

Bisphosphonates and risk of lung cancer

Protocol for a systematic review and meta-analysis

Minghao Li, MD , Muyan Zhong, MD, Chengnong Guan, MD*

Abstract

The association between the use of bisphosphonates (BPs) and the risk of lung cancer has been concerned recently. There is no explicit study indicating that whether the use of BPs would affect the risk of lung cancer. So, we conducted a meta-analysis to figure out the relationship between BPs and lung cancer.

We searched the databases of PubMed and Embase. The random effects were used to calculate the pooled odds ratios (ORs) and 95% confidence interval (CIs) for the risk of lung cancer in BPs users compared with non-users. The stability of our results was evaluated by the sensitivity analysis. The publication bias was assessed in our study. The data in our study comes from the public database, therefore ethical approval is not necessary. Also, our study did not involve patient consent.

Four studies met our inclusion criteria. All the included studies are cohort studies. Our analysis indicated that there was no significant association between the use of BPs and the risk of lung cancer (OR 1.02, 95%CI 0.85- 1.24, I^2 71%). In our secondary analysis, the use of alendronate may increase the risk of lung cancer. The pooled OR of 3 studies is (OR 1.10, 95%CI 0.84–1.45, I^2 77%), but when we performed a sensitivity analysis, 1 of the OR is (OR 1.23, 95%CI 1.02–1.49, I^2 4.1%).

This is the most detailed meta-analysis on this topic. And there was no significant association between the use of BPs and lung cancer. However, exposure to alendronate may increase the risk of lung cancer. More studies are needed to confirm our findings.

Abbreviations: BPs = bisphosphonates, CI = confidence interval, HR = hazard ratio, OR = odds ratio, RR = relative ratio.

Keywords: a systematic review, bisphosphonates, lung cancer, meta-analysis

1. Introduction

Lung cancer is 1 of the most common cancers and it is the leading cause of cancer death among American women.^[1] Therefore, it is essential to emphasize the significance of modifiable risk factors. In addition, identifying other modifiable risk factors may be helpful for developing novel prevention strategies. (<http://links.lww.com/MD/F117>)

Osteoporosis is a major health issue among elder, and it can increase the morbidity and mortality in the older.^[2,3] Osteoporosis can appear in both gender and it is more common for

postmenopausal women and old-age males. At present, bisphosphonate has become a major drug for the treatment of osteoporosis patients.^[4] However, there are some adverse reactions to oral bisphosphonate, such as esophagitis and gastric irritation.^[5–8] Moreover, there are many adverse reactions that have not been found. Our study population is people who suffer from osteoporosis and use bisphosphonate for treatment.

Recently, the study Tao et al^[9] indicated that the risk of lung cancer could be decreased in postmenopausal women who use the bisphosphonates (BPs) and never smoke (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.39–0.84). However, other studies^[10–12] showed that there was no significant association between BPs and lung cancer. Therefore, we could know that BPs may affect the incidence of lung cancer from these studies.

Though some studies have shown that BPs are associated with the decreased risk of breast and colorectal cancer,^[13–15] there are many adverse reactions that have not been found. BPs have been reported to increase the risk of esophageal cancer, but the carcinogenic mechanism of BPs remains unclear.^[16] Most previous studies always focused on the role of BPs in the treatment and prevention of cancer metastasis but little research focused on whether the use of bisphosphonate would affect the risk of cancer. At present, much research has focused on the effects of BPs on the esophagus^[17–19] but little research has been done on the lung, especially lung cancer.

Therefore, we want to figure out the relationship between the incidence of lung cancer and BPs in order to guide patients in the selection of osteoporosis treatments.

2. Methods

2.1. Search strategy

We conducted a systematic review and meta-analysis which followed the MOOSE guidelines.^[20] We searched the databases

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The datasets generated during and/or analyzed during the current study are publicly available.

