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ORIGINAL ARTICLE

Oral bisphosphonate use and lung cancer incidence among postmenopausal women

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Background: Bisphosphonates are common medications for the treatment of osteoporosis in older populations. Several studies, including the Women's Health Initiative (WHI), have found inverse associations of bisphosphonate use with risk of breast and endometrial cancer, but little is known about its association with other common malignancies. The objective of this study was to evaluate the association of bisphosphonate use on the incidence of lung cancer in the WHI.

Patients and methods: The association between oral bisphosphonate use and lung cancer risk was examined in 151 432 postmenopausal women enrolled into the WHI in 1993–1998. At baseline and during follow-up, participants completed an inventory of regularly used medications including bisphosphonates.

Results: After a mean follow-up of 13.3 years, 2511 women were diagnosed with incident lung cancer. There was no evidence of a difference in lung cancer incidence between oral bisphosphonate users and never users (adjusted hazard ratio = 0.91; 95% confidence intervals, 0.80–1.04; $P = 0.16$). However, an inverse association was observed among those who were never smokers (hazard ratio = 0.57, 95% confidence interval, 0.39–0.84; $P < 0.01$).

Conclusion: In this large prospective cohort of postmenopausal women, oral bisphosphonate use was associated with significantly lower lung cancer risk among never smokers, suggesting bisphosphonates may have a protective effect against lung cancer. Additional studies are needed to confirm our findings.

Key words: lung cancer, bisphosphonates, postmenopausal women, epidemiology, Women's Health Initiative

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer death among American women [1]. Although tobacco smoking is the leading cause, identifying other modifiable factors is important and may be useful in developing novel prevention strategies for this highly fatal disease.

Bisphosphonates are commonly prescribed medications for the prevention and treatment of osteoporosis in older populations, particularly among postmenopausal women [2]. Experimental studies have shown that bisphosphonates have a range of direct and indirect antitumor effects, including inhibition tumor angiogenesis and cellular proliferation, prevention tumor cell adhesion and invasion, and induction of tumor cell apoptosis [3]; however, it is still unclear whether they play a role in primary prevention of cancer. A number of recent studies, including the Women's Health Initiative (WHI) have explored the relationships between bisphosphonate use and risk of breast [4–8], gastrointestinal tract [9–11], endometrial and ovarian cancer [12, 13]. A few studies, with inconsistent results have investigated the association of oral bisphosphonate use with lung cancer risk [14–17]. Nonsignificant inverse associations were observed in retrospective studies nested within the United Kingdom (UK) General Practice Research Database (GPRD) [hazard ratio (HR) = 0.85, 95% confidence interval (CI), 0.70–1.03 and odds ratio (OR) = 0.97, 95% CI, 0.88–1.08] [14, 15], while results from combined GPRD and practice-based QRsearch databases showed no association (OR = 1.04, 95% CI, 0.97–1.12) [15].

Results from retrospective studies using Taiwan health insurance system database were conflicting; one suggested no association (HR = 1.17, 95% CI, 0.05–1.43) [16], but another one found positive association (HR = 1.47, 95% CI, 1.00–2.17) [17]. However, these previous studies had very limited information on risk factors of lung cancer including smoking, and none of them explored whether the associations between bisphosphonate use and lung cancer vary by smoking status. Meanwhile, some but not all previous studies have observed associations between exposure to tobacco smoke or tobacco products and low bone mineral density [18–21] and some clinical studies reported that bisphosphonate treatment failure was associated with current smoking status among postmenopausal women with osteoporosis [22]. These findings suggest a potential interaction between bisphosphonate use and smoking. Therefore, we hypothesized that oral bisphosphonate use may have effects on lung carcinogenesis in older women, particularly among those who are never smokers.

To test these hypotheses, we evaluated the relationship between oral bisphosphonates use and lung cancer risk and its potential interaction with smoking status on lung cancer risk in the well-described WHI study, a large prospective cohort of postmenopausal women involving three randomized clinical trials (WHI-CTs) and a large observational study (WHI-OS).

Materials and methods

WHI overview

Details of the WHI study methods have been published elsewhere [23–25]. Briefly, WHI study enrolled 161 808 postmenopausal women in an observational study (WHI-OS) and three clinical trials (WHI-CTs) between 1993 and 1998 from 40 clinical centers across the United States. Eligible women for the WHI study were 50 to 79 years old at baseline with anticipated survival of at least 3 years, accessible for follow-up. Each WHI trial had its own set of eligibility criteria. WHI-OS participants were ineligible or unwilling to be included in a randomized trial. All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards of all respective clinical centers.

Measurement of exposures

Standardized, self-administered questionnaires were completed by participants at the baseline visit, including queries regarding demographic factors, smoking history, medical history, alcohol intake, dietary intake, personal habits, and physical activity.

