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Review Article

Oral bisphosphonates and risk of esophageal cancer: a meta-analysis

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Abstract: Objectives: The association between oral bisphosphonate (BP) intake and esophageal cancer risk has been investigated in several recent studies with conflicting results. Methods: We conducted a detailed meta-analysis of observational studies with sub-analysis of duration, type of BPs and cumulative dose. We identified relevant studies by search of PubMed, the Cochrane Library and Embase in October 2014. The studies that provide the risk estimates and CIs between exposure to oral BPs and risk of esophageal cancer were included in our analysis. When data sets were from the same population, the most recent study was included unless the other studies contains largest number of esophageal cancer case or more detailed data. Results: Overall, 7 studies were included in our meta-analysis. The primary analysis suggested that the bisphosphonate treatment was not associated with risk of esophageal cancer in both cohort studies (RR 1.18, 95% CI 0.70 to 1.97) and nested case-control studies (OR 1.06, 95% CI 0.92 to 1.22). No statistically significant risk was found in sub-analysis of both type of BPs and duration of exposure. Conclusions: This meta-analysis suggests that the use of oral bisphosphonate treatment was not significantly associated with excess risk of esophageal cancer.

Keywords: Bisphosphonates, esophageal cancer, risk factor, meta-analysis

Introduction

Osteoporosis is a major public health concern. 75 million people are suffering from osteoporosis in the US, Europe and Japan [1], leading to increased morbidity and mortality associated with osteoporotic fracture in the elderly [2, 3]. Bisphosphonate (BP) therapy has become the most widely used method for the treatment of osteoporosis [1, 4-6], with a long-term lasting benefit effect [7]. However, oral BPs are well known to cause dyspepsia, esophageal and gastric irritation, and inflammatory change such as erosive esophagitis, delayed healing, and mucosal abnormalities [7-11]. Although some studies have shown that BPs are associate with the reduced risk of breast and colorectal cancer [12-15], it is possible that the adverse effect on the gastrointestinal tract could increase the risk of cancer, especially upper gastrointestinal cancer.

It has long been debated whether BPs increase the risk of the esophageal cancer. The first report on the possible association between BP use and esophageal cancer was from the US Food and Drug Administration (FDA), which listed 23 esophageal cancer cases in oral alendronate users [16]. Observational studies have reported controversial results, with some articles reporting no excess risk [17-21], others reporting increase in risk [22, 23]. Green et al. [23] conducted a nested case control study with 2,954 esophageal cancer cases based on the GPRD. They found a 30% increased risk of esophageal cancer in BP users, and an almost twofold increased risk in users with 10 or more prescriptions for oral bisphosphonates and with prescriptions over 3-year period. However, some studies [17, 21, 24] came to conflict results with no increased risk even based on the same database. Two previously published meta-analysis [25, 26] also came to conflict result.

Thus, the effect of BPs on the risk of esophageal cancer remains undetermined. To address this issue and to figure out the factors influenc-

ing the risk, we conducted a detailed meta-analysis of observational studies with sub-analysis of duration, cumulative dose, and type of BP use.

Method

Search strategy

We searched PubMed, the Cochrane Library and Embase in October 2014 for studies published between 1966 and October 2014 using the following combination of terms: 'bisphosphonate' or trade names of the drugs AND 'esophageal cancer' OR 'esophageal carcinoma' OR 'esophageal neoplasms' OR 'esophageal squamous cell carcinoma' OR 'esophageal adenocarcinoma'. The articles published in languages other than English was excluded. Two investigators (WW Ye and Y Zhou) independently completed the search and assessed the identified titles for relevance. Abstracts were screened for all potentially relevant titles, and full papers were obtained for all abstracts of potential relevance. In addition, regarding trials with several treatment groups, the eligibility of each individual group was assessed and only those relevant were included. The reference lists of the selected papers were also screened for articles that may have been overlooked in the initial search, and references cited in the identified articles were searched manually. Two authors (WW Ye and Y Zhou) extracted data and any discrepancies were resolved by consensus.

Selection criteria

This meta-analysis followed a detailed, pre-specified protocol that set out the objectives, inclusion criteria for studies, data to be collected, and analyses to be completed.

Studies were considered for inclusion if they met the following criteria: (1) the type of study design was prospective, (2) the exposure of interest was exposure to oral BP (alendronate, clodronate, etidronate, ibandronate, risedronate, and tiludronate), (3) the outcome of interest was oesophageal cancer, (4) the relative risk (RR) or odds ratio (OR) estimated with 95% CIs (or sufficient data for their calculation) were reported.

BPs exposure was defined as one or more written or dispensed prescriptions of BPs. When data sets were from the same population with the same study design, the most recentstudy-was included in order to avoid duplicate observation unless the other studies containsa larger numberof esophageal cancer case or more detailed data. For studies from the same database but with a different design, we extracted data and combined estimates of these studies separately.