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of PubMed and Embase from their inception to March 2020 and there was no language restriction in our search. The main search terms were “Lung Cancer” or “Lung Neoplasms” or “Pulmonary Neoplasms” or “Cancer of the Lung” or “bisphosphonate” and “etidronate” or “alendronate” or “ibandronate.” We also reviewed the reference list of included literature for study that may have been overlooked from the search.

2.2. Study selection

Excluded criterion:

- (1) duplicate studies.
- (2) no relevant studies
- (3) no available data in the studies
- (4) reviews, protocol, case reports, commentaries, letters.

Included criterion:

- (1) cohort studies or case-control studies of BPs use.
- (2) studies on the use of BPs and the risk of lung cancer.
- (3) risk estimate was supplied by OR, relative ratio (RR) or hazard ratio (HR).
- (4) 95%CI was reported from the studies.

Two reviewers independently evaluated all relevant studies, and through the discussion of the disagreements were resolved.

2.3. Data extraction

The Newcastle-Ottawa Scale (NOS)^[21] was used to assess the quality of the included literature by 2 authors. The author and published year, country, gender, study type, age, follow-up, sample size, adjusted RR/OR/HR, 95%CI, type of BPs, adjusted variables were extracted from the included literature. We did not contact the authors of the including studies.

2.4. Statistical analysis

The data was analyzed using STATA version 12.0 (Stata Corp, College Station, TX). RR, HR, OR were used to calculate the pooled effect size, and we used the OR as the pooled effect size in our analysis. The main outcome of our analysis was focused on the effect of BPs exposure on the risk of lung cancer, and the secondary outcome was the effect of alendronate exposure on the risk of lung cancer.

We used the Cochran Q statistic to evaluate the heterogeneity, for quantified the degree of heterogeneity we used the I^2 statistic.^[22] Heterogeneity existed when $P < .10$ or $I^2 > 50\%$. We used a random-effects model^[23] to calculate the pooled estimates when substantial heterogeneity appeared ($P < .10$ or $I^2 > 50\%$). The stability of the results was evaluated by the sensitivity analysis. The Egger test^[24] was used to assess publication bias.

3. Result

2837 studies initially identified from the databases of PubMed and Embase. 222 duplications and 2608 studies were excluded by screening the title and abstract. Finally, 4 studies^[9–12] were included in our analysis (Fig. 1).

3.1. Study characteristics

The characteristics of including literature were listed in Table 1. In Tao et al^[9] and Chiang et al^[11] only contained female patients.

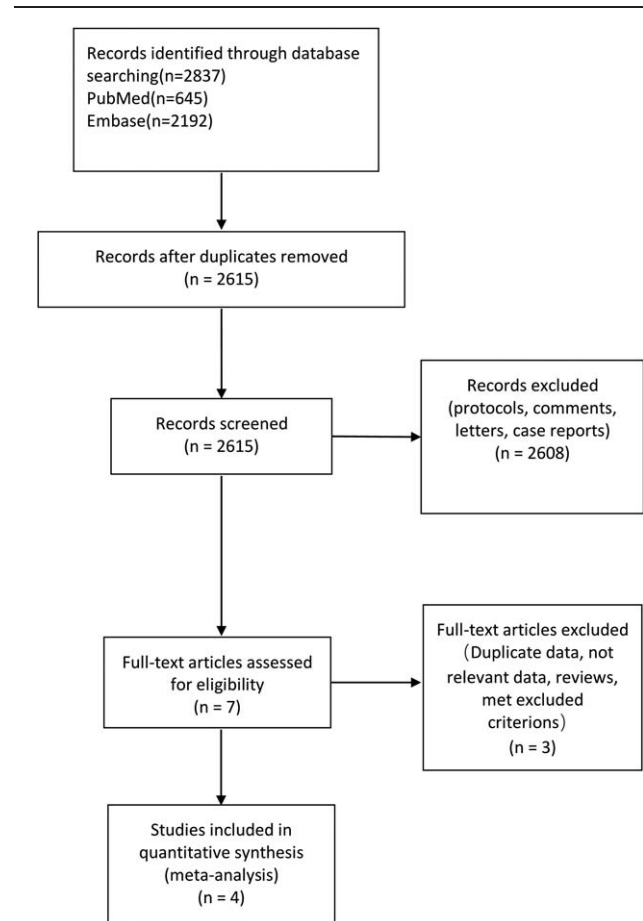


Figure 1. Flow chart of search results.

