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Bisphosphonates in the Treatment of Patients With Metastatic Breast, Lung, and Prostate Cancer

A Meta-Analysis

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Abstract: The purpose of this meta-analysis was to investigate whether bisphosphonates are a key therapy for bone metastases in lung cancer, breast cancer, and prostate cancer by comparing all randomized controlled trials that appraised the effects of bisphosphonates on risk of skeletal-related events (SREs).

PubMed, Embase, and Medline databases (up to December 2014) were used to search all related articles. Using the data from 19 available publications, the authors examined the efficacy in treating or reducing the risk of SREs in lung cancer, breast cancer, and prostate cancer by meta-analysis.

Bisphosphonates have demonstrated efficacy in treating or reducing the risk of SREs in lung cancer [odds ratio (OR) = 0.81, 95% confidence interval (CI) = 0.69–0.95, $P = 0.008$], breast cancer (OR = 0.62, 95% CI = 0.54–0.71, $P = 0.000$), and prostate cancer (OR = 0.62, 95% CI = 0.45–0.86, $P = 0.004$).

This meta-analysis suggests that bisphosphonates have demonstrated efficacy in treating or reducing the risk of SREs in lung cancer, breast cancer, and prostate cancer.

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Abbreviations: CI = 95% confidence interval, MMPs = matrix metalloproteinases, OR = odds ratio, SREs = skeletal-related events.

INTRODUCTION

Lung cancer, breast cancer, and prostate cancer remain the leading cause for cancer mortality worldwide. Lung cancer has an incidence in Europe of 417,000 new cases per year, and a mortality/incidence ratio of 0.88. Breast cancer is the most

common cancer type in women worldwide and is the main cause of cancer mortality in women in the world. Prostate cancer is the most common cancer in men in many western countries, and the second leading cause of cancer death in men.

The skeleton is common site of the metastatic cancer, especially in patients with breast, lung, or prostate cancer.¹ The most common complications of skeletal occurring from bone metastases are named skeletal-related events (SREs), including severe pain of bone, hypercalcemia of malignancy, and pathologic fractures.¹ The bone metastasis of metastatic cancers is associated with a reduced survival rate and a low patients' quality of life.² In addition, cancerous patients with bone metastases and SREs have been shown to cost more hospital resources and money.³

Bisphosphonates, such as zoledronate, pamidronate, and alendronate, have been shown to inhibit osteoclast-mediated bone resorption^{4,5} and be effective for the treatment and prevention of SREs in breast cancer,⁶ prostate cancer,⁷ and lung cancer.⁸ The efficacy and safety of bisphosphonates, however, are still uncertain. As a result, we carried out a meta-analysis using data from randomized controlled trials to identify the effectiveness and safety of bisphosphonates in patients with breast, lung, and prostate cancer.

This meta-analysis aims to support the use of bisphosphonates in patients with lung cancer, breast cancer, or prostate-developing bone metastases. Its efficacy and safety, as well as its cost-effectiveness, are highlighted.

MATERIAL AND METHODS

Publication Search

We obtained relevant randomized controlled trials from PubMed, Embase, and Chinese biomedicine database that treated with either zoledronic acid or another bisphosphonates to prevent SREs in breast, lung, or prostate cancer. For the computer searches, we used the following key words: "bisphosphonates," "ibandronate," "ibandronic acid," "zoledronic acid," "zoledronate," "SREs," "breast cancer," "prostate cancer," or "lung cancer" in the title or abstract, and was limited by "clinical trials, meta-analysis, randomized controlled trial, and review" published in English between 2003 and 2014. Studies contained available data, which showed the association of bisphosphonates treatment in breast cancer, prostate cancer, and lung cancer between SREs. Among the studies with overlapping data published by the same author, only the complete study was included in this meta-analysis. Furthermore, included studies had to show their results as an odds ratio (OR) and 95% confidence interval (CI).

Data Extraction and Classification

For each study characteristics, data were extracted, including the first author, publication year, patients' country, disease

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characteristics, treatment medication, OR, and risk estimates with corresponding 95% CI. Skeletal-related events were defined as pathologic bone fracture, the bone surgery, the bone radiation therapy, or change in anticancer therapy to relieve bone pain.