Data extraction

We collected the following information by a standardized data extraction form: last name of the first author, publication year, study design, Region, study database, age, gender, number of cases, number of controls, total sample size, median follow up time in cohort studies or observation period in case-control studies, type of bisphosphonate used, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs and the duration of exposure to bisphosphonates, adjustment factors of interest, definition of exposure and measure of exposure. Studies with risk estimates for different types of bisphosphonate exposure were included as separate risk estimates. For example, Vestergaard [22] provided separate data for exposure to alendronate and etidronate. For 'any' bisphosphonate analysis, we combined the data for alendronate and etidronate and calculate a summative outcome. The two responsible trial investigators resolved any queries and verified the final database entries. We also contacted author of primary studies for additional information when it is necessary.

Statistical analysis

Data were analyzed using Review Manager Software (RevMan version 5.2; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and STATA version 12.0 (Stata Corp, College Station, TX, USA). The primary outcome of the pooled analysis was focused on the effect of bisphosphonate exposure on the risk of esophageal cancer. We also performed further risk-stratification analysis for duration (short-term group-defined as BPs use shorter than 1 year, long-term group-defined as BPs use longer than 3 years) and type (including alendronate group and etidronate group) of BPs use. Subgroup analysis was done based on the availability of the data. The I^2 test and associated *p* values were used to

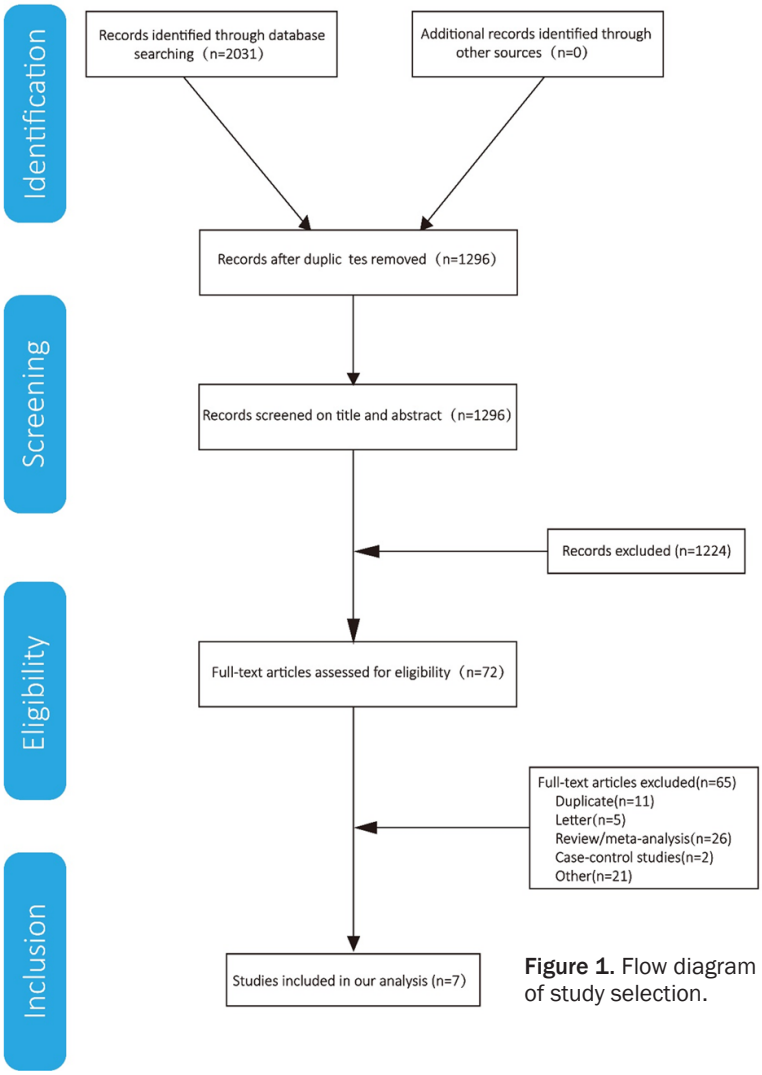


Figure 1. Flow diagram of study selection.

assess the heterogeneity of the studies. We measured inconsistency across trials using the I^2 statistic; results ranged between 0% (i.e., no observed heterogeneity) and 100%, an I^2 value less than 25% was considered to be homogeneous, an I^2 value between 25% and 50% was considered to have low heterogeneity, an I^2 value between 50% and 75% to have moderate heterogeneity, and an I^2 value above 75% to have high heterogeneity. *P* values < 0.10 were considered statistically significant heterogeneity [27, 28]. A fixed effects model was applied when the studies were homogeneous or the statistical heterogeneity was low. However, when the statistical heterogeneity was moderate or high, we used the random effects model.

To examine the contribution of individual studies to heterogeneity, we conducted sensitivity analyses to investigate the influence of a single study on the overall risk estimate by excluding individual studies one at a time. The robustness of the meta-analysis to the publication bias was assessed by various bias indicators, including the Egger's test [29] and the begg's test. Two independent reviewers evaluated the studies' eligibility, assessed the quality, and assessed the extracted data, aiming for achieving a high level of correlation in the quality and validity of the findings. Disagreements were resolved by consensus.