However, the patients in the study of Cardwell et al^[12] and Lee et al^[10] were man and woman. Three studies^[9–11] provided the risk of lung cancer on alendronate. All included studies were cohort studies and provided adjusted RR/OR/HR and 95%CI.

3.2. Bisphosphonate and lung cancer

No significant relevance was found between the use of BPs and the risk of lung cancer (OR 1.02, 95%CI 0.85–1.24, I^2 71%) (Fig. 2). The sensitivity analysis was performed by excluded 1 study in this group at a time, and the result was stable. We did not find publication bias through the Egger test.

3.3. Alendronate and lung cancer

Three studies^[9–11] provided the risk of lung cancer with alendronate in included literature. In our study, we found that the use of alendronate might increase the risk of lung cancer. The pooled estimate showed that there was no relevant association between alendronate and lung cancer (OR 1.10, 95%CI 0.84–1.45, I^2 77%) (Fig. 3). However, we performed sensitivity analysis in this group, and found that when we excluded Tao et al^[9] the heterogeneity disappeared and the result have changed which indicated that the use of alendronate would increase the risk of lung cancer (OR 1.23, 95%CI 1.02–1.49, I^2 4.1%). We did not find publication bias through the Egger test.

Table 1
Detailed characteristics of included studies in this meta-analysis.

Author and published year	Country	Gender	Study type	Age(yr)	Follow-up (yr)	Sample size	Adjusted RR/ OR / HR (95% CI)	Type of BPs	Adjusted variables
Cardwell 2012	UK	M/F	Cohort	70.0±11	Case: 4.5±2.6 Control: 4.4±2.6	83652	BPs: 0.85 (0.7–1.03)	BPs	Age, sex, general practice, BMI, cigarette smoking, alcohol intake, hormone therapy, NSAID use, Barrett's esophagus, GERD, H2 receptor antagonist use, proton pump inhibitor use
Lee 2012	Taiwan	M/F	Cohort	NA	Treatment: 2.92 Control: 3.04	21918	Alendronate: 1.47 (1–2.17)	Alendronate	Smoking habits, alcohol consumption, body-mass index, socioeconomic status, and family history of cancer
Tao 2018	America	F	Cohort	50-79	Mean 13.3	151432	BPs: 0.91 (0.8–1.04) Alendronate: 0.89 (0.77–1.02)	BPs, Alendronate, Risedronate	Adjusted for baseline age, ethnicity, education, smoking status, number of cigarettes per day, duration of regular smoking in years, alcohol use status, body mass index, physical activity, total calcium intake, total vitamin D intake, statins use, and hormone treatment status and stratified on WHI study component.
Chiang 2012	Taiwan	F	Cohort	73.4±8.4	4.3±2.5	27603	Alendronate: 1.17 (0.95–1.43)	Alendronate	Adjusted for age and gender

BMI=body mass index, BPs=bisphosphonates, F=female, GERD=gastroesophageal reflux disease, M=man, NA=not available, NSAID=non-steroidal anti-inflammatory drug.

3.4. Female and mixed gender

There was no relationship between BPs and the risk of lung cancer in the mix gender group (OR 1.09, 95%CI 0.64–1.86, I^2 83.7%) or female group (OR 1.02, 95%CI 0.80–1.30, I^2 75.7%). (Fig. 4)

3.5. Patient with smoking history

Only 1 study^[9] was included in this group. We found that the risk of lung cancer decreased in female bisphosphonate users who never smoke (OR 0.57, 95%CI 0.39–0.84). But there was no