Statistical Analysis

The measure of effect of interest is the OR and the corresponding 95% CI. We showed all results as OR for simplicity and quantified the association of bisphosphonates treatment in breast cancer, prostate cancer, and lung cancer between SREs using random effects models⁹ of OR comparing the highest with the lowest category. The summary OR estimates were obtained from random effects models.⁹

For all analysis, *P* values <0.05 were considered significant. Publication bias was assessed by a Begg-adjusted rank correlation test (funnel plot method) and Egger linear regression asymmetry test.¹⁰ All meta-analyses were carried out using Stata software (version 9.0, StataCorp, College Station, TX).

An Ethics Committee

The ethical approval was not necessary. Our research does not involve ethics.

RESULTS

Characteristics of Studies for Meta-Analysis

A total of 19 publications were identified for inclusion in the SREs for the 3 malignancies (Table 1). Among the

19 studies, 11 were conducted in the United States, 2 in Europe, 2 in Japan, and the other 4 were not reported. We separate the results by different malignancies, including lung cancer, breast cancer, and prostate cancer. With the exception of 7 studies comparing bisphosphonates (zoledronic acid + chemotherapy versus chemotherapy,^{11–14} zoledronic acid versus ibandronate¹⁵ in lung cancer, and zoledronic versus pamidronate in breast cancer),¹⁶ all studies compared bisphosphonates with placebo. Of the 19 placebo-controlled studies, 16 showed that bisphosphonates were effective in reducing the incidence of SREs in lung cancer, breast cancer, and prostate cancer.

Lung Cancer

Most patients with bone metastases from lung cancer experience SRE. The association of bisphosphonates treatment of lung cancer between SREs was identified in 7 studies, including comparisons of zoledronic acid versus ibandronate and zoledronic acid versus placebo (Table 1). Pooled estimates showed a statistically significant 19% reduction in the risk of developing new SREs with bisphosphonates (OR = 0.81, 95% CI 0.69–0.95, *P* = 0.008; Figure 1; Table 2). This data indicate that bisphosphonates were associated with a reduction in skeletal mortality rate.

Breast Cancer

Seven studies in breast were identified in the analysis, including comparisons of zoledronic versus pamidronate and

TABLE 1. The Distribution and Odds Ratios (95% Confidence Interval) for Studies on 3 Cancer Models and Bisphosphonates

Cancer Model	Author	Publication Year	Country	Group	OR (95% CI)	Reference
Lung cancer	Rosen	2003	USA	Zoledronic acid + chemotherapy versus chemotherapy	0.80 (0.66–0.96)	12
	Scagliotti	2006	Europe	Zoledronic acid + chemotherapy versus chemotherapy	0.74 (0.39–1.40)	13
	Kritikos	2008	Greece	Zoledronic acid versus placebo	0.77 (0.41–1.40)	17
	Zarogoulidis	2009	Greece	Zoledronic acid + chemotherapy versus chemotherapy	0.87 (0.20–3.80)	14
	Murakami	2011	Japan	Zoledronic acid + chemotherapy versus chemotherapy	0.75 (0.44–1.30)	11
	Francini	2011	USA	Zoledronic acid versus ibandronate	0.74 (0.27–2.00)	15
	Oster	2014	USA	Zoledronic acid versus placebo	1.29 (0.63–2.62)	18
Breast cancer	Rosen	2003	USA	Zoledronic versus pamidronate	0.69 (0.53–0.91)	16
	Body	2004	Europe	ibandronate versus placebo	0.62 (0.48–0.79)	19
	Kohno	2005	Japan	Zoledronic acid versus placebo	0.57 (0.36–0.86)	20
	Swenson	2009	No report	Zoledronic acid versus placebo	0.27 (0.03–2.76)	21
	Coleman	2011	National Cancer Research Network	Zoledronic acid versus placebo	0.64 (0.46–0.89)	22
	Gnant	2011	No report	Zoledronic acid versus placebo	0.73 (0.33–1.60)	23
	Oster	2014	USA	Zoledronic acid versus placebo	0.49 (0.33–0.73)	28
Prostate cancer	Saad	2004	USA	Pamidronate versus placebo	0.63 (0.45–0.90)	24
	Small	2003	No report	Clodronate versus placebo	1.22 (0.71–2.07)	25
	Dearnaley	2003	USA	Zoledronic acid versus placebo	0.71 (0.56–0.92)	26
	Ryan	2006	USA	Zoledronic acid versus placebo	0.23 (0.25–1.00)	27
	Greenspan	2007	USA	Alendronate versus placebo	0.73 (0.37–1.45)	28
	Greenspan	2008	USA	Alendronate versus placebo	0.51 (0.32–0.80)	29

