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Original Article

Safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density: a meta-analysis

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Abstract: *Purpose:* The aim of this meta-analysis was to assess the safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density (BMD). *Methods:* Safety of denosumab was compared with placebo or bisphosphonates. A systematic literature search without language restriction was conducted up to January, 2014. The RevMan 5.1 software was used for statistical analysis. *Results:* A total of 11 English literatures were eventually identified. The pooled data in the overall analysis revealed that there was no significant difference when compared denosumab with placebo or bisphosphonates in any adverse events (AAE) (RR=0.99, 95% CI=0.98-1.01, p=0.29), serious adverse event (SAE) (RR=1.05, 95% CI=0.98-1.13, p=0.18), neoplasm/cancer (RR=1.14, 95% CI=0.95-1.37, p=0.16) and deaths (RR=0.77, 95% CI=0.57-1.04, p=0.09). However, significant differences were found when compared denosumab with placebo or bisphosphonates in SAE related to infection (RR=1.23, 95% CI=1.00-1.52, p=0.05) and non-vertebral fracture (RR=0.86, 95% CI=0.74-1.00, p=0.05). Subgroup analysis was performed by the type of drugs which was used in the control group. The results of subgroup analysis did not demonstrate the differences between denosumab and bisphosphonates in SAE related to infection (RR=1.13, 95% CI=0.63-2.03) and non-vertebral fracture (RR=1.31, 95% CI=0.87-1.98). *Conclusions:* Compared to placebo, denosumab treatment significantly decreased the risk of non-vertebral fracture but increased the risk of SAE related to infection in the postmenopausal women with osteoporosis or low BMD. However, no difference between the safety of denosumab and bisphosphonates was found.

Keywords: Denosumab, osteoporosis, postmenopausal women, meta-analysis

Introduction

Osteoporosis is a common disease characterized by a systemic impairment of bone mass, strength, and microarchitecture which increases the propensity of fragility fractures [1]. There is higher prevalence of osteoporosis among postmenopausal women and the elderly [2]. Approximately 30% of all postmenopausal women in the United States and Europe have osteoporosis [3]. In Korea, the prevalence of osteoporosis has been reported to be 31% in postmenopausal women aged 45-64 years, 53% in those aged 65-74 years [4]. Shao et al. [5] reported that the prevalence of osteoporosis was as much as 60% in postmenopausal Chinese women.

The treatment of osteoporosis and prevention of osteoporotic fractures consist of non-drug and drug therapy [6]. Drug therapy of osteoporosis is based on the knowledge of mechanisms of bone turnover and the manipulation of the cellular components of bone turnover in recruitment, activation and apoptosis [7]. Bisphosphonates is one of the drugs that are currently available for postmenopausal osteoporosis by inhibiting bone turnover [8].

Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor-κB ligand (RANKL) [9]. RANKL is a cytokine member of the tumour necrosis factor family that is the principal final mediator of osteoclastic bone resorption [10]. It is the key molecule responsi-