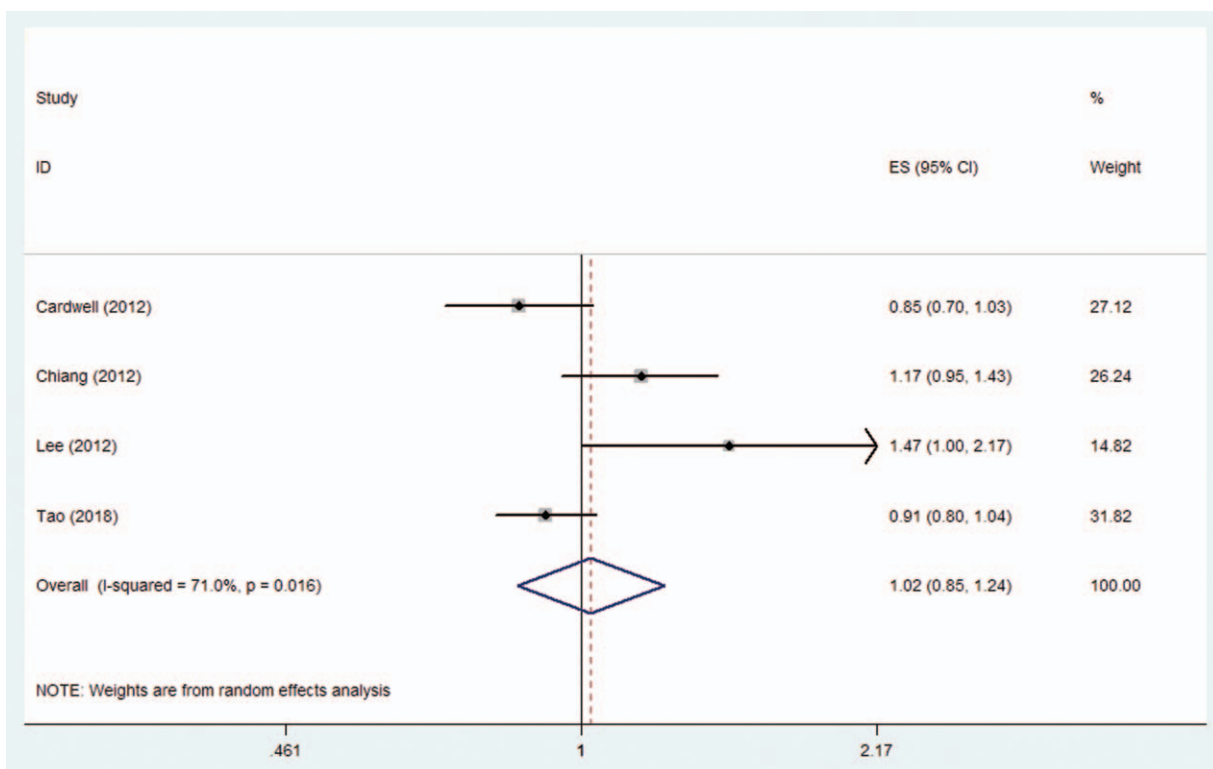


Figure 2. Forest plot showing the combined estimates of bisphosphonate use and the risk of lung cancer.