A medication inventory of all current, regularly used medications, including bisphosphonates, was taken at the baseline and at year 3 clinic visits for all WHI participants, and additionally at years 1 and 6 after random assignment for WHI-CT participants. Participants were instructed to bring all medication containers for those prescribed and over the counter medications taken at least twice per week during the previous 2 weeks. The medication information (type and frequency) was obtained directly from the medication containers and entered into the WHI database by trained research staff. Each medication was matched to the Medi-Span® (Indianapolis, IN) Master Drug Database to ascertain detailed ingredient information. For those reporting use of bisphosphonates, the type of the compound and the duration of use was recorded and validated by checking pill box labels. No information on dose was collected. A validity study was conducted among 223 WHI participants for whom we had bisphosphonate use information from both medication inventory and pharmacy records; the agreement between sources was high (current bisphosphonate use: sensitivity = 80%; duration of bisphosphonate use: $\kappa = 0.95$) [26].

Extensive information on smoking was collected at baseline in the WHI study; participants were asked whether they had ever smoked ≥100 cigarettes in their lifetime and whether they smoked currently to identify current and former smokers. A woman was defined as former smoker if she did not smoke currently but had ever smoked ≥100 cigarettes in the past. The number of cigarettes smoked per day and the number of years as a regular smoker were also queried. Never smokers were defined as participants who reported having ever smoked <100 cigarettes in their lifetime. The 10-year probability of hip fracture was calculated using a WHO developed fracture Risk Assessment Tool (FRAX)® to evaluate a hip fracture risk [27]. It is based on individual patient models that integrate the risk associated with clinical risk factors measured at baseline [27].

Ascertainment of outcomes

Self-reported health outcomes, including lung cancer, were ascertained semiannually for WHI-CT or annually for WHI-OS using a health update questionnaire until 2005 and then annually for all WHI participants thereafter. Lung cancer diagnoses that were reported were confirmed and adjudicated using medical records and pathology reports reviewed by centrally trained study physicians blinded to study components, medication, or randomization assignments [24]. Tumor characteristics were coded according to the Surveillance, Epidemiology, and End Results (SEER) guidelines at the WHI Coordinating Center [24]. Follow-up was censored at the earliest of the following event: last known follow-up or 30 September 2013.

Study participants

We excluded participants who had not turned 50 years old at baseline, had a prior history of lung cancer at baseline, or had missing data on follow-up time, or lacked information of medication inventory at baseline and at year 3 for all participants and additionally at year 1 and 6 for WHI-CT participants. The current analyses finally included 151 432 WHI participants.

Statistical analysis

We estimated HRs and 95% CIs using Cox proportional hazards regression models [28] to examine the associations between time since initiation of oral bisphosphonate use and lung cancer incidence. Oral bisphosphonate use was, in general, dichotomized as a time-varying never/ever variable by updating baseline use at years 1, 3 or 6 clinic visits among women at risk of lung cancer in the CT women and year 3 in the OS women (nonusers could become ever users over time). Therefore, nonusers in the Cox regression model referred to women who never reported oral bisphosphonate use during those follow-up visits before the occurrence of lung cancer. Quartile distributions among oral bisphosphonate users were used to categorize total duration of use. In the age-adjusted analyses, the Cox proportional hazards models were adjusted for age and stratified on WHI study component and for those in the WHI-CT's randomization arm. In more general multivariate analyses, the Cox regression models were adjusted for covariates measured at baseline, including age, ethnicity, education, smoking status, number of cigarettes smoked per day, total years of smoking, alcohol use status, physical activity, body mass index (BMI), personal prior hormone therapy use, statin use, total calcium intake, and total vitamin D intake. Previous studies have shown significant correlation between calculated hip fracture risk score with BMD [8]. Therefore, in current study, we also assessed potential confounding by 10-year probability of hip fracture and history of bone fracture after age 54 years, and these two factors did not alter point estimates by ≥10% and were excluded from final models.

Lung tumor histology, stage, and grade were compared between users of any type of oral bisphosphonate and nonusers with χ^2 tests. Tumors with missing information were not included in these analyses.

Multiplicative interactions between oral bisphosphonate use and other covariates of interest measured at baseline, including smoking status and continuous total calcium intake, were tested using the Wald test. All statistical tests were based on two-sided probability. Statistical analyses were conducting using SAS, Version 9.4 (SAS Institute, Cary, NC).

