age (years)				
<55	18.8	24.4	17.4	24.1
55 to <60	21.6	23.0	21.0	22.9
60 to -<65	19.4	17.9	20.0	17.9
65 to <70	18.4	16.0	18.9	16.1
≥70	21.7	18.8	22.7	18.9
Education				
≤High school graduate	17.0	20.9	16.4	20.7
Some college	39.3	38.0	38.6	38.2
College or advanced degree	43.7	41.1	45.1	41.1
Race				
White	94.2	92.9	94.6	92.9
Non-white	5.8	7.1	5.4	7.1
Gender				
Male	38.7	50.5	37.8	49.7
Female	61.4	49.5	62.2	50.3
Body mass index (kg/m^2)				
<25.0	34.5	34.4	34.2	34.4
25.0 to 29.9	40.1	41.3	39.9	41.2
≥30.0	25.5	24.4	25.9	24.4
Smoking status				
Never	50.1	47.2	50.0	47.5
Former (≥10 years since quit)	40.0	36.5	40.3	36.7
Recent (<10 years since quit)	5.4	6.9	5.2	6.8
Current	4.9	9.3	4.5	9.0
Duration of smoking (years)[a]				
Mean (SD)	21.0 (13.1)	23.4 (13.6)	20.9 (13.0)	23.3 (13.6)
Cigarette pack-years[a]				
Mean (SD)	23.1 (21.8)	26.7 (23.6)	23.2 (21.6)	26.5 (23.5)
Number of first-degree relatives with lung cancer				
None	87.2	87.4	87.0	87.4
1	11.8	11.8	12.0	11.7
≥2	0.9	0.9	0.9	0.9
NSAID use[b,c]				
Nonuser	39.4	55.1	37.3	54.2
Low	36.0	27.6	36.8	28.1
High	24.6	17.3	25.9	17.7

Multivitamin use				
Nonuser	16.7	39.1	16.4	37.4
Former	7.5	7.7	7.5	7.7
Current	75.9	53.2	76.1	54.9
Chronic-Obstructive Pulmonary Disease				
No	96.7	96.4	96.7	96.4
Yes	3.3	3.6	3.4	3.6
Osteoarthritis or chronic joint pain				
No	29.3	57.3	26.7	55.5
Yes	70.7	42.7	73.3	44.5
Rheumatoid arthritis				
No	94.8	96.4	94.9	96.3
Yes	5.2	3.6	5.1	3.7

Abbreviations: NSAID, non-steroidal anti-inflammatory drug;

[a] Among current and former smokers

[b] Includes aspirin, ibuprofen, celecoxib, rofecoxib, and other pain relievers such as indomethacin and piroxicam (women only)

[c] 10-year use: Nonuser; low use, <4 days/week or <4 years; high use, ≥4 days/week and ≥4 years

Table 2. Associations between glucosamine and chondroitin and lung cancer risk among VITAL participants (*n* = 76,904).

Supplement	**Cases (*n* = 808), *n* (%)**	**Non-cases (*n* = 76,097), *n* (%)**	**Age & Gender-adjusted HR (95% CI)**	**Multivariable-adjusted HR (95% CI)[a]**
Glucosamine				
Nonuser	691 (85.63)	60,611 (79.71)	1.00 (reference)	1.00 (reference)
User	116 (14.37)	15,430 (20.29)	0.62 (0.51-0.76)	0.80 (0.65-0.99)
10-year use[b]				
Nonuser	691 (85.63)	60,611 (79.71)	1.00 (reference)	1.00 (reference)
Low	73 (9.05)	9,899 (13.02)	0.64 (0.50-0.81)	0.82 (0.63-1.06)
High	43 (5.33)	5,531 (7.27)	0.60 (0.44-0.82)	0.77 (0.56-1.07)
P trend			<0.0001	0.04
Chondroitin				
Nonuser	732 (90.71)	65,749 (86.40)	1.00 (reference)	1.00 (reference)
User	75 (9.29)	10,348 (13.60)	0.60 (0.48-0.77)	0.79 (0.62-1.02)
10-year use[b]				
Nonuser	732 (90.71)	65,749 (86.40)	1.00 (reference)	1.00 (reference)
Low	40 (4.96)	6,718 (8.83)	0.52 (0.37-0.71)	0.69 (0.50-0.95)
High	35 (4.34)	3,630 (4.77)	0.75 (0.54-1.06)	0.96 (0.67-1.37)
P trend			<0.001	0.21

