Ther Adv Med Oncol
2019, Vol. 11: 1–16
DOI: 10.1177/1758835919855235

The incidence and relative risk of adverse events in patients treated with bisphosphonate therapy for breast cancer: a systematic review and meta-analysis

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Abstract

Background: Adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival. However, the risk of adverse events associated with bisphosphonate therapy for breast cancer remains poorly defined.

Methods: A literature search was conducted using the PubMed, EMBASE, Cochrane and Web of Science libraries. Risk ratio (RR) was calculated to evaluate the adverse events of the meta-analytic results. Osteonecrosis of the jaw (ONJ) incidence was calculated using the random effect model (D+L pooled) for meta-analysis.

Results: A total of 47 studies comprising 20,607 patients were included; 23 randomized controlled studies (RCTs) provided data of adverse events for bisphosphonate therapy *versus* without bisphosphonates. Bisphosphonates were significantly associated with influenza-like illness (RR = 4.52), fatigue (RR = 1.08), fever (RR = 1.82), dyspepsia (RR = 1.25), anorexia (RR = 1.29), and urinary tract infection (RR = 1.32). No differences were observed in other adverse events. We combined the incidence of ONJ in 24 retrospective studies to analyze the incidence of ONJ using bisphosphonates. The pooled probability of ONJ toxicity in the bisphosphonates group was 2%.

Conclusions: Bisphosphonates were significantly associated with influenza-like illness, fatigue, fever, dyspepsia, anorexia, and urinary tract infection. Furthermore, bisphosphonates increase the risk of ONJ toxicity.

Keywords: adverse events, bisphosphonates, breast cancer, neoadjuvant therapy, osteonecrosis of the jaw

Received: 10 February 2019; revised manuscript accepted: 8 May 2019.

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Introduction

Breast cancer is the most common malignant cancer among women worldwide, in both developing and developed countries. The survival rate of breast cancer is highly correlated with the degree of disease at the time of diagnosis, with early stage disease conferring superior survival rates. However, the majority of patients with advanced breast cancer develop bone metastases.[1] Some studies have reported that increased osteoclast activity in patients with breast cancer and breast cancer bone metastases leads to skeletal-related events (SREs), which include bone fractures, hypercalcemia, nerve compression, and severe pain.[2] These skeletal complications, in turn, increase the need for palliative radiation or surgery to bone, limit functional independence, adversely affect quality of life, and continue to cause morbidity of the affected patients.[3,4]

Bisphosphonates are effective inhibitors of osteoclast-mediated bone resorption and have been approved for the prevention and treatment of postmenopausal osteoporosis and corticosteroid-induced bone metastases.[5–7] Bisphosphonates are analogues to pyrophosphates, which inhibit bone

resorption by interfering with osteoclast activation and promoting osteoclast apoptosis.[8,9] Due to their antiresorptive properties, bisphosphonates are used to prevent excessive activation of osteoclasts due to cancer cells in the bone. Therefore, by blocking the vicious circle, bisphosphonates can prevent bone complications caused by tumor-induced osteolysis.[10,11] Zoledronic acid (ZOL), ibandronate, pamidronate, and clodronate are approved for the prevention of skeletal complications in breast cancer patients with bone metastases.[12–14] In the randomized, double-blind ProBONE II trial, a 2-year treatment with ZOL 4 mg intravenous every 3 months prevented cancer-treatment-induced bone loss in premenopausal women with breast cancer, and maintained bone mass density (BMD) up to 3 years post-treatment.[15] At present, bisphosphonates are the standard treatment for the prevention of SREs, especially for patients with breast cancer and metastatic bone disease.[16]

Although bisphosphonates can be effective in the prevention of SREs in patients with breast cancer and breast cancer bone metastases, they have been associated with an increased risk of adverse events such as renal toxicity,[17,18] acute-phase reactions, osteonecrosis of the jaw (ONJ), and intravenous administration.[19] However, these are rare events among patients enrolled in clinical trials, and individual studies designed to demonstrate efficacy of each of these agents have been ineffective in detecting statistically significant differences in the incidence of adverse events. In addition, it is difficult to determine which of these adverse events are caused by bisphosphonates and which are caused by cancer. Since the clinical use of bisphosphonate therapy should be based on a balance between efficacy and safety, a solid understanding of the safety profile of these drugs is of critical clinical value. To determine the risk of adverse events associated with these agents, we conducted a systematic review and meta-analysis of the literature to determine the incidence and risk of adverse events induced by bisphosphonates in patients with breast cancer.

Methods

Search strategy

This study was reported in accordance with both the PRISMA statement for reporting systematic reviews and meta-analyses.[20] A systematic literature search of the PubMed, EMBASE, Cochrane and Web of Science databases up to November 2018 was conducted by two study investigators (YYL and XRL) independently. The following search terms, treated as free text or mesh terms, were used: 'bisphosphonates,' 'alendronate,' 'clodronate,' 'ibandronate,' 'pamidronate', 'risedronate,' 'zoledronic acid,' combined with 'breast neoplasms' or 'breast cancer,' or 'breast tumor.' The search was restricted to human studies. The title and abstract of studies identified in the search were reviewed by two authors (YYL and XRL) independently to exclude studies that did not address the research question of interest. References of identified articles were also retrieved to assess potentially eligible studies. Inclusion was not restricted on the basis of language of publication.