Results

Oral bisphosphonate use at baseline was uncommon ($n = 3146$ users, 2.1%) but had increased to 9.7% (14 721 users) by year 6 (Table 1). About 72.3% of baseline users of bisphosphonate reported a physician diagnosis of osteoporosis compared with only 6.6% of nonusers. Compared to nonusers, baseline users were older, more likely to be white, had higher educational level, and substantially higher estimated 10-year probability of hip fracture. Baseline users also reported higher physical activity, had lower BMI, higher total calcium and vitamin D intakes, were less likely to be current smokers, have less total pack-years of smoking and were less likely to use hormone therapy before enrollment than nonusers (Table 1). Moreover, baseline characteristics of WHI study participants by their smoking status are presented in Table A1.

After 13.3 years' (mean) cumulative follow-up, 2511 women were diagnosed with incident lung cancer (2257 nonusers and 254 ever users of oral bisphosphonates) (Table 2). The crude incidence of lung cancer was similar among nonusers and women reporting any type of oral bisphosphonates use. Based on the multivariable-adjusted model, the HR for use of any type of oral bisphosphonates compared with never use was not significantly different (HR = 0.91, 95% CI, 0.80–1.04, $P = 0.16$). The magnitude of the associations was stronger for long-term users of bisphosphonate than for short-term users, particularly for 1.50–2.99 years use (HR = 0.65, 95% CI, 0.46–0.93; $P = 0.02$); however, there was no dose–response relationship for duration of use (P for trend = 0.25). Alendronate was the most common type of oral bisphosphonate in the study population during the follow-up (>90% of users); however, risk estimates for risedronate and other types of bisphosphonate use were not very precise. Additionally, we conducted sensitivity analyses by further excluding lung cancer cases diagnosed within one year of enrollment of the WHI, and similar results were observed (data not shown).

Two subgroup analyses were carried out (Table 3). We found that the association patterns with bisphosphonate use differed in never smokers and ever smokers (P interaction = 0.02). Among never smoking women, oral bisphosphonate use was inversely associated with lung cancer risk in the multivariate adjusted models (HR = 0.57, 95% CI, 0.39–0.84, $P < 0.01$); the association was stronger for total duration of use ≥1.5 years (HR = 0.36, 95% CI, 0.18–0.73). Among ever smokers, bisphosphonate use was not related to lung cancer risk. The reduced risk associated with oral bisphosphonate use was stronger among women with lower baseline total calcium intake, but the multiplicative interaction test was not statistically significant (P interaction = 0.13).

The incidences of small cell lung cancer and nonsmall-cell lung cancer (NSCLC) were similar in bisphosphonate users. However, among never smoking women, oral bisphosphonate use was inversely associated with NSCLC risk (HR = 0.62, 95% CI, 0.41–0.92; $P = 0.02$). Similarly, a nonsignificant inverse association with adenocarcinoma was found among never smokers (HR = 0.70, 95% CI, 0.46–1.07; $P = 0.10$). No association of bisphosphonate use with NSCLC was found in ever smokers (data not shown). There were no apparent differences in the stage or grading of lung cancer in oral bisphosphonate users (Table 4).

Discussion

We did not find statistically significant association between ever use oral bisphosphonate and lung cancer risk in this large prospective cohort study of postmenopausal women. However, an inverse association of oral bisphosphonate use with lung cancer risk was found among never smokers. Furthermore, our results suggested associations between longer duration of use and reduced lung cancer risk.

Our results are consistent with those from Cardwell et al. [14], where a nonsignificant inverse association was observed (HR = 0.85, 95% CI, 0.70–1.03). However, there are some differences between their analyses and ours. WHI had larger sample size (2511 lung cancer cases among 151 432 postmenopausal women at risk), confirmed bisphosphonate use, type and duration through assessments of medication packages, and collected detailed information on risk factors for lung cancer and other potential confounding factors. Cardwell et al. [14] determined bisphosphonate use from prescription or medical claim records, which limited potential recall bias. However, their pharmacy databases had limited ability to adequately control for confounding such as smoking habits. Moreover, their analysis may have failed to estimate an association among women alone due to limited sample size.

Usage of oral alendronate, a nitrogen-binding bisphosphonate and subsequent lung cancer risk has been evaluated among osteoporosis patients based on a population-based health insurance system database of Taiwan [16, 17]. Chiang et al. [16] reported no association between oral alendronate and risk of lung cancer among postmenopausal women with osteoporosis. In the same database, a later report included both male and female osteoporosis patients, and found a positive association with risk of lung cancer among osteoporosis patients in Taiwan, and the association was stronger among patients with higher dosage of alendronate (≥1.0 g/year) [17]. The inconsistent results from the same database may be partially due to sample differences in the two analyses. The studies from Taiwan only adjusted for age and sex due to little information on possible confounding factors in their health insurance databases.