Result

The literature search identified 2,031 trials until October 2014 of which 72 were considered potentially relevant. Additional trials were identified by searching the reference lists of trials included in the study. **Figure 1** illustrates the process of study selection. Seven trials [17-22, 30] were finally designed to evaluate BP use and the risk of esophageal cancer and fulfilled the inclusion criteria for published studies (including safety reports).

Study characteristics

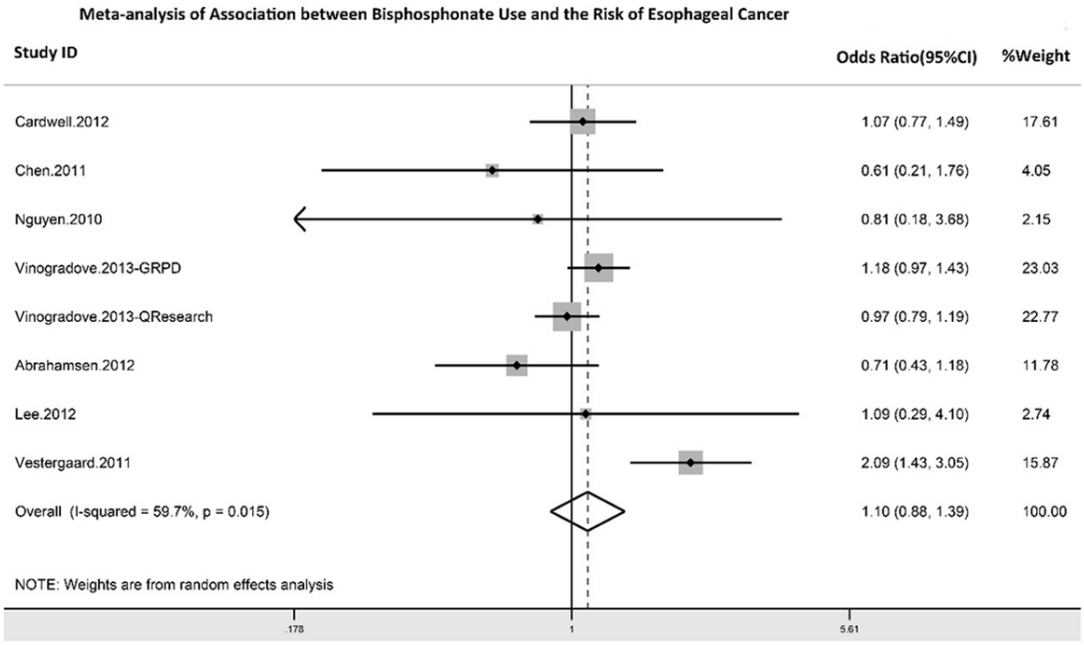
The characteristics and information of the included studies were presented in **Table 1**. Overall, there are 3 nested case-control studies [17, 20, 30] and 4 cohort studies [18, 19, 21, 22] included in our studies. The 3 nested case-control studies reported 10,894 esophageal cancer cases and 52,661 controls. Almost 635,128 subjects participated in 4 cohort studies and among them, 392 subjects develop esophageal cancer. Only one studies [22] showed a significant correlation between bisphosphonate use and risk of esophageal cancer, and no significant association was found in the remaining six studies [17-21, 30].

