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# Bisphosphonates and Risk of Subtrochanteric, Femoral Shaft, and Atypical Femur Fracture: Sensitivity and Trim and Fill Studies

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*Objective:* This study carried out sensitivity analysis and trim-fill analysis between bisphosphonates and subtrochanteric, femoral shaft, and atypical femur fracture. *Methods:* A random-effects model was used finally. Sensitivity, trim and fill, and publication bias analyses were done. *Results:* Under a random-effects model ($I^2 = 87.535$), the $Z$-value = 5.672, $p$-value of test of null < 0.001. Bisphosphonate exposure was associated with an increased risk of atypical femur fracture (3.243 [95% CI 2.160–4.870]). When any study is removed, the remaining sensitivity analysis results are still significant. Trim and fill results show that two studies were missed. After filling them, a funnel plot of precision by log risk ratio was more symmetrical. *Conclusion:* This study suggests that (1) there is an increased risk of subtrochanteric, femoral shaft, and atypical femur fracture in bisphosphonate users; (2) any single study does not influence the total sensitivity; (3) two studies have been lost, theoretically.

## Introduction

Osteoporosis is a progressive systemic skeletal disease characterized by low bone mass and deterioration of bone microarchitecture. It has a relationship with bone fractures that significantly increases the morbidity and mortality of affected patients. It mainly affects postmenopausal women; about 50% of women older than 50 years will sustain an osteoporosis-related fracture during their lifetime (Ioannidis *et al.*, 2009; Papaioannou *et al.*, 2009). According to the radiographic appearance, femoral fractures were classified as stress fractures or nonstress fractures. Medications, such as bisphosphonates, are therefore increasingly used to prevent and treat osteoporosis. A number of studies showed that bisphosphonates could reduce the overall risk of fracture in patients with osteoporosis (Black *et al.*, 2006). However, concerns have been raised about the potential risk of these drugs during long-term use. Some other studies showed an increased risk of subtrochanteric and femoral shaft fractures with the use of bisphosphonates (Park-Wyllie *et al.*, 2011; Schilcher *et al.*, 2011; Vestergaard *et al.*, 2011). Among them, stress fractures (commonly called atypical femoral fractures) were more common in patients who received bisphosphonates than in those who did not (Lenart *et al.*, 2009; Girgis *et al.*, 2010). Some studies also showed that bisphosphonates could negatively affect bone remodeling and lead to increased microdamage (Mashiba *et al.*, 2000; Odvina *et al.*, 2005). However, these reports are controversial and the detailed mechanism of this phenomenon is unknown.

More recently, Gedmintas *et al.* (2013) published a meta-analysis that indicated that there is an increased risk of subtrochanteric, femoral shaft, and atypical femoral fractures among bisphosphonate users. However, they did not perform two very important statistics, sensitivity analysis and trim and fill analysis. To analyze this issue more thoroughly and deeply, we performed this comprehensive study.

## Materials and Methods

### *Identification of eligible studies*

We searched the MEDLINE and EMBASE databases, from January 1990 to October 2012 for studies examining the association of bisphosphonate use and atypical femur fracture, as well as subtrochanteric and femoral shaft fractures. Only

