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ORIGINAL ARTICLE

Bisphosphonate treatment and risk of esophageal cancer: a meta-analysis of observational studies

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Abstract
Summary The use of bisphosphonates and the risk of esophageal cancer have recently received increasing concern and related studies have yielded controversial results. The present meta-analysis of observational studies shows that no clear association between bisphosphonate treatment and risk of esophageal cancer was observed.
Introduction Epidemiological evidence suggests that bisphosphonate treatment can increase the risk of esophageal cancer. However, data on this issue are unstable and controversial. We conducted a meta-analysis to provide a quantitative assessment of the association between use of bisphosphonates and risk of esophageal cancer.
Methods We searched the Medline and Embase databases up to May 2012 to identify studies related to bisphosphonates and esophageal cancer. Summary effect estimates with 95 % confidence intervals (CI) were derived using a fixed or random effects model, depending on the heterogeneity of the included studies.
Results Seven epidemiologic studies that consisted of four cohort studies and three case–control studies were included in this meta-analysis. In our primary analysis, bisphosphonate treatment was not associated with risk of esophageal cancer in both cohort studies [pooled relative risk (RR) 1.23, 95 % CI 0.79–1.92] and case–control studies [pooled odds ratio (OR) 1.24, 95 % CI 0.98–1.57]. Evidence for the presence of significant heterogeneity was found in cohort studies (p=0.009, I^2=74 %) but not in case–control studies (p=0.338, I^2=7.8 %). In our secondary analysis, no significant increased risk of esophageal cancer was found in alendronate users (pooled RR 1.08, 95 % CI 0.67–1.75 in cohort studies; pooled OR 1.16, 95 % CI 0.82–1.63 in case–control studies).
Conclusions Based on current evidences, bisphosphonate treatment was not significantly associated with excess risk of esophageal cancer.

Keywords Bisphosphonates · Case–control study · Cohort study · Esophageal cancer · Meta-analysis

Introduction

Osteoporotic fractures among older people are a major problem leading to increased mortality and morbidity and significant costs on public health budgets [1, 2]. Bisphosphonates have become a mainstay of therapy for the prevention and treatment of osteoporosis in both men and women [3, 4], with a long-term lasting beneficial influence [5]. However, growing data suggested that there are multiple potential harms and serious adverse events of bisphosphonate use, such as osteonecrosis of the jaws [6, 7], atrial fibrillation [8, 9], atypical fractures [10, 11], and esophageal cancer [12–14].

Oral bisphosphonate prescription causes local stimulus of the upper gastrointestinal mucosa, such as esophageal or gastric irritation, esophageal ulcers, and esophageal strictures, which are well recognized side effects and the most common causes for quitting bisphosphonate therapy [15–17]. An adverse influence on the risk of esophageal cancer might be expected for such gastrointestinal side effects in bisphosphonate users. Nevertheless, combined

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with early case reports and studies, whether bisphosphonate use could increase the risk of esophageal cancer has not been clearly elucidated. The first report of the association was from the US Food and Drug Administration (FDA), in which they received reports of 23 esophageal cancer cases with oral alendronate as the suspected drug or the concomitant drug [14]. Later observational studies were conducted following this report; however, even within the same database, results were inconsistent [12, 18].

Therefore, it is crucial to clarify whether people receiving bisphosphonate treatment could be at an elevated risk of esophageal cancer. The present systematic review of the literature aims to obtain an overview of the association between bisphosphonate use and the risk of esophageal cancer.

Methods

Search strategy

We conducted a systematic review of published works without language restrictions and in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement whenever applicable [19]. We searched Medline and Embase from their inception to May 2012 and systematically identified observational studies that evaluated the use of bisphosphonates on the risk of esophageal cancer. The main search terms were "diphosphonate" or "biphosphonate" or "ibandronate" or "etidronate" or "clodronate" or "zoledronate" or "pamidronate" or "alendronate" in combination with "gastrointestinal neoplasms" or "gastrointestinal cancer" or "esophageal neoplasms" or "esophageal cancer" or "oesophageal cancer" with no restrictions. We scanned the reference lists from published original articles and previous reviews for more relevant studies not identified in the database search. Because of the high potential for intractable confounding and reverse causation, we excluded cross-sectional studies in this meta-analysis.