Table 1. Study characteristic

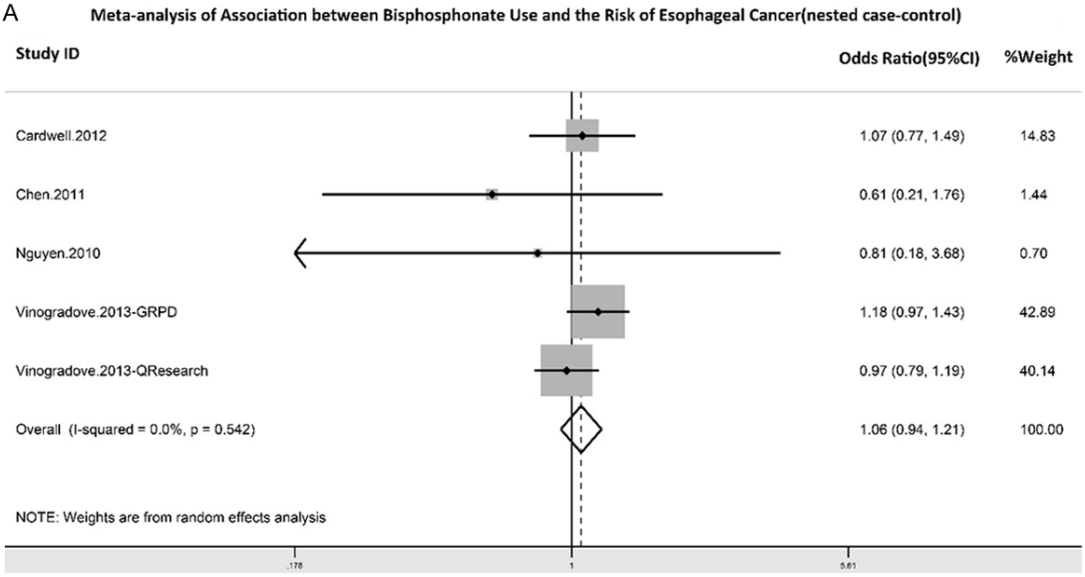
Source	Region	Sex	Study period	Study database	Study type	Study population	Type of drug
Lee. 2012	Taiwan	M/F (84.1%)	E:1998-2009 F/U:-2009	NHIRD	Retrospective cohort study	ALN: 3/5624 (0.05%) esophageal cancer cases Control: 8/16294 (0.05%) esophageal cancer cases	ALN
Abrahamsen. 2012	Denmark	F	E:1995-2005 F/U:-2005	NPD CoDR LPR	Retrospective cohort study	ALN: 19/30606 (0.06%) esophageal cancer cases Control: 99/122424 (0.08%) esophageal cancer cases	ALN
Vestergaard. 2011	Denmark	M/F (84.7%)	E:1996-2006 F/U:-2006	Danish Medicines Agency	Retrospective cohort study	BPs: 46/96300 (0.05%) esophageal cancer cases Control: 66/280228 (0.02%) esophageal cancer cases	ALN (orally) ETI (orally) CLO (orally)
Cardwell. 2012	UK	M/F (81.4%)	E:1996-2006 F/U:2008	GRPD	Retrospective cohort study	BPs: 79/41826 (0.2%) esophageal cancer cases Control: 72/41826 (0.2%) esophageal cancer cases	Any bisphosphonate use
Vinogradove. 2013	UK	M/F: (40.1%)	E:1997-2011 F/U:-2011	GRPD	Nested case control study	Cancer cases: 262/5132 (5.1%) BPs users Control: 943/24053 (3.9%) BP users	ALN, ETI, RIS, IBA
Vinogradove. 2013	UK	M/F: (40.1%)	E:1997-2011 F/U:-2011	QResearch	Nested case control study	Cancer cases: 252/5364 (4.7%) BPs users Control: 1071/25101 (4.3%) BP users	ALN, ETI, RIS, IBA
Chen. 2011	Taiwan	M/F	E:2001-2008 F/U:-2008	NHIRD	Nested case-control study	Cancer Case: 88/282 (31.2%) BP users Control; 761/2811 (27.1%) BP users	ALN
Nguyen. 2010	American	M/F (2.6%)	E:2000-2002 F/U:-2002	VA	Nested Case-control study	Patients with Barrett's esophagus Cancer Case: 2/116 (1.7%) BP users Control: 13/696 (1.9%) BP users	Oral bisphosphonate

Source	Age range (years)	No. of exposure/ case	No. of control	Follow-up or Observation period (years)	Adjustment for covariates	Definition of Exposure	Measure of exposure
Lee.2012	NA	5624	16294	T: 2.92 C: 3.04	Smoking habits, alcohol consumption, body-mass index, socio-economic status, and family history of cancer	NA	NA
Abrahamsen. 2012	71.9±10 (50+)	30606	122424	3.5 (range 1-11)	Age, individual Charlson comorbidity index components, the number of co-medications, PPI use, and upper endoscopy history, Hormone replacement therapy, NSAID use	At least one prescription in the observation	Prescription information within the observation period
Vestergaard. 2011	70.5±11.4	96300	280228	T:2.8 C:5.5	Age, sex, alcoholism, use of inhaled bronchodilator or corticosteroid drug, antacid drugs, NSAIDs, working or not, married or not, income above vs. below median, and gastric surgery before	At least one prescription in the observation	Prescription information within the observation period
Cardwell. 2012	70.0±11.	NA	NA	case: 4.5±2.6 Control: 4.4±2.6	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	NA	NA
Vinogradove. 2013	≥ 50 year	5364	25101	About 2	BMI, cigarette, alcohol intake, ethnicity, history of osteoporosis, H2 receptor antagonist use, proton pump inhibitor use, NSAID	At least one prescription in the observation period	Prescription information within the observation period
Vinogradove. 2013	≥ 50 year	5132	24053	About 2	BMI, cigarette, alcohol intake, ethnicity, history of osteoporosis, H2 receptor antagonist use, proton pump inhibitor use, NSAID antagonist use, proton pump inhibitor use, NSAID	At least one prescription in the observation period	Prescription information within the observation period
Chen. 2011	NA	280	2811	NA	NA	NA	NA
Nguyen. 2010	Case: 65±10.3 Control: 64.7±10.3	116	696	2	Race, noncancer disease comorbidity index, PPI and NSAIDs prescription	At least one prescription in the observation	Prescription information within the observation period

M for male, F for female, E for enrollment duration, F/U for follow up duration, BP for bisphosphonate, ALN for Alendronate, ETI for Etidronate, CLO for Clodronate, RIS for Risedronate, IBA for Ibandronate, T for treatment, C for control, NA for not available.