Abbreviations: HR, Hazards Ratio; CI, Confidence Interval

[a] Adjusted for age, race, education, gender, body mass index, family history of lung cancer, non-steroidal anti-inflammatory drug use, years smoked, pack-years, pack-years squared, chronic-obstructive pulmonary disease, multivitamin use, joint pain or osteoarthritis, and rheumatoid arthritis

[b] 10-year use: Nonuser; low use, <4 days/week or <3 years; high use, ≥4 days/week and ≥3 years

Table 3. Associations between glucosamine and chondroitin with lung cancer risk, stratified by inflammation-associated conditions among VITAL participants (*n*=76,904).

	Glucosamine				**Chondroitin**			
	Nonuser		User		Nonuser		User	
	Cases/non-cases	HR (95% CI)[a]	Cases/non-cases	HR (95% CI)[a]	Cases/non-cases	HR (95% CI)[a]	Cases/non-cases	HR (95% CI)[a]
Gender								
Male	387/30,577	1.00 (reference)	61/5,947	0.99 (0.74-1.32)	412/32,631	1.00 (reference)	36/3,901	0.91 (0.64-1.30)
Female	304/30,034	1.00 (reference)	55/9,483	0.64 (0.47-0.87)	320/33,118	1.00 (reference)	39/6,447	0.68 (0.49-0.96)
P-interaction				0.12				0.41
NSAID Use (10 year use)[b]								
Nonuser	340/30,843	1.00 (reference)	44/5,699	0.85 (0.61-1.19)	357/32,934	1.00 (reference)	27/3,628	0.84 (0.56-1.25)
Low	162/15,423	1.00 (reference)	34/5,223	0.65 (0.43-0.96)	175/17,070	1.00 (reference)	21/3,590	0.55 (0.36-0.91)
High	135/9,652	1.00 (reference)	30/3,566	0.89 (0.59-1.35)	143/10,709	1.00 (reference)	22/2,521	0.99 (0.62-1.58)
P-interaction				0.99				0.75
Body Mass Index								
<25.0	246/19,766	1.00 (reference)	39/5,089	0.80 (0.56-1.14)	261/21,480	1.00 (reference)	24/3,396	0.80 (0.52-1.23)
≥25.0	401/37,779	1.00 (reference)	73/9,663	0.84 (0.65-1.10)	427/40,954	1.00 (reference)	47/6,520	0.82 (0.60-1.11)
P-interaction				0.69				0.81
Body Mass Index at 45 years								
<25.0	418/31,614	1.00 (reference)	62/8,471	0.73 (0.55-0.97)	440/34,388	1.00 (reference)	237/27,842	0.75 (0.54-1.05)
≥25.0	220/25,736	1.00 (reference)	47/6,243	0.98 (0.70-1.37)	40/5,718	1.00 (reference)	30/4,168	0.92 (0.62-1.36)
P-interaction				0.07				0.20
Osteoarthritis or chronic joint pain								
No	358/34,753	1.00 (reference)	34/4,520	1.06 (0.74-1.53)	371/36,531	1.00 (reference)	21/2,762	1.09 (0.70-1.70)
Yes	333/25,841	1.00 (reference)	82/10,910	0.71 (0.55-0.91)	361/29,200	1.00 (reference)	54/7,586	0.69 (0.51-0.94)
P-interaction				0.11				0.14
Chronic-Obstructive Pulmonary Disease								
No	569/58,492	1.00 (reference)	97/14,941	0.78 (0.62-0.98)	603/63,478	1.00 (reference)	63/10,011	0.78 (0.59-1.02)
Yes	122/2,102	1.00 (reference)	19/489	0.94 (0.57-1.57)	129/2,253	1.00 (reference)	12/337	0.91 (0.49-1.68)
P-interaction				0.81				0.98
Smoking								
Former smoker (≥10 years quit)	278/21,860	1.00 (reference)	56/6,054	0.78 (0.57-1.05)	299/23,813	1.00 (reference)	35/4,128	0.71 (0.50-1.03)
Current/Recent smoker (<10 years quit)	352/9,487	1.00 (reference)	51/1,527	0.95 (0.69-1.29)	369/10,046	1.00 (reference)	34/973	1.01 (0.70-1.45)
P-interaction				0.61				0.13