Selection criteria

Two authors (YYL and XRL) independently extracted data from selected studies. Disagreements between the two reviewers were resolved by consensus, or by deference to a third author (XZJ) where needed. Reasons for exclusion were documented. If there were multiple reports of the same trial, we included data from the most up-to-date reference possible.

We classified studies on bisphosphonates, focusing on adverse events of using bisphosphonates in the treatment of breast cancer. Adverse events studies were RCT studies. The studies corresponding to ONJ were retrospective studies. Therefore, we conducted a separate meta-analysis of ONJ studies.

Inclusion criteria were formed using the participants, intervention, control, outcomes, and study designs (PICOS) strategy.[21] For the two meta-analyses in this paper, the inclusion criteria were different:

(1) RCT studies on adverse events after treatment of breast cancer patients with/without the use of bisphosphonates. RCT studies should fulfill following prespecified PICOS criteria. P (participants): breast cancer patients; I (intervention): intravenous bisphosphonates; C (control): without bisphosphonates; O (outcomes): incidence of adverse events; S (study designs): RCT.
(2) For the ONJ studies in breast cancer patients after treatment with bisphosphonates, eligible trials had to satisfy the

following prespecified PICOS criteria. P (participants): patients with solid tumors; I (intervention): with bisphosphonates; C (control): without bisphosphonates; O (outcomes): incidence of ONJ.

Assessment of risk of bias

The Cochrane Risk of Bias tool was used to assess the quality of RCTs. Two reviewers (YJH and XZJ) extracted data and assessed risk of bias in the included studies independently. Disagreements were resolved via the consensus of the two reviewers.

Data extraction and analysis

We selected 28 adverse events, and, for each adverse event, we combined the risk ratio (RR) of the intervention group and the control group. For analysis by ONJ, we extracted data related to breast cancer, did not adopt data related to ONJ incidence of other types of cancer, and conducted a merge to achieve overall incidence of ONJ.

Statistical methods

We combined the RR (m-h, Fixed, 95% CI) and heterogeneity test (I^2) of each adverse event, and drew a forest plot of the combined risk ratio of 28 adverse events. Of the 23 studies, 28 important adverse events were selected for the combined analysis. It is worth pointing out that the number of studies included in each adverse event was different, and that there is the possibility of bias between studies.

We combined the ONJ incidence of 24 studies and the heterogeneity test (I^2), and we used the random effects model (D+L pooled) for meta-analysis. In addition, in these 24 studies, we extracted data only of breast cancer patients. Data synthesis and graphical representation were performed using Review Manager 5, version 5.3., and Stata14.

Results

Eligible studies

A search in PubMed, EMBASE, Cochrane and Web of Science databases identified 5125 unique records. After eligibility assessment, 47 studies comprising a total of 20,607 patients were included (Figure 1). Of these 47 studies, 2 evaluated alendronate, 3 clodronate, 2 ibandronate, 2 pamidronate, 2 risedronate, and 12 zoledronic, while 24 studies evaluated ONJ.

Description of studies

The publications included in the analyses comprised 23 RCTs and 24 retrospective studies. The characteristics of these studies are summarized in Table 1.

Among the studies selected, 23 RCTs aimed to explore adverse events after treatment of breast cancer patients with/without the use of bisphosphonates. We classified bisphosphonates into different categories. The number of studies, patients in treatment groups and patients in control groups involved in trials were shown in Table 1. We evaluated 28 adverse events and compared the RR of adverse events in the bisphosphonate intervention group *versus* the control group. The quality of the 23 RCT studies was assessed by the modified Cochrane risk of bias tool (Figure 2); all studies were randomized and a few studies were unblinded. In our study, all six included studies were blinded. Most studies had prospective adverse event monitoring using well-described, objective criteria, although the types of adverse events studied and their definition varied between trials. Therefore, we classified the adverse events to minimize the risk of such bias. The second meta-analysis included 24 retrospective studies related to incidence of ONJ in breast cancer after treatment with bisphosphonates (Table 2). We combined the incidence of ONJ in these 24 retrospective studies to analyze the incidence of ONJ using bisphosphonates and assess the hazard ratio compared with the control group.

Assessment of adverse events

Here, a total of 23 RCT studies was assessed for the adverse events of breast cancer patients. This meta-analysis included a pooled study population that consisted of 12,073 individuals, with 6484 being patients with bisphosphonates and 5598 being patients without bisphosphonates.

In the included studies, we observed a total of 105 adverse events. Those adverse events mentioned in fewer than three studies were excluded as rare or individual variations rather than truly common adverse events. The descriptions of same adverse events might vary from study to