Meta-analysis of Association between Bisphosphonate Use and the Risk of Esophageal Cancer
Study ID
Odds Ratio(95%CI)
%Weight
Cardwell.2012
1.07 (0.77, 1.49)
17.61
Chen.2011
0.61 (0.21, 1.76)
4.05
Nguyen.2010
0.81 (0.18, 3.68)
2.15
Vinogradove.2013-GRPD
1.18 (0.97, 1.43)
23.03
Vinogradove.2013-QResearch
0.97 (0.79, 1.19)
22.77
Abrahamsen.2012
0.71 (0.43, 1.18)
11.78
Lee.2012
1.09 (0.29, 4.10)
2.74
Vestergaard.2011
2.09 (1.43, 3.05)
15.87
Overall (I-squared = 59.7%, p = 0.015)
1.10 (0.88, 1.39)
100.00
NOTE: Weights are from random effects analysis
.178
1
5.61

A


Meta-analysis of Association between Bisphosphonate Use and the Risk of Esophageal Cancer(nested case-control)
Study ID
Odds Ratio(95%CI)
%Weight
Cardwell.2012
1.07 (0.77, 1.49)
14.83
Chen.2011
0.61 (0.21, 1.76)
1.44
Nguyen.2010
0.81 (0.18, 3.68)
0.70
Vinogradove.2013-GRPD
1.18 (0.97, 1.43)
42.89
Vinogradove.2013-QResearch
0.97 (0.79, 1.19)
40.14
Overall (I-squared = 0.0%, p = 0.542)
1.06 (0.94, 1.21)
100.00
NOTE: Weights are from random effects analysis
.178
1
5.61

B

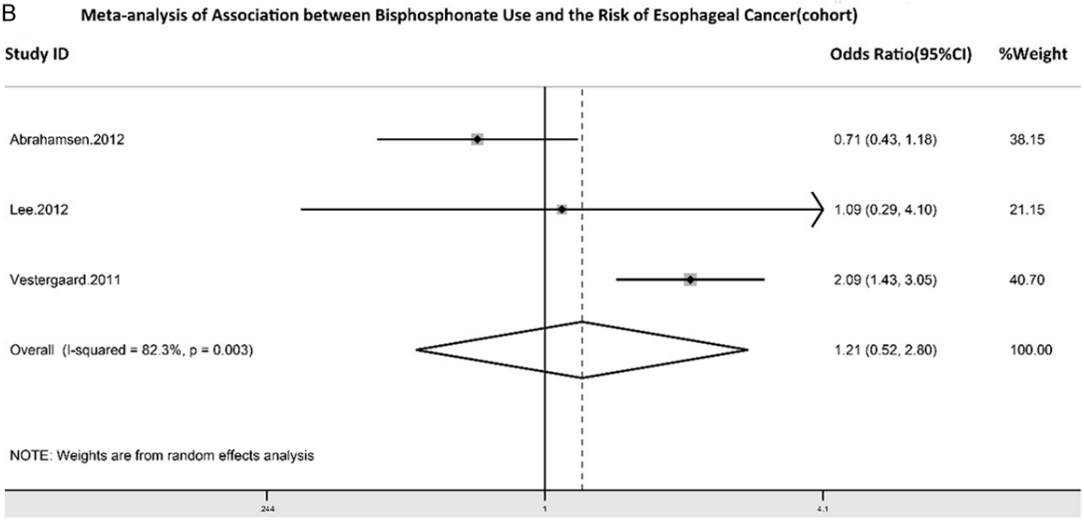

Meta-analysis of Association between Bisphosphonate Use and the Risk of Esophageal Cancer(cohort)
Study ID
Odds Ratio(95%CI)
%Weight
Abrahamsen.2012
0.71 (0.43, 1.18)
38.15
Lee.2012
1.09 (0.29, 4.10)
21.15
Vestergaard.2011
2.09 (1.43, 3.05)
40.70
Overall (I-squared = 82.3%, p = 0.003)
1.21 (0.52, 2.80)
100.00
NOTE: Weights are from random effects analysis
.244
1
4.1

Figure 2. A. Meta-analysis of association between bisphosphonate use and the risk of esophageal cancer (nested case-control); B. Meta-analysis of association between bisphosphonate use and the risk of esophageal cancer (cohort).