Study selection

We included studies in the meta-analysis that met all of the following criteria: (1) the study had a case–control or cohort design, (2) published original data relevant to a possible association between use of bisphosphonate and risk of esophageal cancer, and (3) reported the odds ratio (OR) or relative risk (RR) and its 95 % confidence interval (CI). In case multiple publications had overlap their populations and reported with the same study design, the most recent publication was included in order to avoid duplicate observations, unless more inclusive and detailed data were found in other publications. For studies from the same database but with a different design, we extracted data and combined estimates of these studies separately. To gather more relevant information, we consulted researchers with professional knowledge at this area for the presence of unpublished reports.

Data extraction

Two of our reviewers (K. Sun and J.M. Liu) independently evaluated all relevant articles and identified eligible studies from the databases. During data abstraction, differences and disagreements were resolved through discussion to come to an agreement. The following information was recorded by a standardized data extraction form: last name of the first author, publication year, geographic region of original study, mean length of follow-up in cohort studies and observation period in case–control studies, composition and age range of the study population, unadjusted and adjusted risk with corresponding 95 % CI of esophageal cancer for bisphosphonate users compared with nonusers, and adjustment factors of interest. When necessary, we contacted authors of the primary studies for additional information.

Statistical analysis

The primary outcome of the pooled analysis was focused on a comparison of the summary effect of esophageal cancer in bisphosphonate users versus nonusers. The hazard ratio was directly considered as RR. When studies presented results from various covariate analyses, we used the one which adjusted the most study-specific confounders, such as age, sex, body mass index, alcohol consumption and smoking, and the use of other prescription drugs. The combined estimates were calculated separately by averaging the natural logarithmic OR or RR weighted by their inverse of variance based on a fixed or random effects model between study variations, depending on the overall heterogeneity. Heterogeneity of effect size across studies was assessed by using Cochran's Q and the I^2 statistic [20, 21] and p value$<$ 0.10 or I^2 value$>$50 % was considered to be heterogeneous. When substantial heterogeneity was detected, pooled effect estimates were calculated using a random effects model by the method of DerSimonian and Laird [22]. If not, the combined estimates were presented based on the fixed effects model by using the inverse variance method [23]. As one study that separated risk estimates for alendronate users and etidronate users, we combined the two groups into a single one and calculated a study-specific effect size of bisphosphonate users with the fixed effects model [13]. Alendronate is a first-line prescription in postmenopausal women and the most cost-effective medicine for anti-osteoporosis therapy [24–26]. Therefore, data for the association between alendronate use and risk of esophageal

cancer were also extracted and analyzed. To assess the influence of individual studies on the pooled result, we conducted sensitivity analyses to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn. We used Begg's adjusted rank correlation test and Egger's regression asymmetry test to detect publication bias, and $p>0.05$ for both tests was considered to be no significant publication bias [27, 28]. All statistical analyses were performed using STATA version 11.0 (Stata Corp, College Station, TX, USA).

Results

We identified 496 citations (266 from PubMed and 230 from Embase) with the electronic literature search. We excluded 476 citations based on the first screening, and after this, 20 remaining citations and one retrieved citation were full-text-reviewed. Finally, seven citations that met the inclusion criteria were included in the meta-analysis. The details of the literature search were shown in Fig. 1.

The characteristics and information of the included studies were presented in Table 1. In total, we investigated 423 esophageal cancer cases in cohort studies (average follow-up period ranging from 3.5 to 5.5 years) and 3,352 esophageal cancer cases in case–control studies. Among the seven studies included, all risk estimates were relevant to an association between oral bisphosphonates and risk of esophageal cancer. Two studies showed a significant correlation between bisphosphonate use and risk of esophageal cancer [12, 13], and no significant association was found in the remaining five studies [18, 29–32].