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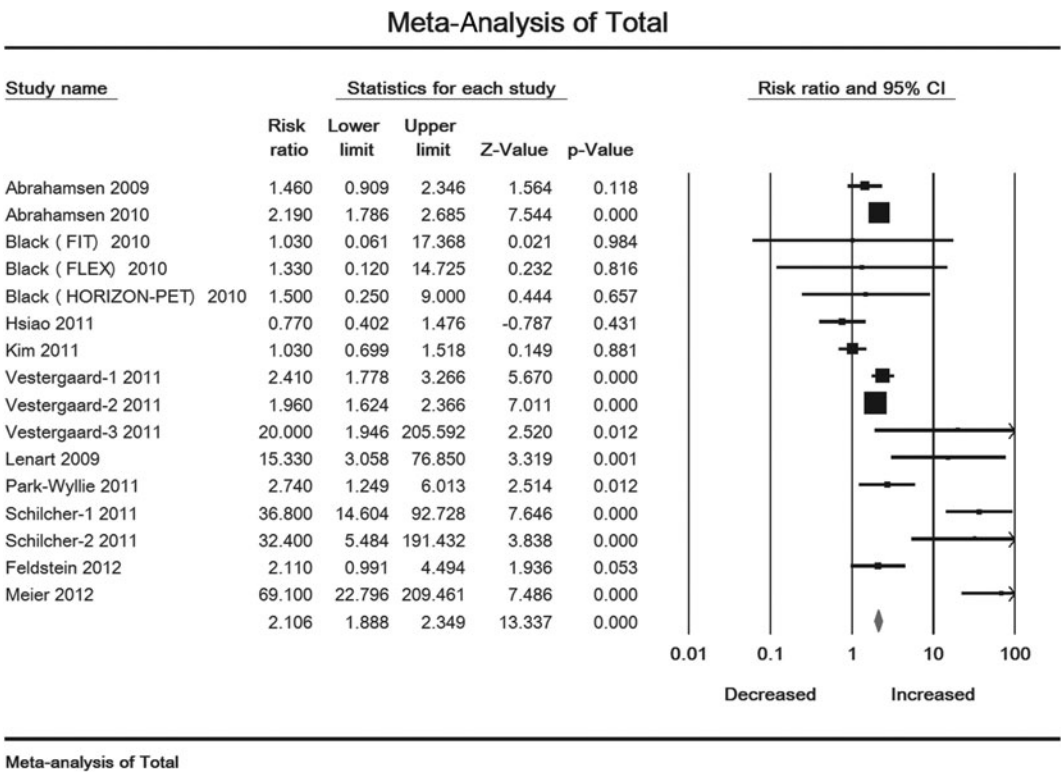


**FIG. 1.** Fixed-model meta-analysis of the relationship between bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture. The overall odds ratio (OR) is shown. The OR of each study is marked with a black square. The overall OR is indicated by diamond.

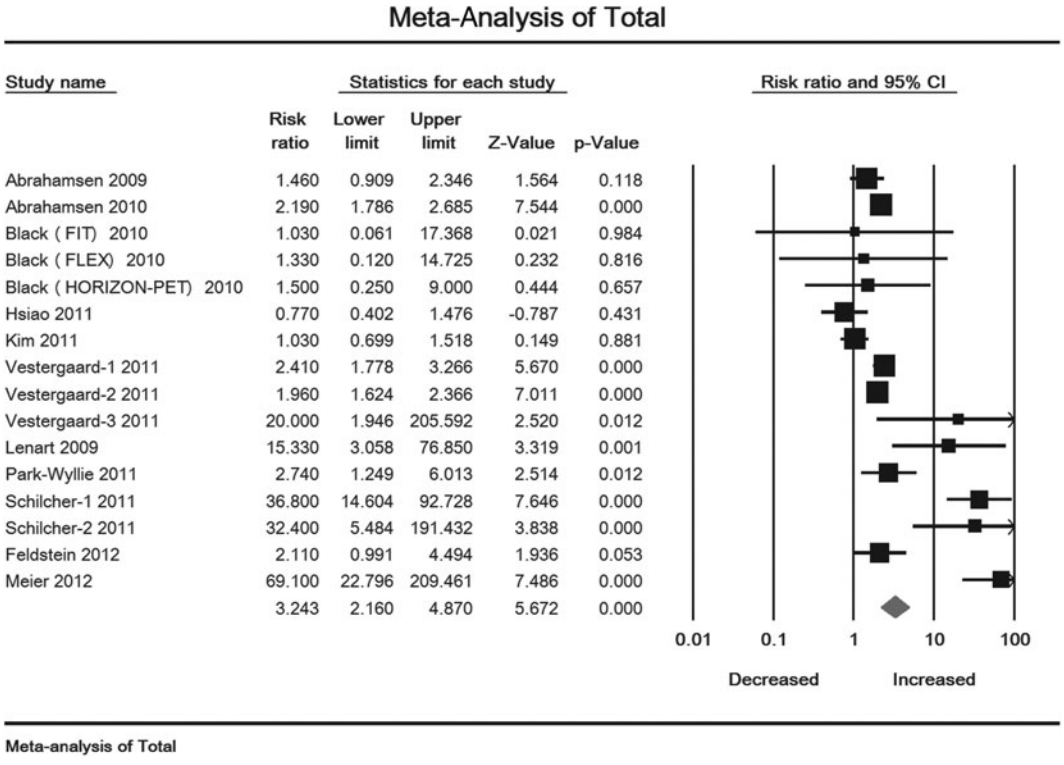


**FIG. 2.** Random-model meta-analysis of the relationship between bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture. The overall OR is shown. The OR of each study is marked with a black square. The overall OR is indicated by diamond.