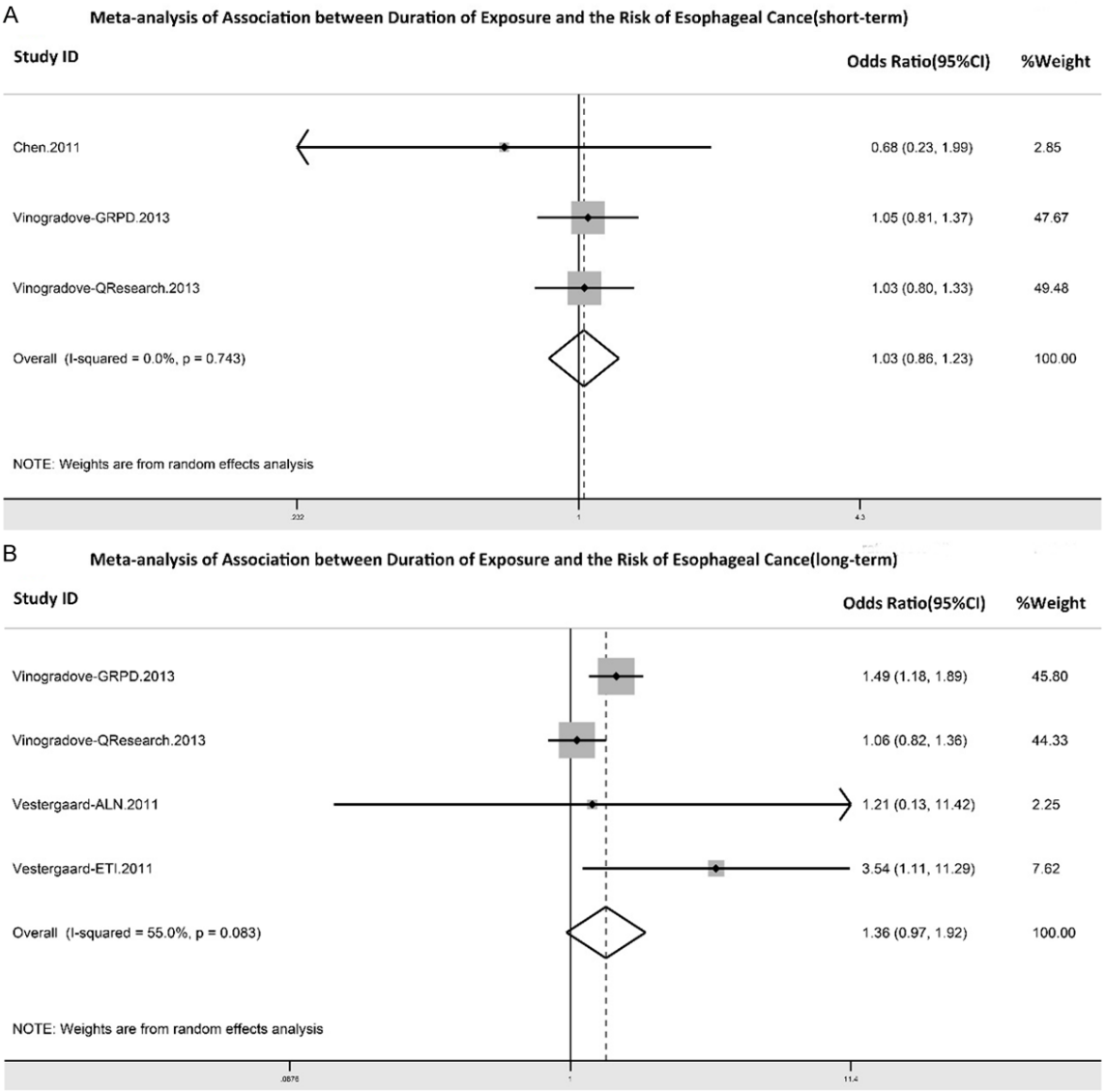


Figure 3. A. Meta-analysis of association between duration of exposure and the risk of esophageal cancer (short-term). B. Meta-analysis of association between duration of exposure and the risk of esophageal cancer (long-term).

Association between bisphosphonate use and the risk of esophageal cancer

No statistically insignificant negative association between bisphosphonate use and the incidence of esophageal cancer were found in both cohort studies (**Figure 2A**, RR 1.18, 95% CI 0.70 to 1.97) and case-control studies (**Figure 2B**, OR 1.06, 95% CI 0.92 to 1.22). Statistically significant evidence of heterogeneity was found in cohort studies (P = 0.005, I^2 = 76.5%) but not in case-control studies (P = 0.378, I^2 = 3.0%). A sensitivity analysis identified Vestergaard [22] to be contributing to the heterogeneity of cohort studies group, with the heterogeneity largely disappearing with the exclusion of that study (I^2 = 0.0%, P = 0.41), and the risk estimate decreased (OR 0.95; 95% CI: 0.73-1.25). There was no indication of publication bias either from the result of Egger's test