In the overall analysis of the selected studies, the use of bisphosphonates was not associated with risk of esophageal cancer in both cohort studies (Fig. 2a, pooled RR 1.23, 95 % CI 0.79–1.92) and case–control studies (Fig. 2b, pooled OR 1.24, 95 % CI 0.98–1.57). Statistically significant evidence of heterogeneity was found in cohort studies ($p=0.009$, $I^2=74$ %) but not in case–control studies ($p=0.338$, $I^2=7.8$ %). There was no indication of publication bias either from the result of Egger's test ($p=0.95$ for cohort studies and $p=0.27$ for case–control studies) or from Begg's test ($p=1.00$ for cohort studies and $p=1.00$ for case–control studies). As shown in Fig. 3, similar results were found in alendronate users, while compared with nonusers, no significant increased risk of esophageal cancer was detected in cohort studies (Fig. 3a, pooled RR 1.08, 95 % CI 0.67–1.75) and in case–control studies (Fig. 3b, pooled OR 1.16, 95 % CI 0.82–1.63).

Sensitivity analyses of our primary outcome were carried out by excluding one study at a time, and the combined RRs of overall risk estimates in the four selected cohort studies were consistent, with a range from 1.02 (95 % CI 0.79–1.31) to 1.46 (95 % CI 0.95–2.26). However, in the three selected case–control studies, the pooled effect by excluding each study one by one was fluctuated and ranged from a low of 0.67 (95 % CI 0.28–1.57) to a high of 1.29 (95 % CI 1.01–1.63).

Discussion

The relationship between prolonged use of bisphosphonates and esophageal cancer development is controversial. For such widespread prescriptions of bisphosphonates, even a small increase in the risk of esophageal cancer may induce to numerous additional cases and must be addressed. The findings of our meta-analysis showed no clear evidence of an association between the use of bisphosphonates and the