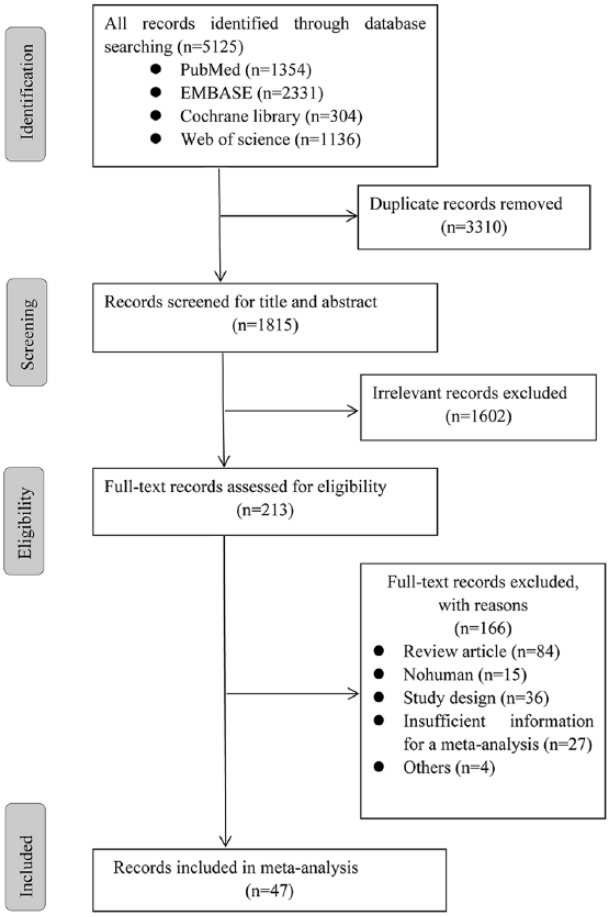

Figure 1. Flowchart of selection of studies for inclusion in meta-regression.

Table 1. Summary of studies included in the meta-analysis of adverse events except ONJ.

Agent	Number of studies	Patients in treatment groups	Patients in control groups
Alendronate	2[22,23]	78	284
Clodronate	3[14,24,25]	1216	1233
Ibandronate	2[13,26]	1911	1004
Pamidronate	2[27,28]	941	944
Risedronate	2[29,30]	161	160
Zoledronic	12[12,15,31–40]	2177	1973
Total	23	6484	5598

ONJ, osteonecrosis of the jaw.

study. We combined the studies, resulting in 28 adverse events being analyzed in this study. These 28 adverse events were classified according to organ system (Table 3). Each adverse event was described in a different number of included studies. We combined and calculated the incidence separately for all 28 adverse events, noting that the numbers of studies mentioning each adverse event were inconsistent. We combined the RR of the bisphosphonates group with