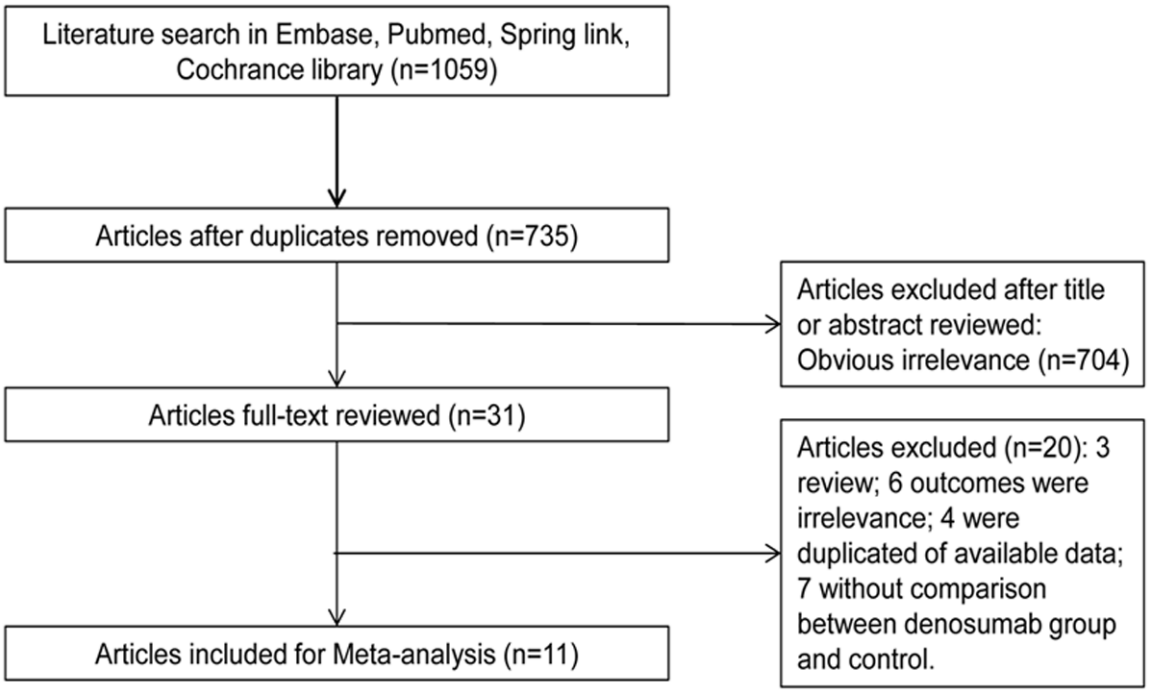


Figure 1. Literature search and study selection.

ble for the bone loss observed in osteoporosis [11]. By binding to RANKL and preventing its binding to the RANK receptors on the surface of osteoclasts and osteoclast precursors, denosumab inhibits the development, activation and survival of osteoclasts [12]. Although denosumab had been recommended as one of the clinical medicines by American Association of Clinical Endocrinologists (AACE) [13], it is lack of large sample size studies to perfectly evaluate the effectiveness and safety of denosumab. Therefore, we performed a meta-analysis to assess the safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density (BMD).

Materials and methods

Search strategy

A systematic literature search without language restriction was conducted up to January, 2014 by using the electronic databases such as PubMed, Embase, Springer link, Cochrane library. The key words included "denosumab", "osteoporosis", "postmenopausal women", and "low bone mineral density". Furthermore, paper literatures were retrieved by manual search. Review articles and reference lists of retrieved articles were also inspected to find additional eligible studies.

Study selection

Studies that met the following criteria were included in the meta-analysis: (1) the studies were randomized controlled trials; (2) the subjects were the postmenopausal women with osteoporosis or low BMD; (3) the studies were designed to compare the safety of denosumab with placebo or bisphosphonates; (4) one of the following risk indicators must be included: any adverse events (AAE), serious adverse event (SAE), SAE related to infection, non-vertebral fracture, neoplasm/cancer and deaths. Studies were excluded if they were (1) animal studies; (2) studies that had unavailable data or lack of enough data; (3) reviews, letters and comments; (4) repeated publication articles.

Data extraction and quality assessment

Two evaluators independently selected studies and extracted data. Discrepancies were resolved by discussion with a third investigator. For each study, the following information was extracted: the first author name, year of publication, region, age of subjects, number of subjects, dosage of denosumab and outcomes.

Table 1. Characteristics of 11 studies included in meta-analysis

Author	Year	length of study (years)	Location	n, age trial mean (SD)	Treatment of trial	n, age control	Treatment of control	lumbar spine BMD T-scores	Outcomes	Jadad Score
Bone	2008	2	North America	166 59.8 (7.4)	60 mg every 6 months	166 58.9 (7.5)	placebo	(-2.5, -1.0)[+]	SAE; AAE; SAE related to infection; Neoplasm; Deaths; Non-vertebral fracture.	4
Cummings	2009	3	multicenter, international	3902 72.3 (5.2)	60 mg every 6 months	3906 72.3 (5.2)	placebo	(-4.0, -2.5)	SAE; SAE related to infection; Neoplasm; Deaths; Non-vertebral fracture.	4
Ellis	2008	2	North America	127 59.7 (9.7)	60 mg every 6 months	125 89.2 (8.9)	placebo	(-2.5, -1.0)	SAE; SAE related to infection; Neoplasm; Deaths.	4
Kumagai	2011	9 months	Japan	30 40-66[*]	0.03, 0.1, 0.3, 1.0, 3.0 mg/kg	10 59.6 (3.1)	placebo	NP	AAE	3
Lewiecki	2007	2	United States	319 62.3 (8.0)	6, 14, 30 mg/ 3 months; 14, 60, 100, 210 mg/6 months	46 63.7 (9.1)	placebo	(-4.0, -1.5)	SAE; SAE related to infection; Neoplasm; Deaths; AAE	4
						47 62.8 (8.2)	Alendronate 70 mg/week			
Nakamura	2012	1	Japan	157 65.2 (6.8)	60 mg every 6 months	55 64.6 (7.0)	placebo	(-4.0, -2.5)	SAE; SAE related to infection; Neoplasm; AAE	4
Seeman	2010	1	multicenter, international	83 60.3 (5.9)	60 mg every 6 months	82 60.8 (5.2)	placebo	(-3.0, -2.0)	AAE; SAE	5
						82 60.7 (5.2)	Alendronate 70 mg/week			
Brown	2009	1	multicenter, international	594 64.1 (8.6)	60 mg every 6 months	595	Alendronate 70 mg/week	≤2.0	SAE; AAE; SAE related to infection; Neoplasm; Non-vertebral fracture.	3
Kendler	2010	1	multicenter, international	253 66.9 (7.8)	60 mg every 6 months	251 68.2 (7.7)	Alendronate 70 mg/week	(-4.0, -2.0)	SAE; AAE; SAE related to infection; Neoplasm; Deaths; Non-vertebral fracture.	5
Recknor	2013	1	United States and Europe	417 67.2 (8.1)	60 mg every 6 months	416 66.2 (7.8)	ibandronate 150 mg/month	(-4.0, -2.0)	AAE; SAE; SAE related to infection; Neoplasm; Non-vertebral fracture; Deaths.	3
Roux	2014	1	multicenter, international	435 67.8 (7.0)	60 mg every 6 months	435 67.7 (6.8)	risedronate 150 mg/month	-2.3 (1.1)[&], -2.2 (1.2)	SAE; AAE; SAE related to infection; Deaths; Non-vertebral fracture.	3