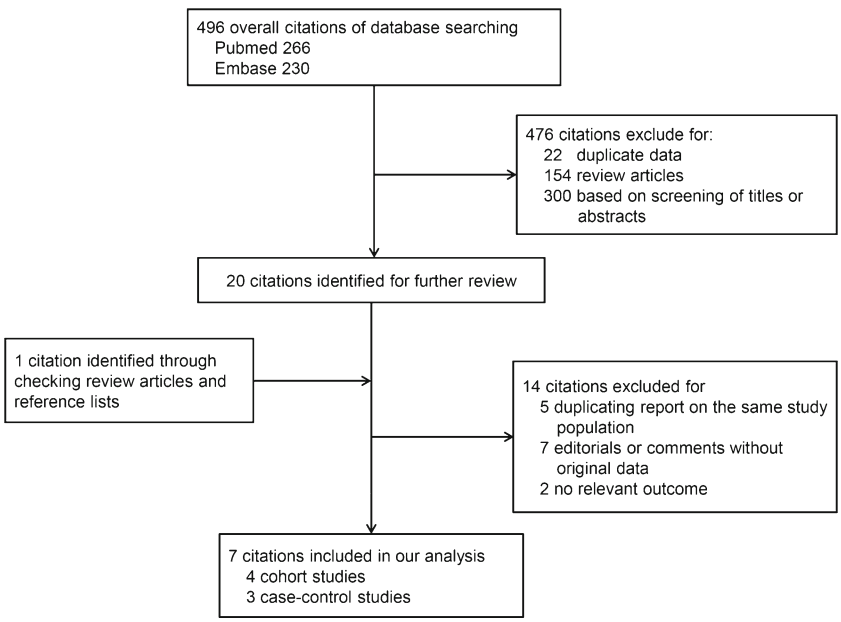

Fig. 1 Flow diagram of included studies in the systematic review

Table 1 Characteristics of included studies

Source	Region	Sex	Study type	Age range (years)	Follow-up or observation period (years)	Study population	Adjusted RR/ OR (95 % CI)	Adjustment for covariates
Abrahamsen et al. [29]	Denmark	F	Retrospective cohort study	Treatment group—71.9±10 Control group—71.9±10	3.5 (1–11)	19 esophageal cancer cases from 30,606 alendronate users (0.06 %) 99 esophageal cancer cases from 122,424 nonusers (0.08 %)	0.71 (0.43–1.19)	Age, individual Charlson comorbidity index components, the number of co-medications, PPI use, and upper endoscopy history
Chiang et al. [31]	Taiwan	M/F	Retrospective cohort study	Treatment group—73.4±8.4 Control group—73.5±8.4	Treatment group—4.3±2.5 Control group—4.9±2.6	13 esophageal cancer cases from 6,906 alendronate users (0.2 %) 29 esophageal cancer cases from 20,697 |nonusers (0.1 %)	1.50 (0.78–2.88)	Age, hypertension, diabetes, chronic obstructive pulmonary disease, estrogen use, dyslipidemia, chronic kidney disease, coronary artery disease, colorectal polyp, benign breast disease, morbid obesity, and statin use
Cardwell et al. [18]	UK	M/F	Retrospective cohort study	Treatment group—70.0±11.4 Control group—70.0±11.4	Treatment group—4.5±2.6 Control group—4.4±2.6	79 esophageal cancer cases from 41,826 bisphosphonate users (0.2 %) 72 esophageal cancer cases from 41,826 nonusers (0.2 %)	1.07 (0.77–1.49)	BMI, alcohol, smoking, hormone therapy prescription, NSAIDs prescription, Barrett esophagus diagnosis, gastro-esophageal reflux disease diagnosis, H_2 receptor antagonist prescription, and PPI prescription
Green et al. [12]	UK	M/F	Case–control study	40+	7.5	90 bisphosphonate users from 2,954 esophageal cancer cases (0.03 %) 345 bisphosphonate users from 14,721 cancer-free control (0.02 %)	1.30 (1.02–1.66)	Smoking status, alcohol intake, and BMI
Vestergaard [13]	Denmark	M/F	Retrospective cohort study	Treatment group—70.5±11.4 Control group—70.5±11.4	Alendronate user—2.8 Etidronate user—5.5	49 esophageal cancer cases from 92,975 bisphosphonate users (0.05 %) 66 esophageal cancer cases from 278,569 nonusers (0.02 %)	Alendronate user—2.10 (1.01–4.35) Etidronate user—1.99 (1.24–3.18)	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
Nguyen et al. [32]	American	M/F	Case–control study	Esophageal cancer group—65±10.3 Control group—64.7±10.3	NA	2 bisphosphonate users from 116 esophageal cancer cases (1.7 %) 13 bisphosphonate users from 696 cancer-free control (1.9 %)	0.81 (0.18–3.72)	Race, noncancer disease comorbidity index, PPI and NSAIDs prescription
Chen et al. [30]	Taiwan	M/F	Case–control study	NA	NA	88 bisphosphonate users from 282 esophageal cancer cases (31.2 %) 761 bisphosphonate users from 2,811 cancer-free control (27.1 %)	0.61 (0.21–1.75)	NA

F female, *M* male, *BMI* body mass index, *PPI* proton pump inhibitor, *NSAIDs* nonsteroidal anti-inflammatory drugs, *NA* not recorded or available