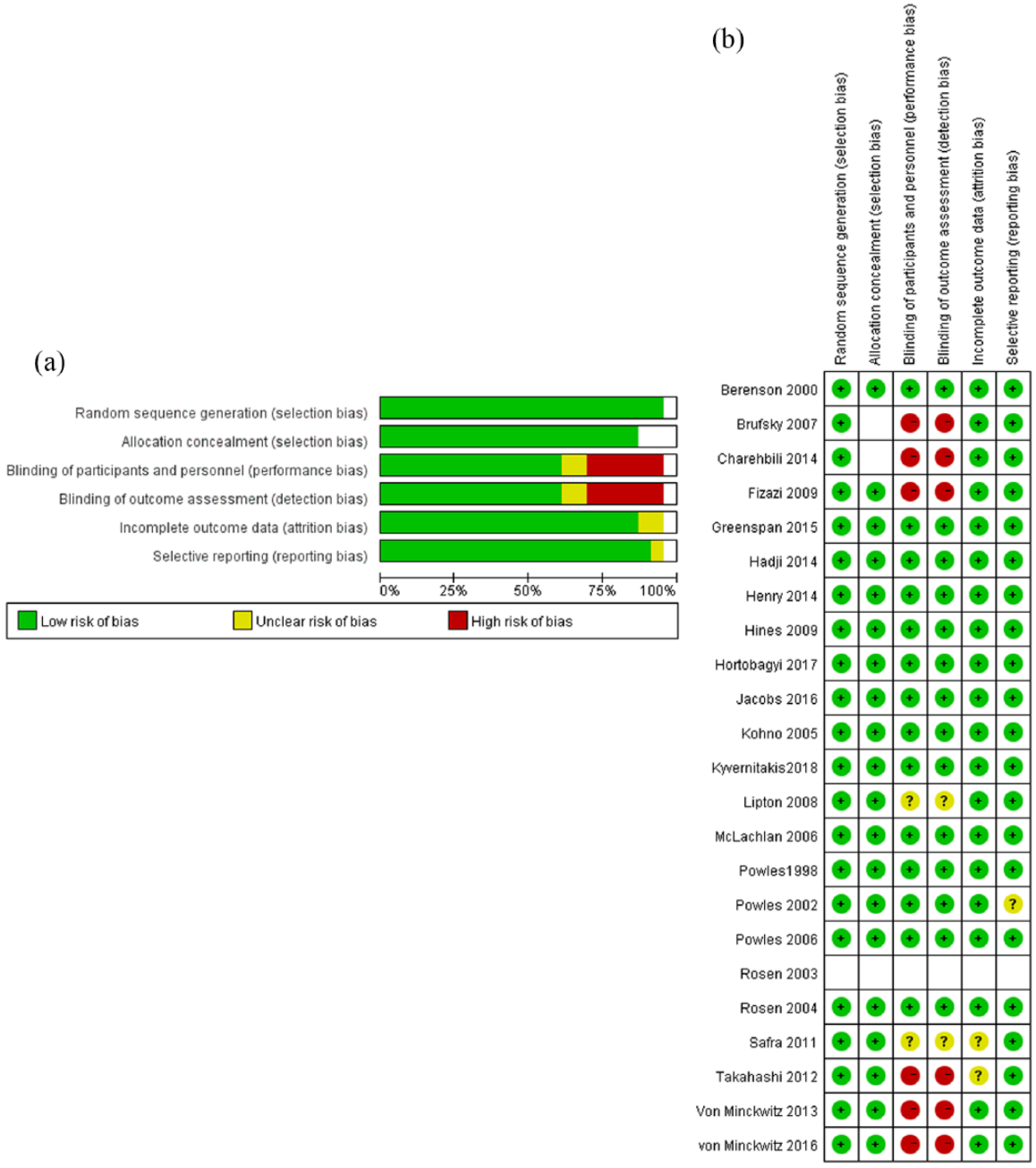

Figure 2. (a) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included randomized controlled trial (RCT) studies. (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT study.

that of the control group for the incidence of adverse events. When compared with the control group, the most substantial increase in adverse events was noted for influenza-like illness. The RR of influenza-like illness was estimated at 4.52 (95% CI 2.22–9.23; $p < 0.0001$; $I^2 = 33\%$). Increased fatigue rates were reported by 21 studies, and the relative risk of fatigue was estimated at 1.08 (95% CI 1.01–1.16; $p = 0.02$; $I^2 = 7\%$). Bisphosphonates were also associated with a significantly higher RR of fever (RR 1.82, 95% CI 1.28–2.59; $I^2 = 59\%$), dyspepsia (RR 1.25, 95% CI 1.1–1.42; $I^2 = 48\%$), anorexia (RR 1.29, 95% CI 1.13–1.46; $I^2 = 48\%$), and urinary tract infection (RR 1.32, 95% CI 1.02–1.72). We did not observe significantly higher RR for the other 22

Table 2. Characteristics of studies included in the meta-analysis of ONJ.

Study first author	Year	Country	Sample size	Number of ONJ	Percentage of ONJ	Population	Study design
Aguiar Bujanda[41]	2007	Spain	35	4	0.114	Patients receiving zoledronic acid for bone metastasis	Retrospective study
Bamias[42]	2005	Greece	70	2	0.029	Cancer patients started treatment with bisphosphonate since January 1997 until December 31, 2003 and received at least six infusions.	Retrospective study
Boonyapakorn[43]	2008	Germany	10	5	0.500	Multiple myeloma and other malignancies treated with bisphosphonate	Prospective study
Brufsky[44]	2013	United States	159	6	0.038	Women with bone metastases from BC treated with intravenous bisphosphonates from January 1999 to June 2008.	Retrospective cohort study
Christodoulou[45]	2009	Greece	75	2	0.027	Osseous metastases from various tumors from June 2007 to June 2008	Retrospective cohort study
Ding[46]	2012	China	181	1	0.006	Breast cancer patients with BM	Retrospective study
Fehm[47]	2009	Germany	345	10	0.029	Breast cancer or gynecological malignancies receiving bisphosphonates	Retrospective study
Fusco[48]	2013	Italy	78	27	0.346	Cancer and myeloma patients treated with bisphosphonates	Retrospective study
Guarneri[49]	2010	Italy	425	10	0.024	Cancer patients receiving i.v. bisphosphonate s for ⩾24 months	Retrospective study
Guarneri[50]	2005	Italy	48	3	0.063	Patients with HER2-negative LR/MBC	Prospective cohort study
Hoff[51]	2008	Brazil	1338	16	0.012	Patients treated with intravenous bisphosphonates between 1996 and 2004	Retrospective study
Ibrahim[52]	2008	Italy	220	5	0.023	Patients with bone metastases treated from June 2002 to December 2006 with i.v. bisphosphonates	Retrospective study
Loyson[53]	2018	Belgium	192	13	0.068	Patients with solid tumors and bone metastases treated with denosumab after prior treatment with bisphosphonates	Retrospective study
Manfredi[54]	2017	Italy	111	12	0.108	Patients treated with zoledronic acid for bone metastases from solid tumors	Retrospective study

Table 2. (Continued)

Study first author	Year	Country	Sample size	Number of ONJ	Percentage of ONJ	Population	Study design
Pilanci[55]	2015	Turkey	97	13	0.134	Patients with metastatic breast cancer who had bone metastases and underwent treatment with ZA between March 2006 and December 2013	Retrospective study
Rathbone[56]	2013	England	1678	26	0.015	Women with stage II or III breast cancer	Randomized Controlled Trial
Ripamonti[57]	2009	Italy	966	26	0.027	Patients with bone metastases (PRE-Group) and treated for the first time with bisphosphonates from January 1999 to April 2005	Retrospective study
Rugani[58]	2014	Austria	48	10	0.208	From 2000 to 2008, 63 hormone receptor-positive, premenopausal breast cancer patients who were free of metastases	Retrospective study
Sanna[59]	2006	Italy	81	5	0.062	Advanced breast cancer patients with bone metastases under bisphosphonate treatment	Observational study
Thumbigere-Math[60]	2012	United States	576	18	0.031	Patients with cancer treated with intravenous pamidronate and/or zoledronate between January, 2003 and December, 2007	Retrospective study
Vahtsevanos[61]	2009	Greece	1621	80	0.049	Women with Stage IV breast cancer and osteolytic metastases	Retrospective chart review
Vidal-Real[62]	2015	Spain	15	4	0.267	Cancer patients treated with IV bisphosponates,	Retrospective study
Walter[63]	2009	Germany	75	4	0.053	Breast cancer patients treated in the breast unit from January 2000 to March 2006	Retrospective study
Wang[64]	2007	United States	81	2	0.025	Patients evaluated and/or treated between January 1, 2000, and December 31, 2005, and had received zoledronic acid and/or pamidronate	Retrospective chart review
24 studies			8525				