CI = confidence interval, OR = odds ratio.

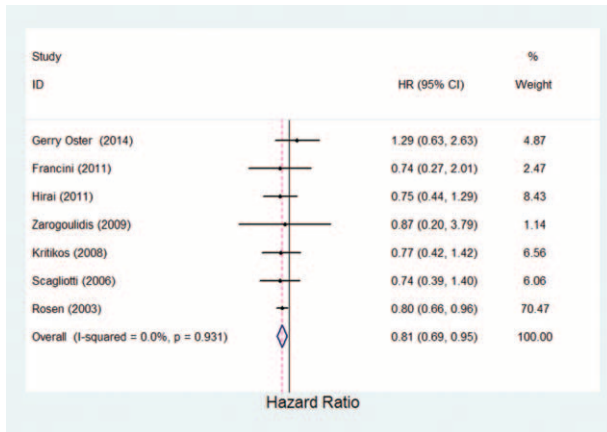


FIGURE 1. Estimated odds ratio of risk for skeletal-related events for patients with lung cancer under bisphosphonates therapy.

TABLE 2. Summary Odds Ratios and 95% Confidence Interval for Bisphosphonates and Skeletal-Related Events Rate Under Different Cancer Models

Cancer Models	OR (95% CI)	P	Begg Test P-Value	Egger Test P-Value
Lung cancer	0.81 (0.69–0.95)	0.008	0.176	0.675
Breast cancer	0.62 (0.54–0.71)	0.000	0.453	0.334
Prostate cancer	0.62 (0.45–0.86)	0.394	0.348	0.574

CI = confidence interval, OR = odds ratio.

zoledronic acid/ibandronate versus placebo (Table 1). The data analysis showed a statistically significant 38% reduction in the risk of developing new SREs with bisphosphonates (OR = 0.62, 95% CI 0.54–0.71, P = 0.000; Fig. 2; Table 2). It suggested that bisphosphonates demonstrate a statistically significant decrease in the risk of developing SREs compared with placebo.

Prostate Cancer

The 7 prostate cancer studies included in the analysis compared zoledronic acid, pamidronate, clodronate, and

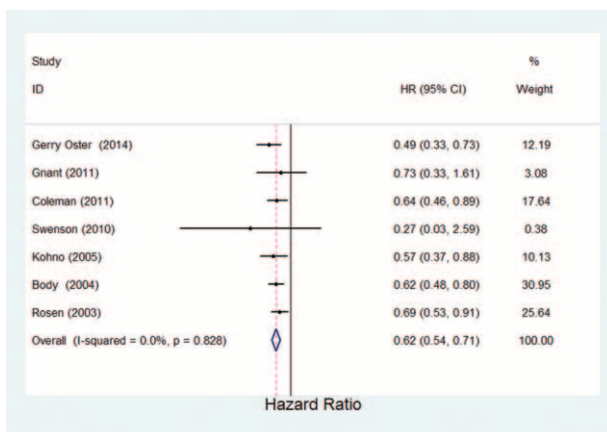


FIGURE 2. Estimated odds ratio of risk for skeletal-related events for patients with breast cancer under bisphosphonates therapy.

alendronate with placebo (Table 1). Because the study by Bhoopalram et al³⁰ of zoledronic acid versus placebo had a higher SRE rate than the other placebo-controlled studies (OR = 4.38, 95% CI = 0.53–6.13). Removing the Bhoopalram study³⁰ from the analysis resulted in a lower SRE rate for bisphosphonates. The meta-analysis had a statistically significant result of 38% reduction in the risk of SREs with bisphosphonates (OR = 0.62, 95% CI 0.45–0.86, P = 0.004; Fig. 3; Table 2). The result indicated that the bisphosphonates favors a decrease in SREs.