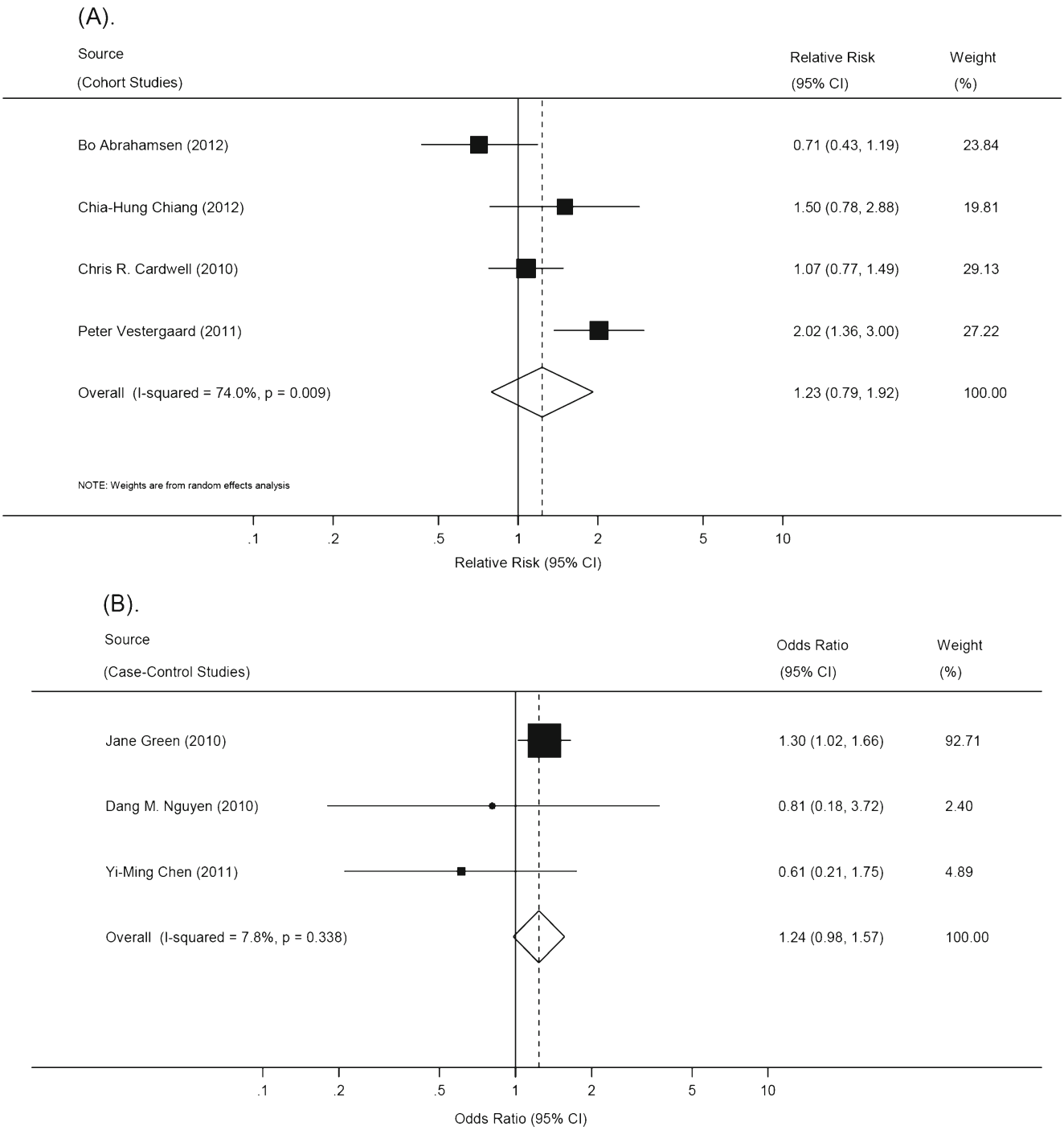

Fig. 2 Forest plot showing combined estimates of bisphosphonate use and risk of esophageal cancer (**a** cohort studies, **b** case–control studies)

risk of esophageal cancer. Similar results were detected in alendronate users. Despite the limited numbers of studies in this area, we found that case–control studies yielding estimates of the pooled effect of bisphosphonates on esophageal cancer risk were in agreement with those from cohort studies.