ONJ, osteonecrosis of the jaw; LR/MBC, locally recurrent or metastatic breast cancer; BM, bone metastasis.

adverse events. Interestingly, the incidence of peripheral edema was lower in treatment with bisphosphonates compared with control groups (RR 0.85, 95% CI 0.73–0.99; $p < 0.05$; $I^2 = 19\%$). The results of the meta-analysis are summarized in Figure 3 and Table 3.

Table 3. Summary of the absolute event rates for adverse events with and without bisphosphonate.

Adverse Events	Classification	Number of studies included	Events with bisphosphonate	Events without bisphosphonate	Overall effect RR	Overall effect *p* value
Abdominal pain	Gastrointestinal Disorders	5	219/1379	189/1387	1.16	0.15
Anorexia		7	452/2227	325/2024	1.29	0.0001
Constipation		10	648/2819	651/2829	0.98	0.61
Diarrhea		12	602/2841	486/2890	1.27	0.07
Dyspepsia		11	471/3720	341/2879	1.25	0.0008
Nausea		27	1893/6925	1870/6963	1.01	0.63
Alopecia	General disorders and administration site conditions	5	229/1554	202/1562	1.14	0.15
Back pain		8	358/1993	320/1982	1.1	0.27
Dizziness		3	138/875	117/682	0.98	0.87
Fatigue		21	1295/5195	1196/5375	1.08	0.02
Fever		8	449/1419	352/1597	1.82	0.0009
Headache		11	390/2179	417/2182	0.92	0.21
Hot flashes		7	214/1009	229/1013	0.94	0.47
Influenza-like illness		3	38/115	8/111	4.52	< 0.0001
Metabolic and nutritional disorders		3	43/2254	32/1354	1.31	0.62
Peripheral edema		10	263/1816	303/1860	0.85	0.03
Anemia	Hematologic disorders	8	583/2175	544/2177	1.06	0.23
Granulocytopenia		9	179/1835	178/1847	1.01	0.94
Hepatic dysfunction	Hepatobiliary disorders	3	74/2705	57/1857	1.33	0.45
Urinary tract infection	Infections: urinary tract	6	147/2611	86/1583	1.32	0.04
Arthralgia	Musculoskeletal and connective tissue disorders	14	622/2477	539/2473	1.09	0.08
Myalgia		31	1608/8124	1354/7120	1.09	0.21
Depression	Psychiatric disorders	7	190/3158	175/2321	1	1
Insomnia		8	184/1302	215/1342	0.87	0.12
Coughing	Respiratory disorders	7	285/1405	250/1438	1.15	0.06
Dyspnea		10	519/2411	513/2414	0.97	0.61
Dermatologic	Skin/rash	7	210/3089	194/2241	1.04	0.82
Renal AEs	Urinary disorders	5	129/3529	98/2649	1.24	0.1