Table 1. The Statistics of Basic Parameters in the Study

| | *Effect size and 95% interval* | | | | *Test of null (2-Tail)* | | | *Heterogeneity* | | | *Tau squared* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Model* | *Number studies* | *Point estimate* | *Lower limit* | *Upper limit* | *Z-value* | *p-Value* | *Q-value* | *df(Q)* | *p-Value* | *I-squared* | *Tau squared* | *Stand error* |
| Fixed | 16 | 2.106 | 1.888 | 2.349 | 13.337 | 0 | 120.334 | 15 | 0 | 87.535 | 0.424 | 0.308 |
| Random | 16 | 3.243 | 2.16 | 4.87 | 5.672 | 0 | / | / | / | | | |

'/' means does not exist.

studies published in English were included. The keywords for searching were the same as Gedmintas *et al*'s (2013).

### *Data extraction and quality evaluation*

The following information was independently extracted from the identified studies by two participants: first author, journal, year of publication, study design, ethnicity of the study population, the number of cases and controls or risk ratios (RR) and 95% confidence interval (CI), country in which the study was conducted, and what type of bisphosphonate was used. The results were compared and any disagreement was discussed and resolved by consensus. According to Gedmintas *et al.* (2013), the Newcastle-Ottawa Quality Assessment Scale was used independently by the two authors (J.L. and H.X.Z.) to help determine the quality of studies included in the study.

### *Statistical analysis*

This study examined the overall association between bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture. The effect size was represented by RR with 95% CI. The Cochran's Q statistical test and the $I^2$ test were used to assess heterogeneity in combined studies. Publication bias was checked using the Begg's test and the Egger's test was used for funnel plot asymmetry (Begg and Mazumdar, 1994; Egger *et al.*, 1997). *p*-Values of overall RR were generated using the *Z* test. Sensitivity analysis was conducted by removing each study and analyzing the others to ensure no single study was totally responsible for the overall results. The significance level was set at 0.05, and all *p*-values were two tailed. This study was performed using Comprehensive Meta Analysis software (Version 2.2.046; BIOSTAT, Englewood, NJ).