In our study, a reduction in lung cancer risk was seen in women using bisphosphonate for ≥1.5 year, particularly for use of 1.50–2.99 years. This finding is consistent with previous reports from UK, which reported a nonsignificant inverse association after 1 year of use (HR = 0.86, 95% CI, 0.63–1.17) [14]. Although no information was collected on dose of the medication in the WHI Study prevented us to explore the dose–response relationship for cumulative prescribed intakes, the likelihood ratio test suggested different effects of long-term use. Consistent with our hypothesis, we firstly found that reduction in lung cancer risk with bisphosphonate use tended to be limited to never smoking women, those who have an overall lower risk of developing lung cancer in this study. However, relative small number of incident

Table 1. Baseline characteristics by oral bisphosphonate use in the WHI study, 1993–2013

Characteristic at baseline	Oral bisphosphonate use			
	At baseline		At baseline, year 1, 3 or 6[a]	
	No ($n = 148\,286$)	Yes ($n = 3146$)	No ($n = 136\,413$)	Yes ($n = 14\,721$)
Age at screening (years) (%)				
<50–59	48 681 (32.8)	406 (12.9)[b]	46 242 (33.9)	2799 (19.0)
60–69	66 993 (45.2)	1462 (46.5)	60 970 (44.7)	7326 (49.8)
70–79	32 612 (22.0)	1278 (40.6)	29 201 (21.4)	4596 (31.2)
Race-ethnicity (%)				
Non-Hispanic white	123 276 (83.3)	2837 (90.3)[b]	112 666 (82.8)	13 186 (89.8)
Black/African American	13 380 (9.1)	44 (1.4)	13 026 (9.6)	376 (2.6)
Hispanic/Latino	5399 (3.7)	86 (2.7)	5115 (3.8)	365 (2.5)
American Indian	632 (0.4)	1 (0.03)	607 (0.4)	26 (0.2)
Asian/Pacific islander	3576 (2.4)	140 (4.5)	3126 (2.3)	585 (4.0)
Other/Unknown	2023 (1.1)	38 (1.1)	1873 (1.1)	183 (1.0)
Education (%)				
High school or less	33 169 (22.5)	606 (19.4)[b]	30 860 (22.8)	2843 (19.5)
School after high school	56 154 (38.2)	1029 (33.0)	51 963 (38.4)	5086 (34.8)
College degree or higher	57 880 (39.3)	1481 (47.5)	52 606 (38.8)	6667 (45.7)
Missing	1083	30	984	125
Smoking status (%)				
Never	74 302 (50.8)	1660 (53.6)[b]	68 121 (50.6)	7789 (53.6)
Former smoker	62 063 (42.4)	1306 (42.1)	57 202 (42.5)	6000 (41.3)
Current smoker	10 012 (6.8)	134 (4.3)	9330 (6.9)	742 (5.1)
Missing	1909	46	1760	190
Pack-years of smoking (%)				
Never	74 302 (52.0)	1660 (55.0)[b]	68 121 (51.8)	7789 (54.9)
<5	20 738 (14.5)	391 (13.0)	19 161 (14.6)	1949 (13.7)
5–20	20 662 (14.4)	413 (13.7)	19 060 (14.5)	1983 (14.0)
≥20	27 287 (19.1)	555 (18.4)	25 186 (19.1)	2471 (17.4)
Missing	5297	127	4885	529
Physical activity (MET/week) (%)				
0–3.00	40 623 (28.7)	692 (22.2)[b]	37 712 (29.0)	3502 (24.5)
>3.00–<11.75	44 801 (31.7)	940 (30.1)	41 126 (31.7)	4529 (31.6)
≥11.75	55 923 (39.6)	1488 (47.7)	51 036 (39.3)	6284 (43.9)
Missing	6939	26	6539	406
Alcohol intake (%)				
Never	15 843 (10.8)	397 (12.7)[b]	14 667 (10.8)	1558 (10.7)
Past drinker	27 776 (18.9)	541 (17.3)	25 892 (19.1)	2366 (16.2)
<1 drink per month	18 331 (12.4)	287 (9.2)	16 963 (12.5)	1612 (11.0)
<1 drink per week	30 217 (20.5)	675 (21.6)	27 736 (20.5)	3102 (21.2)
1–<7 drinks per week	37 818 (25.7)	827 (26.5)	34 444 (25.4)	4121 (28.2)
≥7 drinks per week	17 224 (11.7)	393 (12.6)	15 714 (11.6)	1859 (12.7)
Missing	1077	26	997	103
BMI, kg/m^2 (%)				
<25	50 435 (34.3)	1714 (54.9)[b]	44 563 (33.0)	7480 (51.2)
25–30	51 162 (34.8)	1000 (32.0)	47 212 (34.9)	4843 (33.2)
≥30	45 398 (30.9)	410 (13.1)	43 456 (32.1)	2271 (15.6)
Missing	1291	22	1182	127
Hormone-therapy use (%)				
Never used	61 746 (41.6)	1472 (46.8)[b]	55 976 (41.0)	7099 (48.2)
<5 years	32 788 (22.1)	702 (22.3)	30 241 (22.2)	3195 (21.7)
5 to <10 years	19 560 (13.2)	341 (10.8)	18 214 (13.4)	1653 (11.2)
≥10 years	34 187 (23.1)	631 (20.1)	31 977 (23.4)	2774 (18.8)
Missing	2	0	5	0
Statin use (%)	11 567 (7.8)	375 (11.9)[b]	10 608 (7.8)	1312 (8.9)