RR, Risk ratio

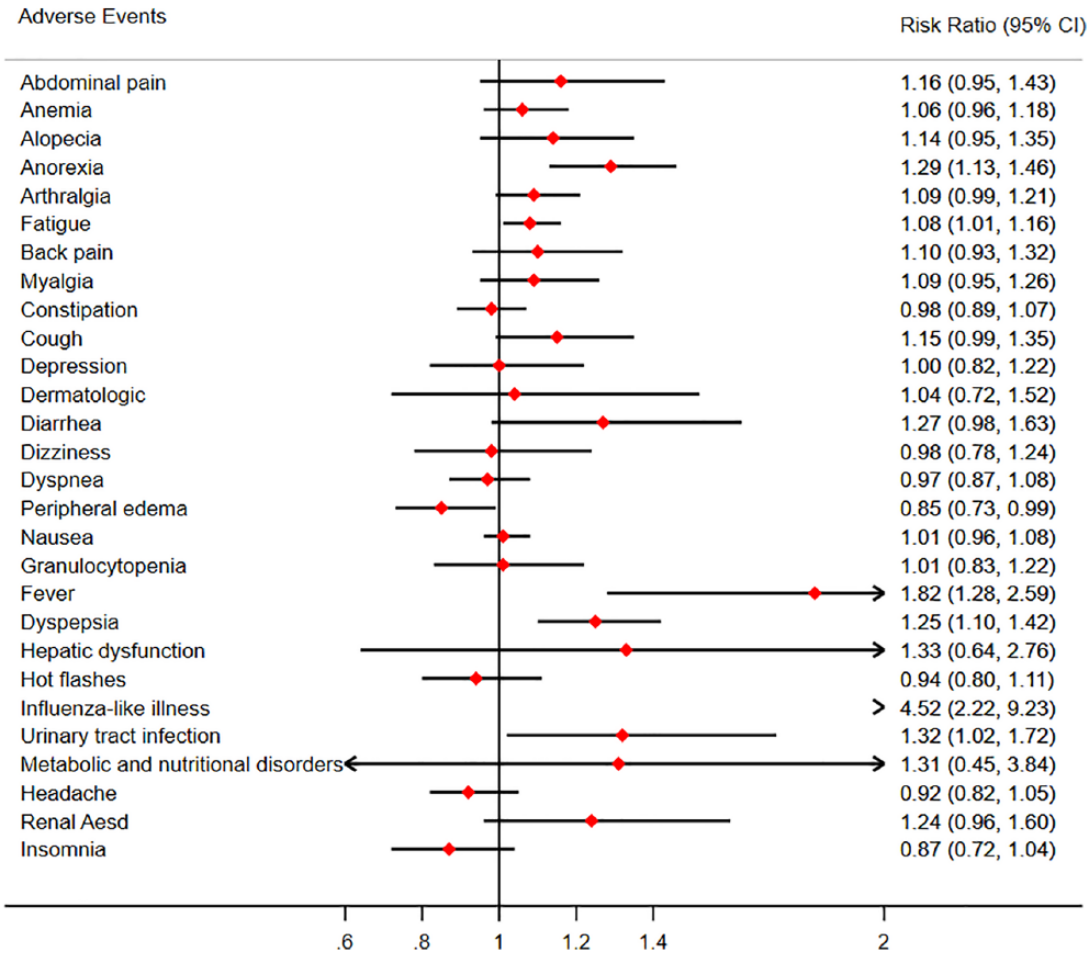

Figure 3. Summary figure demonstrating the risk ratio (RR) for adverse events for patients with and without exposure to bisphosphonates. CI, Confidence interval.

Assessment incidence of ONJ

We next screened the database for our systematic review of the incidence of ONJ. Here, 24 retrospective studies with 8525 patients were pooled in the meta-analysis. Meta-analysis of the incidence of ONJ among patients with bisphosphonates revealed significant between-study heterogeneity ($I^2 = 84.5\%$). Therefore, we used a random effects model for meta-analysis. Of the patients with bisphosphonates, 304 had a diagnosis of ONJ. We found that the overall incidence of ONJ in patients exposed to bisphosphonates therapies is 2% (95% CI 0.02–0.02; $p < 0.001$) (Figure 4).

Assessment of publication bias

We conducted six analyses out of seven comparisons with dominant pooled RR (fatigue, fever, dyspepsia, anorexia, urinary tract infection, peripheral edema) to assessment of publication bias. We did not conduct the Egger's side effect test because of paucity of included studies (as few as three studies) for pooled RR of influenza-like illness. We produced a p value for Egger's test as shown in supplemental Figures S1 and S2. As can be seen, all six p values were >0.1, suggesting no presence of significant publication bias (Table 4).

We also applied Egger's test to the ONJ studies to produce an incidence of ONJ on the basis of pooled comparison; this resulted in a p-value of <0.001, suggesting the presence of publication bias (see Egger's regression chart in Figure 5a and Begg's funnel plot in Figure 5b). We adopted the trim-fill method to further analyze the bias, with the resulting plot (Figure 5c) suggesting that an unbiased state could be achieved through filling with an additional nine studies .