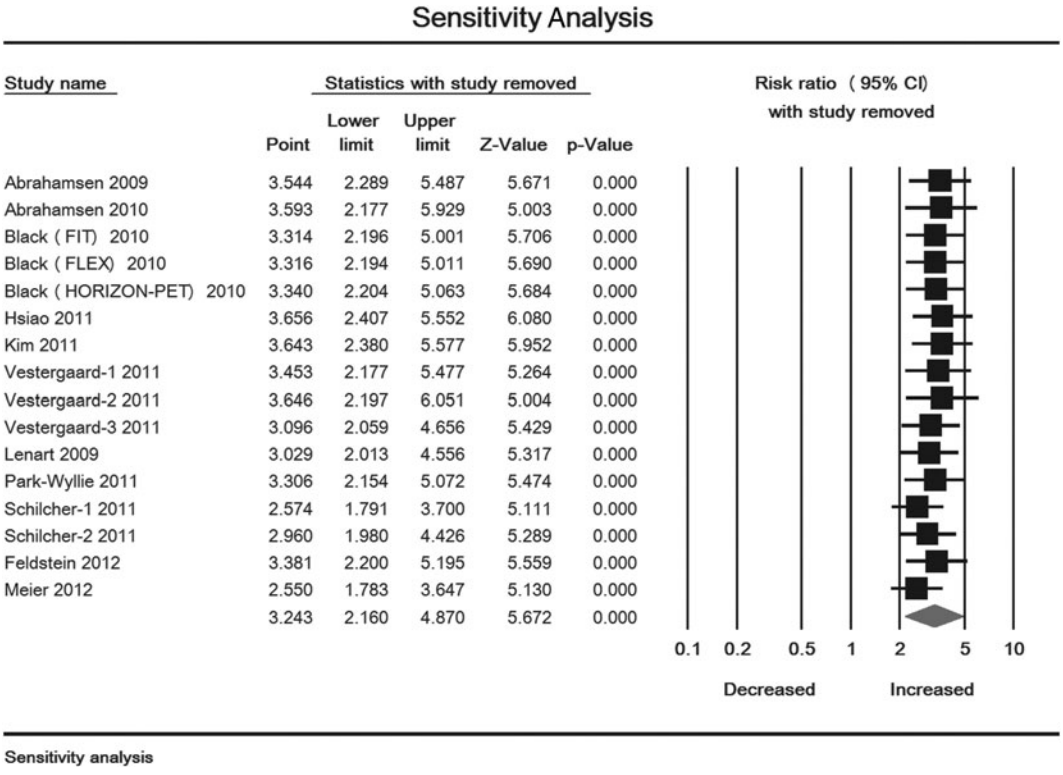


**FIG. 3.** The sensitivity analysis of the studies for the association between bisphosphonate use and subtrochanteric, femoral shaft, and atypical femur fracture. Point (square) and overall (diamond) estimates are given as risk ratios with 95% confidence interval (CI) (horizontal bar).

## Results

Finally, 11 references were selected in this study, including 10 cohort studies and 6 case–control studies (Abrahamsen *et al.*, 2009, 2010; Lenart *et al.*, 2009; Black *et al.*, 2010; Hsiao *et al.*, 2011; Kim *et al.*, 2011; Park-Wyllie *et al.*, 2011; Schilcher *et al.*, 2011; Vestergaard *et al.*, 2011; Feldstein *et al.*, 2012; Meier *et al.*, 2012). The total analyses demonstrate that both the fixed-effects and the random-effects models show a significant association between bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture (fixed-effects model: adjusted RR of 2.106 [95% CI 1.888–2.349]; random-effects model: adjusted RR of 3.243 (95% CI 2.160–4.870]) (Figs. 1 and 2). As *I*-squared ($I^2$) = 87.535, *Q*-value = 120.334, *p*-value of heterogeneity < 0.001, the random-effects model was used to calculate the pooled estimates of adjusted RR. Under this model, the analysis results show *Z*-value = 5.672, *p*-value of Test of null (2-Tail) < 0.001 (Table 1). Sensitivity analysis results demonstrate that when any single study is removed, the remaining results are still significant (Fig. 3). The trim and fill results show that two necessary studies have been missed. After filling these two