[*]: range of age; [+]: range of lumbar spine BMD T-scores; [&]: mean (SD) of lumbar spine BMD T-scores; AE: adverse events; SAE: Serious adverse events; AAE: any adverse events; NP: not provided.

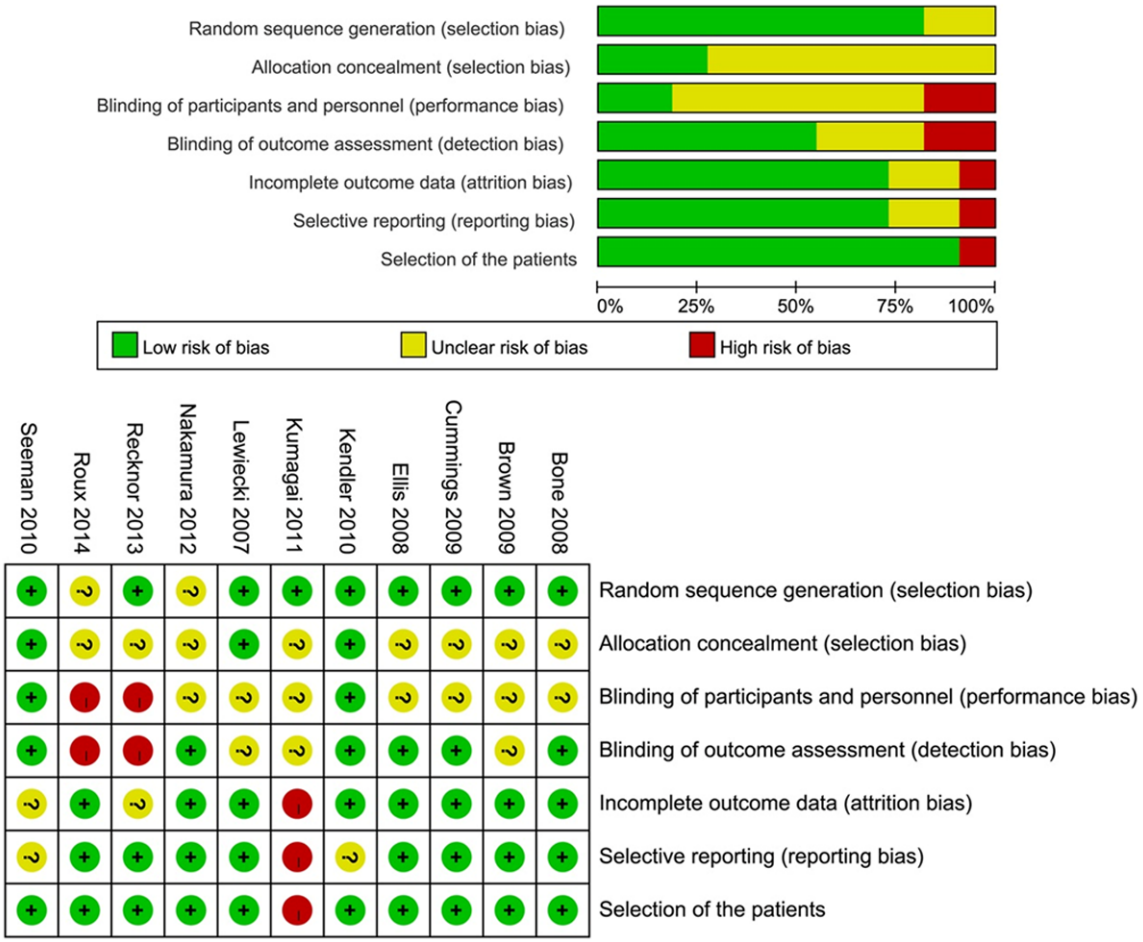


Figure 2. Risk of bias of 11 studies included in meta-analysis.