Publication Bias

We evaluated publication bias by Egger test and Begg test. The results of the Egger test (P > 0.05) and the Begg test (P > 0.05) provided statistical evidence for funnel plot symmetry in the overall results, suggesting the absence of publication bias (Table 2).

DISCUSSION

Our meta-analysis suggests that bisphosphonates have demonstrated efficacy in treating or reducing the risk of SREs in lung cancer, breast cancer, and prostate cancer. Bisphosphonates have a protective effect for SREs, with a 19% lower risk in lung cancer and a 38% lower risk in breast cancer and prostate. The intense inhibition of osteoclast function precipitated by bisphosphonate therapy can lead to inhibition of normal bone turnover.

Bisphosphonates have been proven to display high affinity for inhibiting bone resorption by osteoclasts.³¹ Many nitrogen-containing bisphosphonates, such as alendronate, risedronate, pamidronate, ibandronate, and zoledronic acid are considered as an important part of treatment to reduce the risk for SREs in cancer patients with bone metastases.^{32–34} A great number of studies have identified the effect of bisphosphonates to inhibit tumor cell adhesion, invasion, proliferation, and interplay with the microenvironment components of bone such as matrix metalloproteinases.^{35,36} In addition, it reported that bisphosphonates interfere with signaling pathways required for osteoclast function and survival.³⁷ Malignant cells, such as lung cancer, breast cancer, and prostate cancer have a unique predilection to metastasize to bone, and the microenvironment is highly receptive to metastatic tumor cell.³⁸ Therefore, early diagnosis and therapy of bone metastases will delay the development of common clinical complications associated to bone

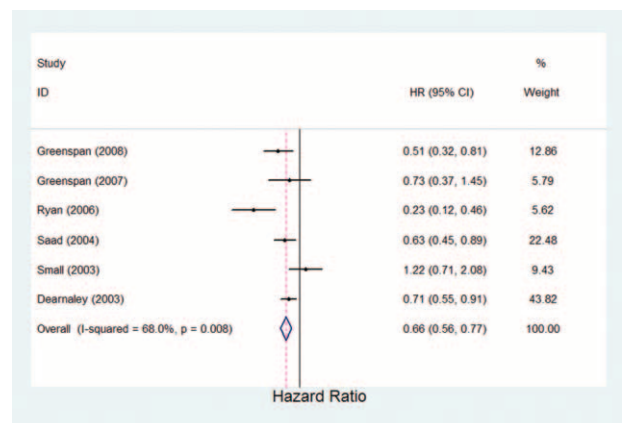


FIGURE 3. Estimated odds ratio of risk for skeletal-related events for patients with prostate cancer under bisphosphonates therapy.

metastases.³⁹ Our meta-analysis showed bisphosphonates are a key therapy for bone metastases and have a proved efficacy in lung cancer, breast cancer, and prostate cancer, resulting in reduced risk of SREs.

There are many limitations that are present in our study. For example, this analysis was based on case-control studies, and the limitation of these studies could influence our results. Furthermore, our findings were likely to be affected by different measurement and range of drug. It will need larger and wider case-control studies to confirm that bisphosphonates reduced the risk of SREs in lung cancer, breast cancer, and prostate cancer.

In summary, our meta-analysis provides some support for the hypothesis that bisphosphonates have demonstrated efficacy in treating or reducing the risk of SREs in lung cancer (OR = 0.81, 95% CI = 0.69–0.95, $P = 0.008$), breast cancer (OR = 0.62, 95% CI = 0.54–0.71, $P = 0.000$), and prostate cancer (OR = 0.62, 95% CI = 0.45–0.86, $P = 0.004$). Future well-designed large studies might be necessary and should consider the interrelations between different bisphosphonates.

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