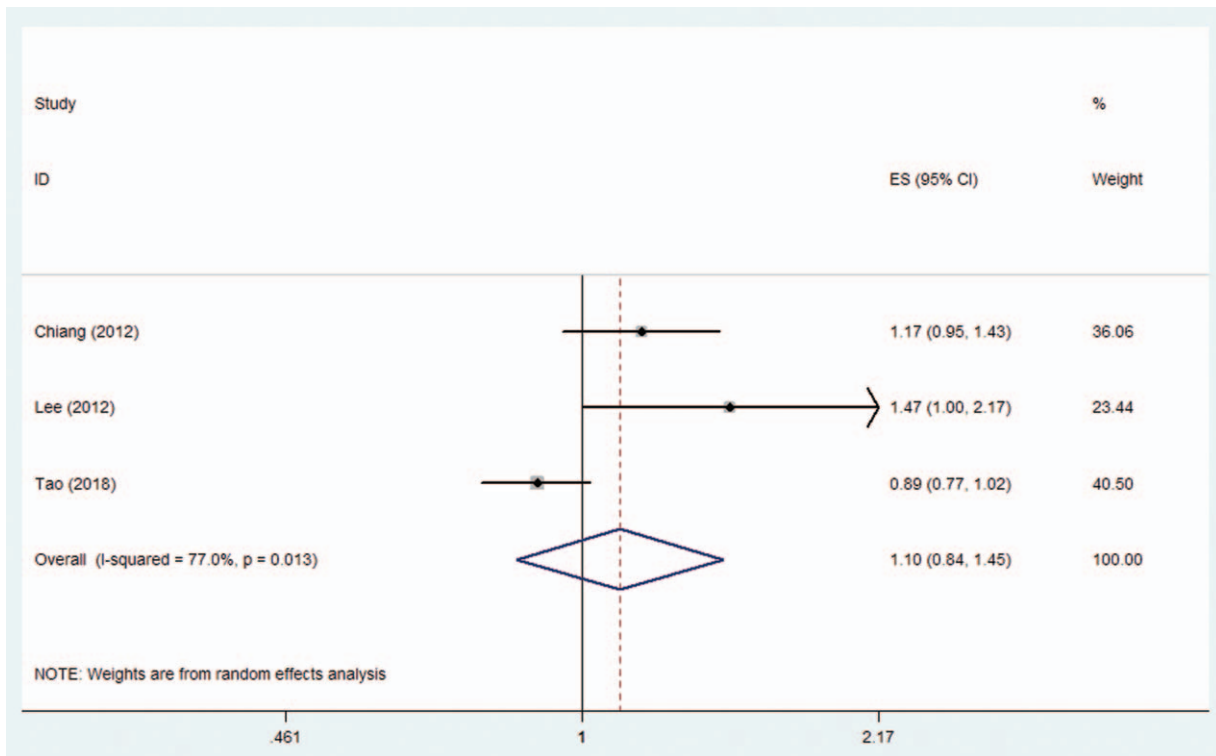


Figure 3. Forest plot showing the combined estimates of Alendronate use and the risk of lung cancer.