Continued

Table 1. *Continued*

Characteristic at baseline	Oral bisphosphonate use			
	At baseline		At baseline, year 1, 3 or 6[a]	
	No ($n = 148\,286$)	Yes ($n = 3146$)	No ($n = 136\,413$)	Yes ($n = 14\,721$)
History of osteoporosis (%)	9602 (6.6)	2251 (72.3)[b]	7975 (5.9)	3849 (26.5)
10-year probability of hip fracture (%)				
<0.53	48 881 (31.6)	270 (8.6)[b]	45 022 (33.0)	2089 (14.2)
0.53–1.68	49 782 (33.6)	752 (23.9)	45 867 (33.6)	4557 (31.0)
≥1.69	51 623 (34.8)	2124 (67.5)	45 524 (33.4)	8075 (54.8)
Total calcium intake (supplements and diet) (mean ± SD, mg/day)	1171.8 ± 741.0	1585.8 ± 867.5[b]	1162.7 ± 741.4	1345.2 ± 771.1
Total vitamin D intake (supplements and diet) (mean ± SD, U/day)	370.7 ± 278.4	500.2 ± 314.2[b]	367.8 ± 277.6	424.8 ± 294.9
WHI study component (%)				
OS	84 511 (57.0)	2312 (73.5)	79 428 (58.2)	7285 (49.5)
Hormone CT	25 071 (16.9)	298 (9.5)	22 372 (16.4)	2898 (19.7)
Dietary modification CT	46 076 (31.1)	585 (18.6)	41 372 (30.3)	5181 (35.2)
Calcium/vitamin D CT	34 250 (23.1)	354 (11.3)	30 736 (22.5)	3778 (25.7)
Enrollment in WHI hormone CT (%)				
No	123 215 (83.1)	2848 (90.5)	114 041 (83.6)	11 823 (80.3)
E-alone placebo group	5067 (3.4)	53 (1.7)	4584 (3.4)	523 (3.6)
E-alone active group	4960 (3.3)	45 (1.4)	4562 (3.3)	418 (2.8)
E+P placebo group	7361 (5.0)	103 (3.3)	6317 (4.6)	1124 (7.6)
E+P active group	7683 (5.2)	95 (3.0)	6909 (5.1)	833 (5.7)
Bisphosphonate type (%)				
Alendronate sodium	–	2913 (92.6)	–	13 467 (91.5)
Risedronate sodium	–	13 (0.4)	–	898 (6.1)
Others[c]	–	220 (7.0)	–	356 (2.4)
Duration of bisphosphonate use (mean ± SD, years)		1.2 ± 1.7		2.5 ± 3.0

[a]Including participants remaining at risk of lung cancer at year 6.

[b]χ^2 tests for categorical variables and Student's *t*-tests for continuous variables were used to compare oral bisphosphonate users with nonusers. *P* value < 0.01.

[c]Others include etidronate disodium, tiludronate disodium, pamidronate disodium and zoledronic acid.

WHI, Women's Health Initiative; CT, clinical trials; OS, observational study; E, estrogen; E + P, estrogen plus progestin; SD, standard deviation.

lung cancer cases among never smokers limited our ability to further explore precise dose–response relationship for duration of use. Further studies are needed to evaluate different patterns of bisphosphonate use on lung cancer risk and to better understand the underlying mechanisms of bisphosphonate use on lung carcinogenesis among never smokers. Also, we found an inverse association between oral bisphosphonate use and lung cancer risk among postmenopausal women with low baseline calcium intake. Previous studies suggested that calcium intake interferes with bisphosphonate absorption and can interplay with bisphosphonate to impact efficacy of osteoporosis treatment [29]. It is possible that bisphosphonate may interact with homeostasis of calcium to influence proliferation of lung cancer cells. Further studies are needed to elucidate the potential interactions between bisphosphonate and calcium on lung carcinogenesis, and to better understand the possible molecular mechanisms.