Abbreviations: HR, Hazards Ratio; CI, Confidence Interval, COPD, chronic-obstructive pulmonary disease

[a] Adjusted for age, race, education, gender, body mass index, family history of lung cancer, non-steroidal anti-inflammatory drug use, years smoked, pack-years, pack-years squared, chronic-obstructive pulmonary disease, multivitamin use, joint pain or osteoarthritis, and rheumatoid arthritis

[b] 10-year use: Nonuser; low use, <4 days/week or <4 years; high use, ≥4 days/week and ≥4 years

Table 4. Associations between glucosamine and chondroitin and risk of lung cancer, by histologic type (*n* = 76,904).

Supplement	**NSCLC, *n* = 608 cases**				**SCLC, *n* = 112 cases**
	Total NSCLC[c] *n* = 608 HR (95% CI)[a]	**Adenocarcinoma, *n* = 280 cases HR (95% CI)[a]**	**Squamous Cell Carcinoma, *n* = 134 cases HR (95% CI)[a]**	**NSCLC, NOS; *n* = 176 cases HR (95% CI)[a]**	**HR (95% CI)[a]**
Glucosamine					
Nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	0.77 (0.60-0.98)	0.64 (0.44-0.90)	0.99 (0.60-1.65)	0.88 (0.56-1.38)	1.01 (0.60-1.72)
10-year use[b]					
Nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Low	0.72 (0.53-0.98)	0.71 (0.47-1.08)	0.60 (0.28-1.31)	0.77 (0.43-1.38)	1.29 (0.72-2.31)
High	0.85 (0.60-1.21)	0.49 (0.27-0.90)	1.60 (0.86-2.96)	1.05 (0.56-1.97)	0.58 (0.21-1.59)
P trend	0.09	<0.01	0.57	0.79	0.61
Chondroitin					
Nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	0.70 (0.52-0.94)	0.55 (0.35-0.86)	1.04 (0.57-1.88)	0.70 (0.39-1.25)	1.01 (0.54-1.88)
10-year use[b]					
Nonuser	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Low	0.52 (0.34-0.79)	0.47 (0.26-0.85)	0.52 (0.19-1.43)	0.52 (0.23-1.18)	1.09 (0.52-2.29)
High	1.01 (0.68-1.49)	0.69 (0.36-1.31)	1.86 (0.93-3.74)	1.00 (0.46-2.16)	0.88 (0.32-2.43)
P trend	0.15	0.03	0.86	0.58	0.93

Abbreviations: NSCLC, non-small cell lung cancer; NOS, not otherwise specified; SCLC, small cell lung cancer; HR, Hazards Ratio; CI, Confidence Interval;

[a] Adjusted for age, race, education, gender, body mass index, family history of lung cancer, non-steroidal anti-inflammatory drug use, years smoked, pack-years, pack-years squared, chronic-obstructive pulmonary disease, multivitamin use, joint pain or osteoarthritis, and rheumatoid arthritis

[b] 10-year use: Nonuser; low use, <4 days/week or <3 years; high use, ≥4 days/week and ≥3 years

[c] Includes adenocarcinomas, squamous cell carcinomas, large cell lung cancers, and NSCLC, NOS