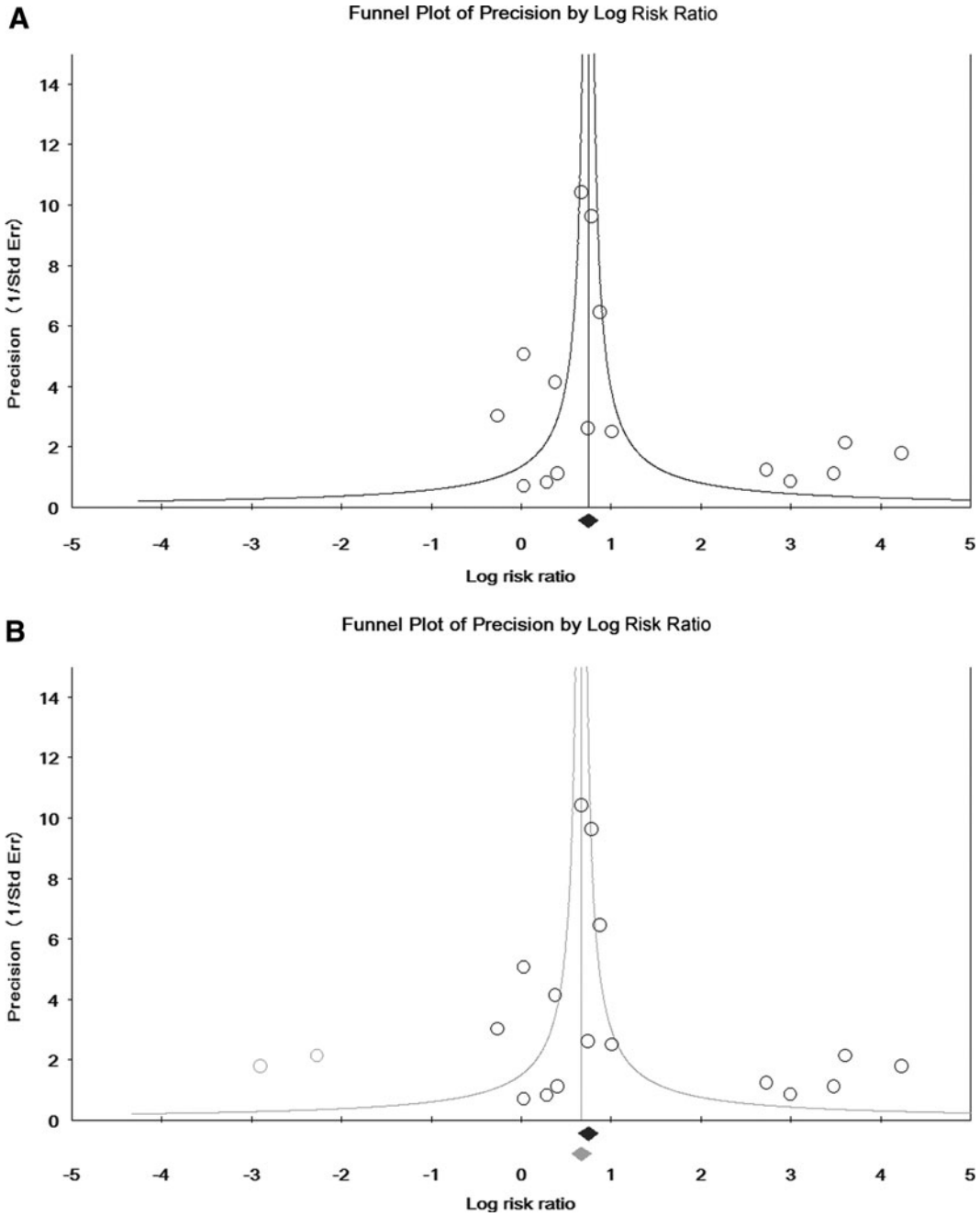


**FIG. 4.** **(A)**. Funnel plot with pseudo 95% confidence limits. **(B)** Funnel plot of all studies with pseudo 95% CI, including the hypothetical studies using the trim and fill method.

in the comprehensive analysis, the funnel plot of precision by the log risk ratio show much more symmetry (Fig. 4A, B).

## Discussion

Bisphosphonates (also called diphosphonates) have been used to treat osteoporosis and similar diseases for several decades. It has been shown that this kind of drug could increase bone mineral density and reduce vertebral and proximal femur fracture risk in patients with osteoporosis. Although bisphosphonates are generally safe and effective, more and more studies indicated that women taking bisphosphonates for osteoporosis have had unusual fractures. Gedmintas *et al.* summarized these published data in a meta-analysis and suggested that long-term use of bisphosphonates was significantly associated with the risk of osteoporosis-related fractures. However, their study had some limitations and some important statistical analyses were not performed.

In this current study, we conducted a comprehensive analysis for the association between bisphosphonate use and risk of subtrochanteric, femoral shaft, and atypical femur fracture. The funnel plot appears asymmetric (Fig. 4A) suggesting publication bias. Therefore, we performed a trim and fill analysis, which is a simple funnel plot-based method of testing and adjusting for publication bias in meta-analysis. This method uses only an iterative approach and simple symmetry assumptions are easy to implement in practice and to estimate the number of missing studies. Following this method, we found that two missing studies should be filled, theoretically. After the trim and fill statistics were taken, the funnel plot seemed much more symmetrical (Fig. 4A, B). On the other hand, the trim and fill analysis did not change the direction of the results, although the magnitude of the association was somewhat weakened, indicating that the association is not an artifact of unpublished negative studies. Sensitivity analysis (Fig. 3) was conducted by removing each study and analyzing the others to ensure that no single study was totally responsible for the overall results. The results indicate that no heterogeneity existed in the population.

The main limitation in our study is the varying definition of an atypical femur fracture. In addition, we were limited by the significant heterogeneity of studies, as the total $I^2 = 87.535$ (Table 1). Many potential factors may cause this heterogeneity, such as patient characteristics, variations in study design and size, type of bisphosphonates and so on. Because of the value of $I^2$, we used a random-effects model to account for both sensitivity analysis and trim and fill analysis. Also, we performed a statistical analysis of the basic parameters of this study (Table 1).

## Conclusions

Despite these limitations, our current study, demonstrating two very important analyses—sensitivity analysis and trim and fill analysis—supports the study of Gedmintas *et al.* (2013), and makes the analysis on the research area of bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture complete.

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## Author Disclosure Statement

The authors have declared that no competing interests exist.

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