Preclinical and substantial emerging clinical evidence have indicated that bisphosphonates have antitumor activities against a broad range of cancers including breast and prostate cancers [30, 31]. Preclinical studies have shown that bisphosphonates can induce apoptosis, and inhibit cell invasion and tumor angiogenesis [30, 32, 33] through their activation of gamma delta T cells, induction cytokines production, and contribution to immune response to tumor cells [31, 34, 35]. *In vitro* studies showed that zoledronic acid, a third generation bisphosphonate, inhibits the prenylation of small G-proteins such as Ras, reduces the signals and prevents the growth of lung cancer cells [36, 37]. *In vivo* studies also revealed that bisphosphonates show the antitumor and antiangiogenic effects through their ability to inhibit tumor cell growth and vascular endothelial growth factor release in NSCLC cell lines [38, 39]. Furthermore, bisphosphonates were shown to inactive human epidermal growth factor receptors (EGFRs) in both NSCLC cell lines and in mice with NSCLC [36, 40, 41]. The EGFR pathway is particularly relevant to progression of lung adenocarcinoma [42]. It is possible that bisphosphonates may have a protective effect on NSCLC, especially adenocarcinoma, through inactivation of EGFR pathways. In our study, bisphosphonate use was found to be associated with reduced risk of NSCLC in never smokers. More studies with larger sample size

Table 2. Relative risk of lung cancer comparing oral bisphosphonate user to nonusers, Women's Health Initiative (1993–2013)

Oral bisphosphonate use[a]	No. of lung cancer	Person years	Incidence (% per year)	HR (95% CI)[b]	*P*	HR (95% CI)[c]	*P*
Any use							
Never	2257	1 811 696	0.125	Ref.		Ref.	
Ever	254	200 060	0.127	0.89 (0.78–1.02)	0.08	0.91 (0.80–1.04)	0.16
Duration of use, years[d]							
Never	2257	1 811 696	0.125	Ref.		Ref.	
<0.67	65	51 991	0.125	0.90 (0.70–1.15)	0.39	0.91 (0.78–1.17)	0.45
0.67–1.49	76	48 844	0.156	1.11 (0.88–1.39)	0.39	1.18 (0.94–1.49)	0.15
1.50–2.99	32	35 918	0.089	0.63 (0.45–0.90)	0.01	0.65 (0.46–0.93)	0.02
≥3.00	81	63 308	0.128	0.87 (0.70–1.09)	0.22	0.86 (0.69–1.08)[e]	0.19
Type							
Never	2257	1 811 696	0.125	Ref.		Ref.	
Alendronate sodium	227	183 344	0.124	0.87 (0.76–1.00)	0.05	0.89 (0.77–1.02)	0.09
Risedronate sodium	13	12 236	0.106	0.73 (0.42–1.26)	0.26	0.78 (0.45–1.35)	0.37
Others[f]	14	4480	0.313	2.16 (1.28–3.66)	0.01	2.02 (1.19–3.42)	0.01

[a]Users reported at least 2 weeks of use; nonusers included never users and those who used for <2 weeks. Baseline oral bisphosphonate use was updated at years 1, 3 and 6 for women in the WHI-CT and at year 3 for women in the WHI-OS.
[b]Adjusted for age and WHI study component.
[c]Adjusted for baseline age, ethnicity, education, smoking status, number of cigarettes per day, duration of regular smoking in years, alcohol use status, BMI, physical activity, total calcium intake, total vitamin D intake, statins use, and hormone treatment status and stratified on WHI study component.
[d]Quartile cutoff points for total duration of oral bisphosphonate use among ever user (years): 0.67, 1.5 and 3.0.
[e]Likelihood ratio tests were used to test difference between different strata of duration of bisphosphonate use. *P* value < 0.05.
[f]Others include etidronate disodium, tiludronate disodium, pamidronate disodium, and zoledronic acid.

Table 3. Association between oral bisphosphonate use and lung cancer by selected baseline characteristic factors (1993–2013)

Parameter	Oral bisphosphonate use				HR (95% CI)	*P* for interaction
	Never		Ever[a]			
	Cases	Person years	Cases	Person years		
Smoking						
Never	366	913 445.0	29	106 658.0	0.57 (0.39–0.84)[b]*	0.02
Ever	1860	877 056.6	220	90 969.5	0.96 (0.83–1.11)[c]	
Former smokers	1233	763 562.6	162	81 502.8	1.05 (0.89–1.24)[c]	
Current smokers	627	113 494.0	58	9466.7	0.85 (0.64–1.12)[c]	
Total calcium intake (mg/day)						0.13
<800	887	626 538.2	68	50 092.0	0.73 (0.57–0.95)[d]‡	
800–1200	513	446 347.3	54	45 243.3	0.97 (0.72–1.29)[d]	
≥1200	857	738 810.2	132	102 724.9	1.00 (0.83–1.20)[d]	