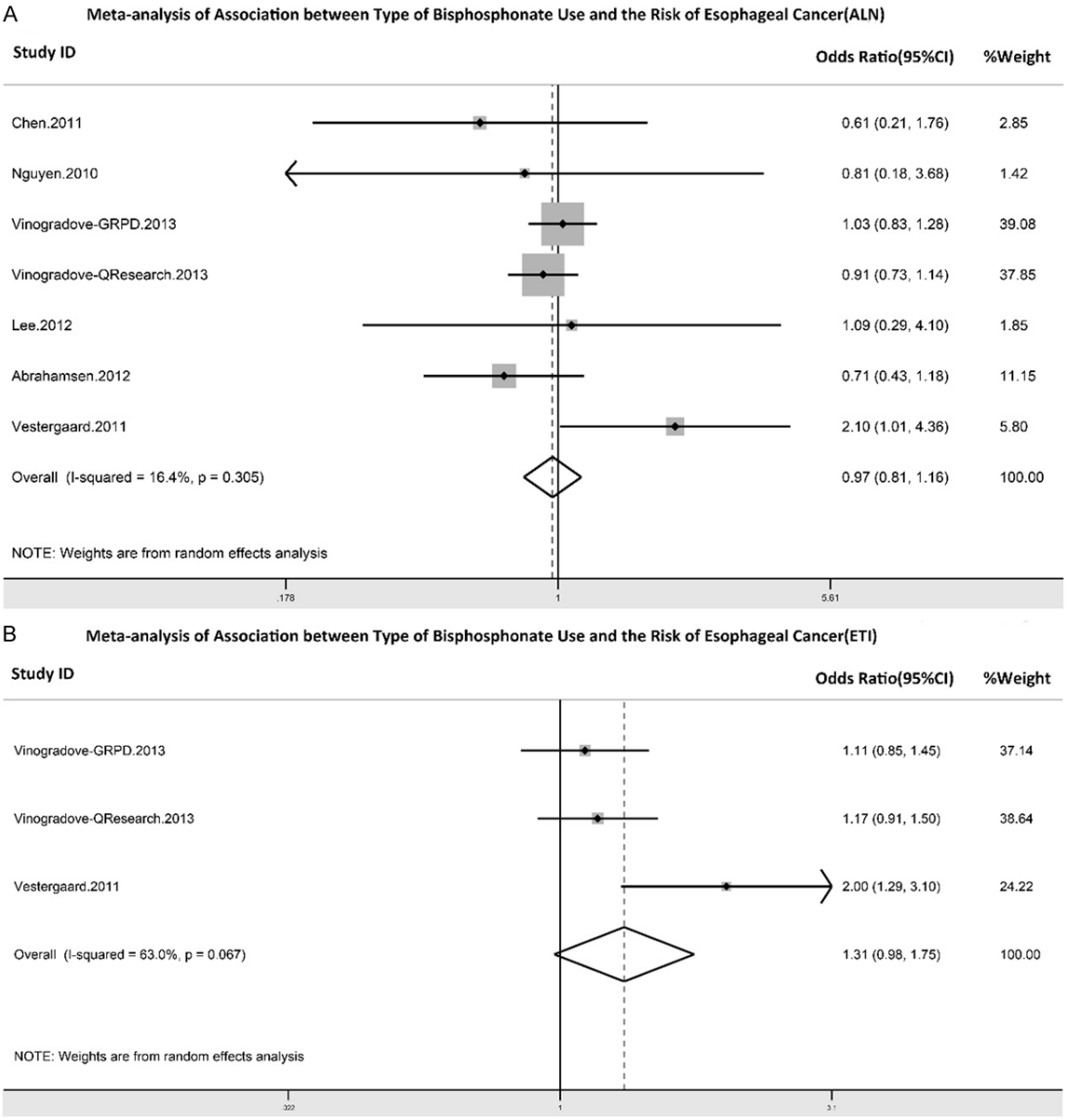


Figure 4. A. Meta-analysis of association between type of bisphosphonate and the risk of esophageal cancer (ALN). B. Meta-analysis of association between type of bisphosphonate and the risk of esophageal cancer (ETI).

(P = 0.79 for cohort studies and P = 0.44 for case-control studies) or from Begg's test (P = 1.00 for cohort studies and P = 1.00 for case-control studies).

Association between duration of exposure and the risk of esophageal cancer

The ORs for each study and pooled ORs for categories of short-term exposure group and long-term exposure group are shown in **Figure 3A** and **3B**. There was no statistically insignificant increased risk between duration of exposure and the incidence of esophageal cancer in both short-term exposure group (**Figure 3A**, OR 1.10, 95% CI 0.93 to 1.31) and long-term exposure group (**Figure 3B**, OR 1.28, 95% CI 0.84 to 1.95). What's more, we found statistically insignificant heterogeneity in the long-term exposure group (I^2 = 58.2%, P = 0.07). When we excluded Vinogradove-b, the heterogeneity largely disappearing (I^2 = 17.2%, P = 0.30) while the risk estimate was not appreciably changed after excluding the specific study

(OR 1.59; 95% CI: 0.97 to 2.63). There was low, statistically insignificant heterogeneity in the short-term exposure group (I^2 = 49.7%, P = 0.94).