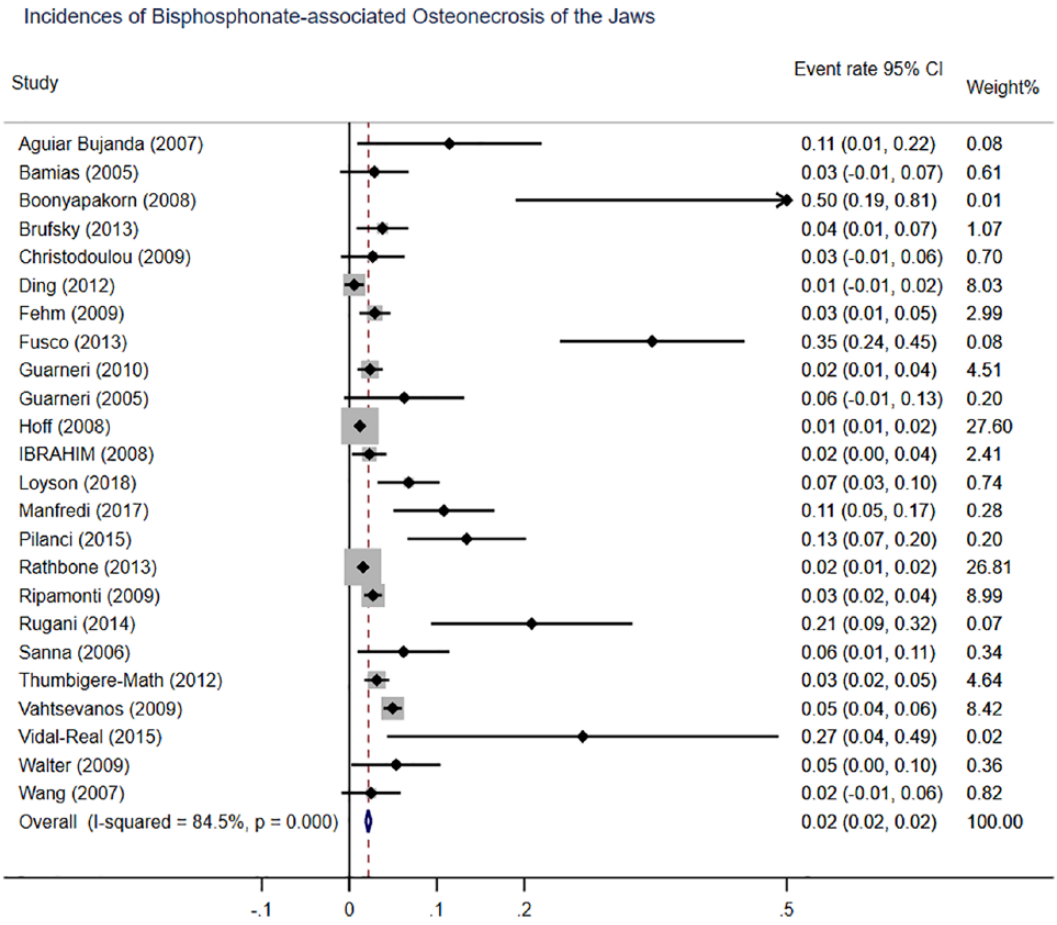

Figure 4. Meta-analysis of incidence of bisphosphonates-associated osteonecrosis of the jaw. CI, Confidence interval.

Table 4. Egger's and Begg's test *p* value.

Adverse events	Egger's *p* value	Begg's *p* value
Anorexia	0.703	0.688
Fatigue	0.213	0.212
Peripheral edema	0.486	0.477
Fever	0.151	0.153
Dyspepsia	0.946	0.954
Urinary tract infection	0.872	0.878

Discussion

Our study enrolled 47 clinical trials involving 20,607 participants in a network meta-analysis. Six bisphosphonates regimens were included: alendronate, clodronate, ibandronate, pamidronate, risedronate, and zoledronic. Our data suggest that patients with breast cancer treated by bisphosphonates are at higher risk of fatigue, anorexia, peripheral edema, dyspepsia, fever, influenza-like illness, and urinary tract infection relative to controls, and that 2% of breast cancer patients treated with bisphosphonates develop ONJ.

In recent years, bisphosphonates have emerged as a highly effective therapeutic option for prevention of SREs, especially in patients who have

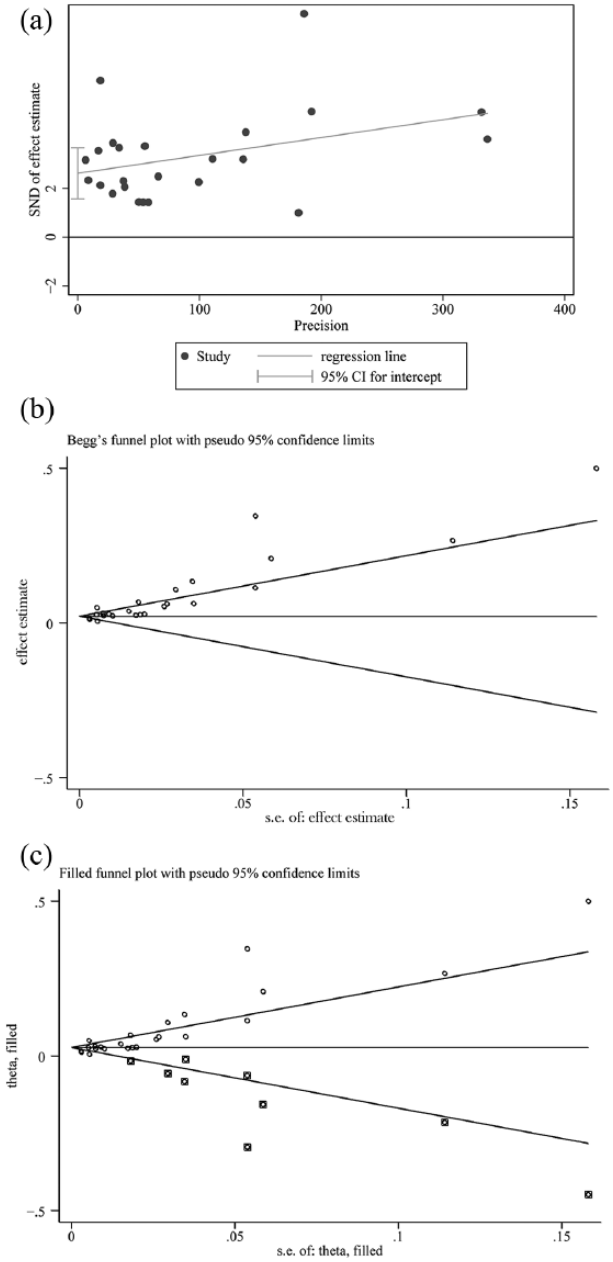

Figure 5. Results of Egger's test (a), Begg's test (b), and the fill method (c) for bisphosphonates-associated osteonecrosis of the jaw (ONJ).

breast cancer and metastatic bone disease.[16,65] Epidemiological studies have suggested that bisphosphonates may increase bone mineral density in lumbar and hip joints in breast cancer patients, including premenopausal and postmenopausal women.[15,39,66] Several experimental studies have also proposed that bisphosphonates might have antitumor effects, including inducing apoptosis, reducing proliferation, and inhibiting tumor cell migration and invasion.[40] Since bisphosphonates are considered as an effective adjuvant drug for prevention of SREs, these adverse effects should be clarified and weighted. Our present systematic review and meta-analysis confirms and quantifies the adverse effects associated with bisphosphonates as an adjuvant treatment. Accordingly, we anticipate that our findings may help physicians and their patients gauge the risk-benefit of adding bisphosphonates to a patient with advanced malignancy.