[a]Users reported at least 2 weeks of use; nonusers included never users and those who used for <2 weeks. Baseline oral bisphosphonate use was updated at years 1, 3 and 6 for women in the WHI-CT and at year 3 for women in the WHI-OS.
*$P \leq 0.01$;
‡$P = 0.02$.
[b]Adjusted for baseline age, ethnicity, education, alcohol use status, BMI, physical activity, total calcium intake, total vitamin D intake, statins use, and hormone treatment status and stratified on WHI study component.
[c]Additionally adjusted number of cigarettes per day, duration of regular smoking in years among smokers.
[d]Adjusted for baseline age, ethnicity, education, smoking status, number of cigarettes per day, duration of regular smoking in years, alcohol use status, BMI, physical activity, total vitamin D intake, and hormone treatment status and stratified on WHI study component.

Table 4. Lung cancer tumor characteristics by oral bisphosphonate use (1993–2013)

Characteristics	Oral bisphosphonate use		*P* value[b]	HR (95% CI)[c]
	Never (%)	Ever (%)[a]		
Histological type[d]				
Small cell	214 (10.4)	26 (11.1)	0.49	1.10 (0.72–1.67)
Nonsmall-cell	1844 (89.6)	209 (88.9)		0.90 (0.78–1.04)
Adenocarcinoma	1112 (49.5)	140 (55.1)		0.97 (0.81–1.17)
Squamous cell carcinoma	315 (14.0)	31 (12.2)		0.88 (0.61–1.29)
SEER stage				
Localized	572 (25.5)	80 (31.5)	0.22	1.16 (0.91–1.48)
Regional	550 (24.5)	63 (24.8)		0.93 (0.71–1.22)
Distant	839 (37.4)	87 (34.2)		0.83 (0.66–1.04)
Unknown	284 (12.6)	24 (9.5)		–
Grading				
Well differentiated	221 (9.8)	31 (12.2)	0.44	1.20 (0.82–1.77)
Moderately differentiated	409 (18.2)	53 (20.9)		1.06 (0.79–1.42)
Poorly differentiated	459 (20.4)	54 (21.3)		1.00 (0.75–1.34)
Anaplastic	108 (4.8)	11 (4.3)		0.84 (0.45–1.58)
Unknown	1050 (46.7)	105 (41.3)		–

[a]Users reported at least 2 weeks of use; nonusers included never users and those who used for <2 weeks. Baseline oral bisphosphonate use was updated at years 1, 3 and 6 for women in the WHI-CT and at year 3 for women in the WHI-OS.
[b]χ^2 tests are for categorical variables comparing oral bisphosphonate users with nonusers.
[c]Adjusted for baseline age, ethnicity, education, smoking status, number of cigarettes per day, duration of regular smoking in years, alcohol use status, BMI, physical activity, total calcium intake, total vitamin D intake, statins use, and hormone treatment status and stratified on WHI study component.
[d]Histologic subtypes were classified according to International Classification of Disease for Oncology and WHO Classification of Tumors for tumors of the lung. Nonsmall-cell lung cancer includes squamous cell carcinoma, adenocarcinoma, large cell carcinoma, sarcomatoid carcinoma and pleomorphic carcinoma.

of NSCLC cases, particularly adenocarcinoma, are needed to help confirm this association.

The strengths of the study include prospective cohort design, the large study population of postmenopausal women, comprehensive measurements of lung cancer risk factors, detailed information on oral bisphosphonate use, the standardized central adjudication of lung cancers, and a relatively large number of incident lung cancer cases allowing subgroup analyses by smoking status and total calcium intake. Nevertheless, several issues regarding the current study should be noted. First, this analytic study design is an observational analysis. Lung cancer was not a predefined study outcome in the WHI. Since the protocol did not require participants to undergo chest radiology imaging tests, some cancers may have been missed. Therefore, nondifferential misclassification of the outcome is still possible. In addition, and perhaps more importantly, there were substantial differences in the characteristics including smoking status between oral bisphosphonate users and nonusers. Although we adjusted for many possible factors that could confound the association, we were unable to eliminate possible residual confounding. Secondhand smoke (SHS) exposure at home and at work since age 18 years was collected only among the WHI-OS participants at the baseline, so we were unable to eliminate potential confounding from SHS exposure. When limiting our analyses in the WHI-OS and additionally adjusting of SHS exposure in the multivariable-adjusted models, we found similar but attenuated results. Subgroup analyses limited to WHI-OS participants who were never smokers generated similar findings. WHI started enrollment before the time bisphosphonates began being widely prescribed; only women enrolled toward the end of the recruitment had the opportunity to use bisphosphonate at baseline. Therefore, the usage was low at baseline (2%). Although the prevalence of bisphosphonate use increased during follow-up, half of these women used bisphosphonates for less than 1.5 years and majority of users took alendronate. No information on dose of medications prevented us to further evaluate the dose–response relationship between oral bisphosphonate use and lung cancer risk. The relative small number of lung cancer cases still limited our ability to explore the duration–response relationship, associations for other bisphosphonate types, associations in different ethnicity groups, or heterogeneity in associations according to histological type of lung cancer. Finally, as the WHI study enrolled volunteer postmenopausal women who may have led a healthier lifestyle than women who were nonvolunteers and over 80% of participants were white, we may have limited ability to generalize our findings to the general US population of postmenopausal women [43].