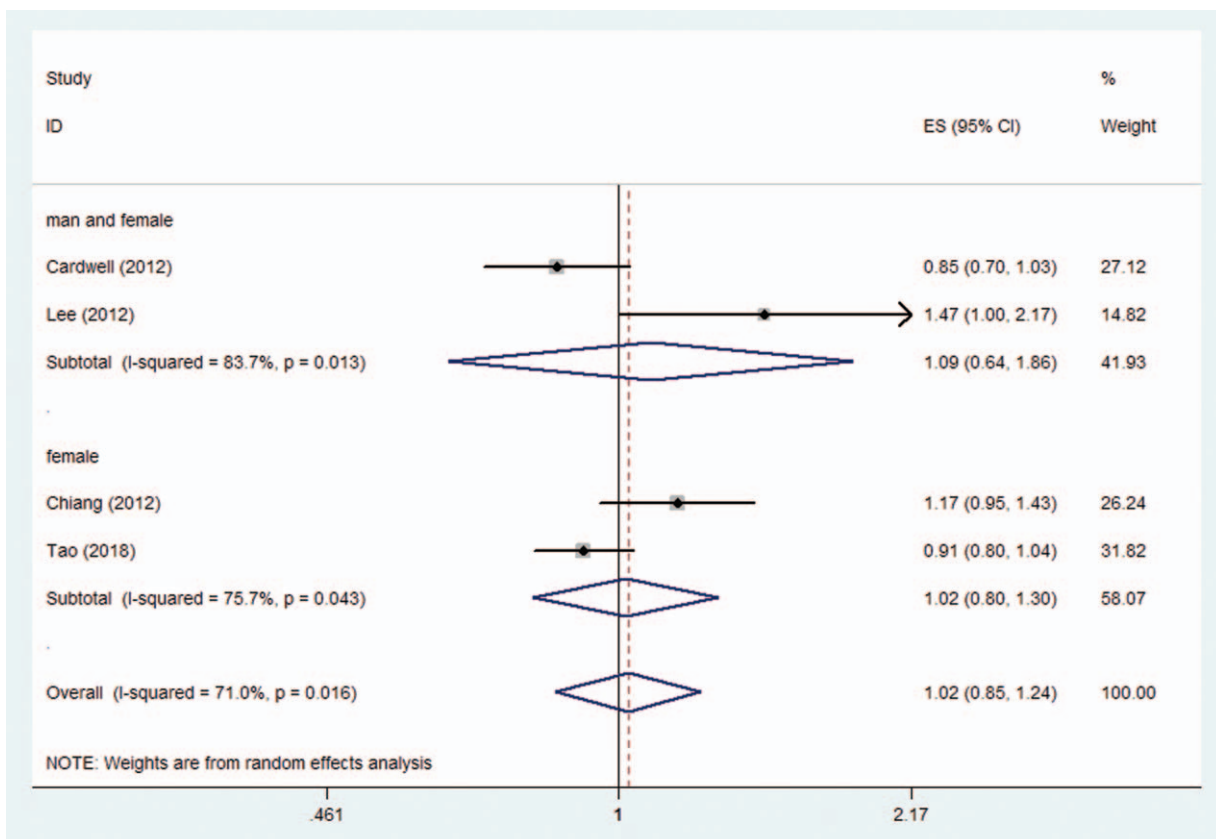


Figure 4. Forest plot showing the combined estimates of bisphosphonate use in the female group or mix gender group and the risk of lung cancer.