Bisphosphonates are widely used in the treatment of osteoporosis and skeletal-related complications from metastatic cancer [33–35]. Basic researches suggested that bisphosphonates may have antiproliferative effect and inhibit cancer development and progression [36–38]. However, previous clinical studies have shown inconsistent results of bisphosphonates on tumorigenesis. Chlebowski et al. [39] showed that oral bisphosphonate use was associated with lower invasive breast cancer but higher in situ ductal breast carcinoma incidence in postmenopausal women. Such discrepant results of

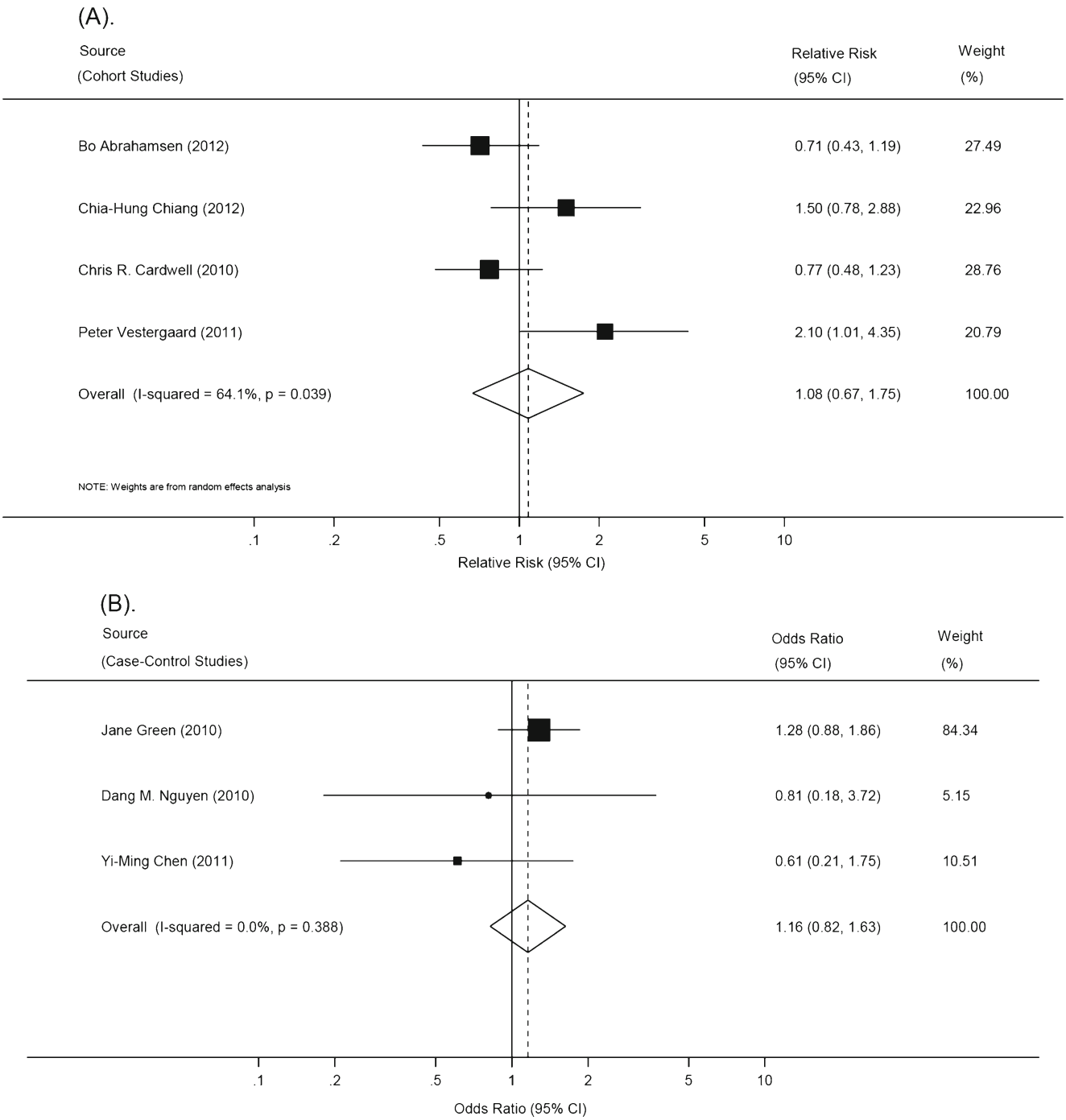

Fig. 3 Forest plot showing combined estimates of alendronate use and risk of esophageal cancer (**a** cohort studies, **b** case–control studies)