In this large population of postmenopausal women, oral bisphosphonate use was associated with lower lung cancer risk among never smokers. These observational study findings need to be confirmed. As the U.S. Food and Drug Administration issued safety announcements related to potential risk of long-

term bisphosphonates use [44, 45], further studies are warranted to investigate how duration of bisphosphonate use may influence risk of lung cancer and evaluate optimal dose of oral bisphosphonates for lung cancer prevention in older women. Further research to explore the mechanisms by which risk is reduced is warranted.

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Appendix

Table A1. Baseline characteristics by smoking status in the WHI study, 1993–2013

Characteristic at baseline	Baseline smoking status[a]	
	Never ($n = 75\,962$)	Ever ($n = 73\,515$)
Age at screening (years) (%)		
<50–59	23 644 (31.1)	24 974 (34.0)[b]
60–69	33 832 (44.5)	33 773 (45.9)
70–79	18 486 (24.3)	14 768 (20.1)
Race-ethnicity (%)		
Non-Hispanic white	62 075 (81.9)	62 532 (85.3)[b]
Black/African American	6485 (8.6)	6661 (9.1)
Hispanic/Latino	3354 (4.4)	2036 (2.8)
American Indian	297 (0.4)	320 (0.4)
Asian/Pacific islander	2643 (3.5)	1050 (1.4)
Other/Unknown	1108 (1.2)	916 (1.0)
Education (%)		
High school or less	18 094 (24.0)	15 223 (20.9)[b]
School after high school	27 464 (36.4)	28 970 (39.7)
College degree or higher	29 849 (39.6)	28 797 (39.4)
Physical activity (MET/week) (%)		
0–3.00	21 062 (29.0)	19 783 (28.2)[b]
>3.00–<11.75	23 627 (32.5)	21 637 (30.8)
≥11.75	27 926 (38.5)	28 845 (41.0)
Alcohol intake (%)		
Never	13 896 (18.4)	2241 (3.1)[b]
Past drinker	13 096 (17.4)	14 917 (20.4)
<1 drink per month	10 300 (13.6)	8174 (11.2)
<1 drink per week	16 015 (21.2)	14 544 (20.0)
1–<7 drinks per week	16 795 (22.3)	21 382 (29.2)
≥7 drinks per week	5391 (7.1)	11 972 (16.4)
BMI, kg/m^2 (%)		
<25	26 352 (35.0)	25 138 (34.5)
25–30	26 030 (34.6)	25 454 (34.9)
≥30	22 947 (30.5)	22 261 (30.6)
Hormone-therapy use (%)		
Never used	32 496 (42.8)	29 853 (40.6)[b]
<5 years	16 455 (21.7)	16 608 (22.6)
5 to <10 years	9676 (12.7)	10 016 (13.6)
≥10 years	17 333 (22.8)	17 036 (23.2)
Statin use (%)	5749 (7.6)	6019 (8.2)[b]
10-year probability of hip fracture (%)		
<0.53	23 727 (31.2)	22 902 (31.2)[b]
0.53–1.68	24 829 (32.7)	25 074 (34.1)
≥1.69	27 406 (36.1)	25 539 (34.7)
Total calcium intake (supplements and diet) (mean ± SD, mg/day)	1187.7 ± 772.1	1174.4 ± 719.7[b]
Total vitamin D intake (supplements and diet) (mean ± SD, U/day)	376.8 ± 280.7	370.4 ± 278.9[b]
Oral bisphosphonate use (%)	1660 (2.2%)	1440 (2.0%)[b]
Duration of bisphosphonate use[c] (mean ± SD, years)	1.22 ± 1.6	1.21 ± 1.8

[a]Missing value were not included in the table.

[b]χ^2 tests for categorical variables and Student's *t*-tests for continuous variables were used to compare oral bisphosphonate users with nonusers. *P* value < 0.01.

[c]Among baseline bisphosphonate users.