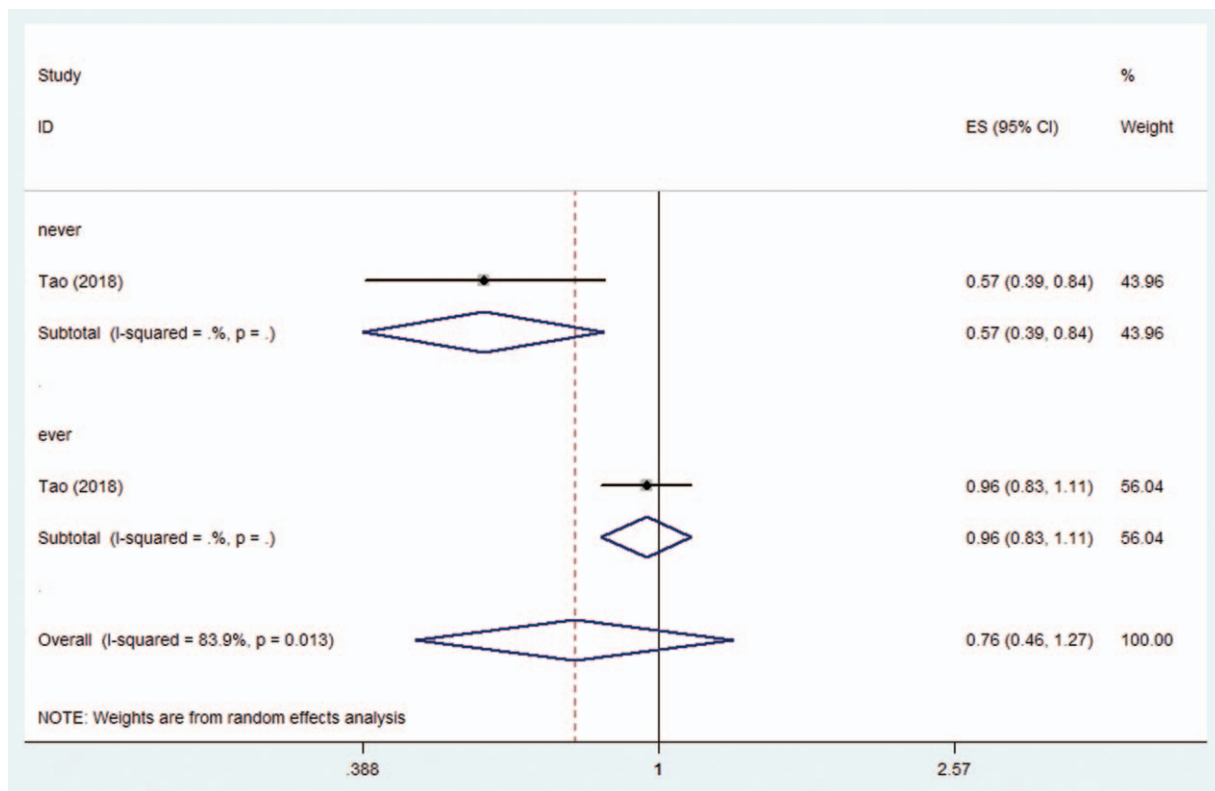


Figure 5. Forest plot showing the combined estimates of bisphosphonate users with smoking history and the risk of lung cancer.

evidence showing that the risk of lung cancer decreased in female bisphosphonate users who ever smoke (OR 0.96, 95%CI 0.83–1.11). (Fig. 5)

4. Discussion

This is the first multifaceted analysis between BPs and lung cancer. There was no publication bias in our analysis. The Included literature was assessed by the NOS, and the quality of these studies was high. Four studies were included in our analysis, which included a total of 284,605 bisphosphonate users.

In our analysis, we could not find a significant relevance between the use of BPs or alendronate and the risk of lung cancer. But there was an interesting thing that in the group of alendronate, we performed a series of sensitivity analyses, when the study Tao et al^[9] was excluded, the heterogeneity disappeared and the result changed which indicated that the use of alendronate would increase the risk of lung cancer (OR 1.23, 95%CI 1.02–1.49, I² 4.1%). It means that alendronate might increase the risk of lung cancer. However, there were only 2 studies of alendronate group after excluding the study Tao et al. It could not provide a strong evidence to prove that alendronate could increase the risk of lung cancer, so future studies should focus on this topic.

We found that the risk of lung cancer decreased in female bisphosphonate users who never smoke (OR 0.57, 95%CI 0.39–0.84). But no evidence showed that the risk of lung cancer decreased in female bisphosphonate users who ever smoke (OR 0.96, 95%CI 0.83–1.11). However, this group had a limitation, which was only 1 literature^[9] was included. Individual studies

cannot yield reliable conclusions, so more research is needed to figure out this confusion. There was high heterogeneity in our analysis, but we could not find the heterogeneous source due to the restriction number of included literature and available data from the original literature.

Our study has multiple strengths:

- (1) This is the first multifaceted analysis between BPs and lung cancer.
- (2) We conducted a comprehensive search strategy and no language restriction in our search strategy.
- (3) The sensitivity analyses were performed in our analysis to examine the stability of the results.
- (4) Previously, it was believed that BPs can be used in lung cancer and can effectively prevent bone metastasis of lung cancer, but few people mentioned whether BPs could be a risk factor for carcinogenesis.

Therefore, our study provided a new research direction for BPs. Whereas, there are some limitations to our study:

- (1) All included studies tried to control for the confounding variables, but not all the confounding variables could be controlled in each literature.
- (2) There was high heterogeneity in our analysis, but we could not find the heterogeneous source due to the restriction number of including studies and available data from the original literature.
- (3) We could not find out the effect of BPs on different histologic types of lung cancer.
- (4) Only 4 studies were included in our analysis.

More studies are needed to confirm our findings.

5. Conclusions

In our analysis, we could not find significant relevant between the use of BPs and the risk of lung cancer. The use of alendronate might increase the risk of lung cancer. The future studies should focus on whether alendronate would increase the risk of lung cancer, and whether the risk of lung cancer decreased in female bisphosphonate users who never smoke.

Author contributions

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Validation: Chengnong Guan.

Visualization: Minghao Li.

Writing – original draft: Minghao Li, Muyan Zhong.

Writing – review & editing: Minghao Li.

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