Association between type of bisphosphonate use and the risk of esophageal cancer

Alendronate: Six studies (167, 406, 495, 519, 611, 668) from five database reported on alendronate use. However, because Abrahamsen et al. [19] and Vestergaard [22], Lee et al. [18] and Chen et al. [20] were overlapping studies, our analysis including the studies by Vestergaard and Lee et al. because it included the largest number of oesophageal cancer cases out of the overlapping studies. No statistically significant association between alendronate use and the risk of esophageal cancer were found (**Figure 4A**, RR 1.00, 95% CI 0.86 to 1.16) with no heterogeneity (I^2 = 17.0%, P = 0.31).

Etidronate: Two studies [17, 22] from three database reported on etidronate use were included in this analysis. We found no statistically significant increased risk of oesophageal cancer associated with etidronate use in our study (**Figure 4B** OR 1.31; 95% CI: 0.98 to 1.75) with moderate, statistically insignificant heterogeneity (I^2 = 63%, P = 0.07).

Discussion

The current meta-analysis summarizes the results of seven epidemiologic studies, including a total of 69,252 esophageal cancer. In the original study, Vestergaard [22] reported that use of alendronate (RR 2.32, 95% CI 1.18 to 4.58) and etidronate (RR 2.00, 95% CI 1.29 to 3.11) increased the risk of esophageal cancer, whereas the others [17-21, 30] showed no association. This meta-analysis indicated that BP use didn't increase the risk of esophageal cancer in both cohort studies (RR 1.18, 95% CI 0.70 to 1.97) and case-control studies (OR 1.06, 95% CI 0.92 to 1.22). Further analysis on duration, cumulative dose and type of BPs use revealed that there was no significant association at duration of both short-term and long-term exposure. No increase of risk was noted for low dose and high dose of exposure. We did not find a statistically significant increase in the risk of esophageal cancer for exposure to either etidronate or alendronate.

However, while interpreting the results, there are several considerations that should be taken into account. First, there were two pairs of studies using the same national database known as NHI [18, 20] and GPRD [17, 21]. We could not use the result from all seven studies to avoid doubling up on results. When studies overlapped in terms of data, we select the study with the most esophageal cancer cases to add power to our study. In addition, Green et al. [23] conducted a well-known nested case control study with 2,954 esophageal cancer cases based on the GPRD. They found a 30% increased risk of esophageal cancer in BP users, and an almost twofold increased risk in users with 10 or more prescriptions for oral bisphosphonates and with prescriptions over 3-year period. But the mean observation time was 7.7 years, much longer than the studies included in this meta-analysis, which means possibility of overestimating cancer risk. The result was, however, adjusted only for smoking status, alcohol intake, and BMI, without adjustment for the important confounders of co-medications. Probably, these factors led to different results in this study as compared with our meta-analysis. Moreover, heterogeneity was present in our meta-analysis. While looking at exposure to any bisphosphonates, statistically significant evidence of heterogeneity was found in cohort studies but not in case-control studies. Vestergaard [22] was suspected to contribute to the heterogeneity using meta regression, with the heterogeneity disappeared with the exclusion of this study (I^2 = 0%, P > 0.10). Vestergaard [22] provide unadjusted risk calculated from raw data. Heterogeneity was also observed in some of the other analyses. Vestergaard [22] and Vinogradova et al. [17] were found to contribute to heterogeneity in these instances. The population from different countries (the UK, Denmark, Taiwan and the US) may cause the heterogeneity. Exactly, it can't be too cautious before conclude such a harmful side effect as esophageal cancer.

This meta-analysis had several limitations that should be acknowledge. First, the study number included in the final analysis was small. Second, the problems related to confounding factors is not able to be solved by a meta-analysis. Although included studies attempted to adjust for potential confounding factors, it is possible that residual or unknown confounding

may have masked an association between the use of bisphosphonates and esophageal and gastric cancer risk. Third, the histologic subtype and anatomic classification subtypes of esophageal cancer were not reported. Although it is possible that the risk of cancer may associate with esophageal adenocarcinoma or squamous cell carcinoma, we were not able to do further subgroup analysis. Forth, measure of exposure was determined from recorded prescriptions, overestimation of usage is possible, because not everyone prescribed bisphosphonates would use them [31, 32]. But estimation of the exposure will be more accurate among people with many prescriptions or long-term follow-up. Interestingly, previous studies [26] suspected that people taking oral bisphosphonate can have more frequent of upper gastrointestinal discomfort and more likely to undergo gastroscopy, which would increase the discovery of esophageal cancers. We therefore suggest the next coming studies adjust for the factor of esophageal and gastro-intestinal checkups. And the relationship between intravenously BPs and esophageal cancer can help us figure out whether BPs infect the risk of upper gastrointestinal cancer without local effect on mucosa.

In summary, the result from our meta-analysis suggest that exposure to oral BPs may not increase the risk of esophageal cancer. And the conclusion was not influenced by the duration, cumulative dose and type of BPs use. With the limitation of the study and the inconsistent evidence of included studies, much more quality studies, such as random controlled trails and cohort studies considering all potential confounding factors as well as type, cumulative dose and duration of BPs use, are urgently needed to make firm conclusion on this issue.

Disclosure of conflict of interest

None.

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