Studies have reported that nephrotoxicity, including toxic acute tubular necrosis and focal segmental glomerulosclerosis, is a potential limiting factor for intravenous bisphosphonates.[67,68] Adverse events such as influenza-like illness and chills were more common in the zoledronate group compared with the placebo group.[15] In addition, the following adverse events were also more frequently observed in the zoledronate group as compared with the observation group: sensory neuropathy and other nervous system disorders, gastrointestinal, skin, myalgia, pain, fatigue, fever, and other general condition disorders.[40] When compared with patients in the placebo group, patients in the ibandronate group had an excess of adverse events in specific system organ classes: infection, cardiac, gastrointestinal, hepatobiliary, and general condition.[13] Our meta-analysis included 23 studies, all of which were RCTs. The results demonstrated that only seven adverse events (i.e. influenza-like illness, fatigue, anorexia, dyspepsia, fever, urinary tract infection, and peripheral edema) are related to the use of bisphosphonates. Influenza-like illness is the most common adverse event. This may indicate that these adverse events are mediated through bisphosphonates. However, no significantly higher risk was shown in the incidence of myalgia and nausea, which were the most common adverse events of bisphosphonates. Interestingly, we observed a decreased risk of peripheral edema in patients treatment with bisphosphonates compared with control groups. Thus, clinicians should be aware of these potential adverse effects in clinical use.

ONJ is a destructive bone process in patients undergoing bisphosphonate therapy who show bone exposure of over 8 weeks of development and who did not undergo radiotherapy of the head and neck.[53,54,62] Some ONJ patients may show no symptoms at all, but in others ONJ may cause severe pain, swelling and bleeding of oral cavity tissue, continuous purulent secretion accompanied with or without fistula in the oral cavity, severe bad breath and an abnormal feeling of the lower lip related to loosened teeth. Predominantly, ONJ leads to a severe deterioration of the patient's quality of life. However, some researchers have shown a very variable prevalence of ONJ. A retrospective study of 194 Spanish patients who had undergone intravenous bisphosphonate therapy showed that the prevalence of ONJ was 12.9%.[62] Another retrospective analysis showed that 8 of 190 patients (4.2%) with breast cancer developed ONJ.[60] Ding and colleagues retrospectively analyzed the safety data of bisphosphonates in 181 breast cancer patients with bone metastasis who received intravenous bisphosphonates for more than 2 years; only 1 of these patients was diagnosed with ONJ, giving an incidence rate of 0.6%.[46] The purpose of the study reported in this article was to determine the prevalence of ONJ in breast cancer patients who have undergone intravenous bisphosphonate therapy, and relate the risk factors described to establish a protocol to reduce the risk of developing ONJ. In the current analysis, we observed that 2.0% of breast cancer patients treated with bisphosphonates developed ONJ. It is worth noting that Boonyapakorn and colleagues reported a relevantly greater number (50%) of ONJ in patients treated with bisphosphonates.[43] The smaller sample in the latter study ($n = 10$) might explain the high incidence of ONJ. The different prevalence of ONJ is not well understood but may possibly be related to each patient's systemic factors, such as diabetes, osteoporosis (in oncology patients), and medication related to steroids, or immunosuppressive and antiangiogenic drugs.[62,69] In addition, local factors are also related to the appearance of ONJ, such as oral hygiene and overall periodontal state.

The present study has certain limitations. First, we analyzed the data on adverse events provided in published clinical trials. These adverse events were chosen by the authors according to varied criteria. Therefore, many related adverse events may have be considered irrelevant and therefore have not been reported. Second, 23 studies of ONJ are single-group trials, rather than RCTs. Nevertheless, major cases are enrolled in the study, and are consistent with the research progress; hence, the conclusions have a certain value and significance. Third, as with any meta-analysis, the results described here are affected by the limitations of the individual clinical trials that were selected for this meta-analysis. Last, the pooled between-studies of ONJ suggested significant publication bias. According to the trim-fill method, publication bias might be corrected to an unbiased state by adding nine studies. At present we lack the relevant studies from among the articles searched.

Conclusion

In summary, the results of this meta-analysis suggest that the use of bisphosphonates is associated with seven adverse events: fatigue, anorexia,

peripheral edema, dyspepsia, fever, influenza-like illness, and urinary tract infection. During bisphosphonate therapy, 2% of patients might develop ONJ. This study should help to convey information to clinicians and patients on the correct and rational use of bisphosphonates in the treatment of breast cancer, avoiding unnecessary dose reduction and treatment interruptions, and thus minimizing the impact on patient quality of life.

Acknowledgements

We thank Beijing Zhiyun Data Technology Co. LTD, for data analysis service.

Funding

This work was funded by the National Natural Science Foundation of China (grant number 81570993) and Beijing Natural Science Foundation (grant number 7162100).

Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplemental material

Supplemental material for this article is available online.

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