Study quality was assessed using the 6-item instrument developed by Jadad et al [13]. The studies with the score from 3 to 5 are high quality studies. According to Cochrane Library Handbook [14], risk assessment tool in RevMan 5.1 was used to evaluate the risk of bias in the following factors: random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessment, incomplete data of outcome, selective reporting and so on.

Statistical analysis

The risk indicators of AAE, SAE, SAE related to infection, fractures, neoplasm/cancer and deaths were used to assess the safety of denosumab in the postmenopausal women with osteoporosis or low BMD. Placebo or bisphosphonates were regarded as control. The RevMan 5.1 software was used for statistical analysis and risk ratio (OR) and 95% confidence intervals (CIs) as summary statistics were calculated. Heterogeneity of effect size across studies was assessed by using Cochran's Q and the I^2 statistic [15]. A Random-effects model was applied if there was significant heterogeneity ($p<0.05$, $I^2>50\%$). Otherwise, a fixed-effects model was used. Subgroup analysis was performed by the type of drugs which was used in the control group. Publication bias was observed with the funnel plot. Sensitivity analysis was performed by omitting special studies to test the stability of pooled results.

Result

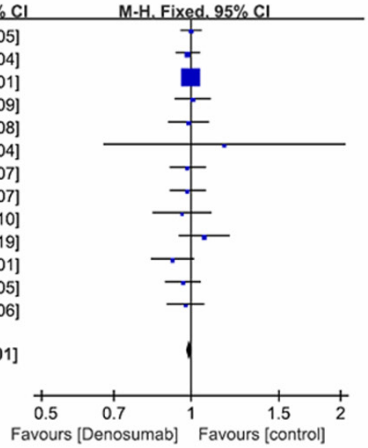
Search results

A total of 1059 potential relevant articles were identified by initial literature research. After removing duplicated articles, 735 literatures were remained. Then, 704 obviously irrelevant literatures were excluded. Finally, 20 literatures

A

Study or Subgroup	Denosumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bone 2008	156	164	157	165	2.9%	1.00 [0.95, 1.05]
Brown 2009	480	593	482	586	8.9%	0.98 [0.93, 1.04]
Cummings 2009	3605	3886	3607	3876	66.3%	1.00 [0.98, 1.01]
Ellis 2008	117	129	108	120	2.1%	1.01 [0.93, 1.09]
Kendler 2010	197	253	196	249	3.6%	0.99 [0.90, 1.08]
Kumagai 2011	21	30	6	10	0.2%	1.17 [0.67, 2.04]
Lewiecki 2007	289	314	43	46	1.4%	0.98 [0.91, 1.07]
Lewiecki 2007	289	314	43	46	1.4%	0.98 [0.91, 1.07]
Nakamura 2012	47	54	49	54	0.9%	0.96 [0.84, 1.10]
Recknor 2013	245	411	230	410	4.2%	1.06 [0.95, 1.19]
Roux 2014	269	429	293	429	5.4%	0.92 [0.83, 1.01]
Seeman 2010	76	83	77	81	1.4%	0.96 [0.89, 1.05]
Seeman 2010	76	83	78	83	1.4%	0.97 [0.89, 1.06]
Total (95% CI)		**6743**		**6155**	**100.0%**	**0.99 [0.98, 1.01]**
Total events	5867		5369			

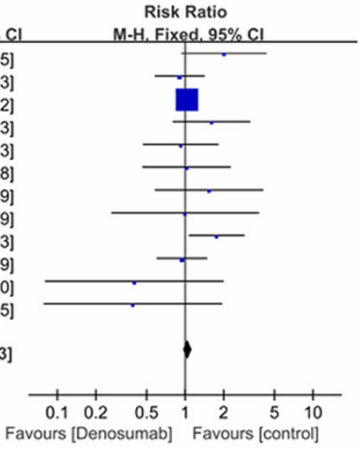
Heterogeneity: Chi² = 5.85, df = 12 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)