malignancy also existed in digestive organs. Cardwell et al. [18] and Green et al. [12] examined the association between exposure to bisphosphonates and risk of esophageal cancer in the same database but came to apparently opposite conclusions. A more recent study conducted in women using oral alendronate found no significant evidence of cancer occurrence in various parts of the body, which included the esophagus, gastrointestinal tract, pancreas, and liver [31]. Therefore, at least for now, the correlation between bisphosphonate use and the occurrence of cancer is still uncertain.

Actually, when reporting a side effect of such a harmful outcome as neoplasm, we cannot be too cautious to jump to conclusions. Based on the current data we have collected, sensitivity analysis of case–control studies just showed an unstable association between the use of bisphosphonates and risk of esophageal cancer. A possible explanation is that

people on oral bisphosphonate treatment can have local irritation of the upper gastrointestinal mucosa and more likely to receive gastroscopy, which would therefore accelerate the discovery of upper gastrointestinal cancers. To clearly elucidate this issue, studies are warranted to clarify whether intravenously administered bisphosphonates, with no effect on local irritation of mucosa, may have different risk estimates for esophageal cancer when compared with orally administered bisphosphonates. Despite this, according to available evidence from the literature, no studies have reported any risk estimates relevant to a possible association between the use of parenterally administered bisphosphonates and risk of esophageal cancer. However, such interpretations may fail to adequately summarize the existing findings, and meanwhile, after strong consideration, related official organizations and medical specialists should provide guidelines and recommendations to proceed that issue.

Recently, experts from FDA have conducted a safety report of the conflicting data on potential increased risk of esophageal cancer in bisphosphonate users [40]. On one hand, they recommended that patients should ask their health care professionals for advice about the benefits and risks on the appropriate duration and frequency of taking oral bisphosphonates. On the other hand, they suggested that patients should consult their doctor when they develop symptoms of esophageal irritation and erosion. In addition to these, patients should be instructed to carefully follow the instructions for the prescribed bisphosphonate drug, for example, drinking a full glass of water to an empty stomach and remain upright for at least 30 min after taking oral medications. Moreover, to gain maximum benefit for patients at increased risk of esophageal cancer, other administration approaches, such as intravenous injection of parenteral zoledronate or pamidronate, which have not been associated with esophageal cancer, should be considered in the process of decision-making [41].

The present meta-analysis had several limitations. First, determining medication use in most studies was retrospectively collected from prescription databases and may not reflect the adherence of bisphosphonate users. In a recent meta-analysis, the overall compliance and persistence rates among bisphosphonate users were found to be suboptimal [42]. Low persistence and compliance with bisphosphonate use would give rise to underestimation of esophageal cancer risk. In that case, observation of such effect will be more accurate among people with large prescription doses and longer term exposure of bisphosphonates. However, a dose–response analysis cannot be carried out due to the limited numbers and data characteristics of the studies included. Second, most of the studies included were not specifically designed to assess the effect of bisphosphonate therapy on risk of esophageal cancer, which may therefore lack some detailed information and other adjunctive therapy. Meanwhile, deficiency of access to individual data of every subject limited our power to further explore the issue. Third, although all included studies made attempt to control for the confounding variables, not all of the residual and potential mediators were adjusted and taken into account, which could contribute to a superficial conclusion of our findings. Nevertheless, all of the four included cohort studies have been adjusted for a wide range of potential confounders (≥9 confounders). Finally, a certain degree of heterogeneity was detected among the cohort studies. However, overall risk estimates of cohort studies did not substantially modify through the sensitivity analyses by excluding one study at a time.

In summary, our meta-analysis collected and synthesized data currently available and found no significant esophageal cancer risk in patients with bisphosphonate treatment. In consideration of the inconsistent evidence of the included studies and limitations of the data consolidation, further investigations are urgently needed to make definite conclusion on this issue.

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Conflicts of interest None.

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