B

Study or Subgroup	Denosumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bone 2008	18	164	9	165	0.8%	2.01 [0.93, 4.35]
Brown 2009	34	593	37	586	3.3%	0.91 [0.58, 1.43]
Cummings 2009	1004	3902	972	3906	85.7%	1.03 [0.96, 1.12]
Ellis 2008	19	129	11	120	1.0%	1.61 [0.80, 3.23]
Kendler 2010	15	253	16	249	1.4%	0.92 [0.47, 1.83]
Lewiecki 2007	42	314	6	46	0.9%	1.03 [0.46, 2.28]
Lewiecki 2007	42	314	4	46	0.6%	1.54 [0.58, 4.09]
Nakamura 2012	4	54	4	54	0.4%	1.00 [0.26, 3.79]
Recknor 2013	39	411	22	410	1.9%	1.77 [1.07, 2.93]
Roux 2014	33	429	35	429	3.1%	0.94 [0.60, 1.49]
Seeman 2010	2	83	5	83	0.4%	0.40 [0.08, 2.00]
Seeman 2010	2	83	5	81	0.4%	0.39 [0.08, 1.95]
Total (95% CI)		**6729**		**6175**	**100.0%**	**1.05 [0.98, 1.13]**
Total events	1254		1126			

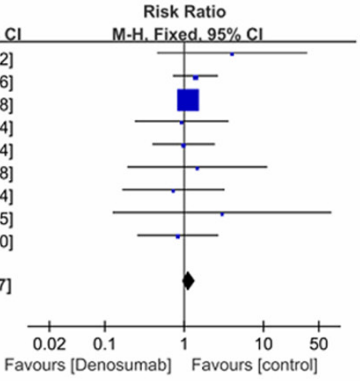
Heterogeneity: Chi² = 12.59, df = 11 (P = 0.32); I² = 13%
Test for overall effect: Z = 1.35 (P = 0.18)



C

Study or Subgroup	Denosumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bone 2008	4	164	1	165	0.5%	4.02 [0.45, 35.62]
Brown 2009	21	593	15	586	7.3%	1.38 [0.72, 2.66]
Cummings 2009	187	3886	166	3876	80.2%	1.12 [0.92, 1.38]
Ellis 2008	4	129	4	120	2.0%	0.93 [0.24, 3.64]
Kendler 2010	9	253	9	249	4.4%	0.98 [0.40, 2.44]
Lewiecki 2007	10	314	1	46	0.8%	1.46 [0.19, 11.18]
Lewiecki 2007	10	314	2	46	1.7%	0.73 [0.17, 3.24]
Nakamura 2012	1	54	0	54	0.2%	3.00 [0.12, 72.05]
Recknor 2013	5	411	6	410	2.9%	0.83 [0.26, 2.70]
Total (95% CI)		**6118**		**5552**	**100.0%**	**1.14 [0.95, 1.37]**
Total events	251		204			

Heterogeneity: Chi² = 2.86, df = 8 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)



D

Study or Subgroup	Denosumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brown 2009	1	593	1	586	1.0%	0.99 [0.06, 15.76]
Cummings 2009	70	3886	90	3876	92.5%	0.78 [0.57, 1.06]
Ellis 2008	1	129	1	120	1.1%	0.93 [0.06, 14.71]
Kendler 2010	1	253	0	249	0.5%	2.95 [0.12, 72.14]
Lewiecki 2007	1	314	0	46	0.9%	0.45 [0.02, 10.83]
Lewiecki 2007	1	314	0	46	0.9%	0.45 [0.02, 10.83]
Recknor 2013	0	411	1	410	1.5%	0.33 [0.01, 8.14]
Roux 2014	0	429	1	429	1.5%	0.33 [0.01, 8.16]
Total (95% CI)		**6329**		**5762**	**100.0%**	**0.77 [0.57, 1.04]**
Total events	75		94			

Heterogeneity: Chi² = 1.48, df = 7 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

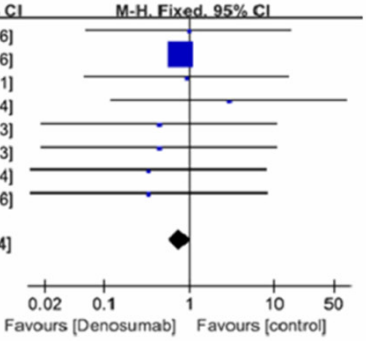


Figure 3. Forest plots of the risk of any adverse events, serious adverse events, neoplasm/cancer and deaths. A: Forest plot of the risk of any adverse events, B: Forest plot of the risk of serious adverse events, C: Forest plots of the risk of neoplasm/cancer, D: Forest plots of deaths.

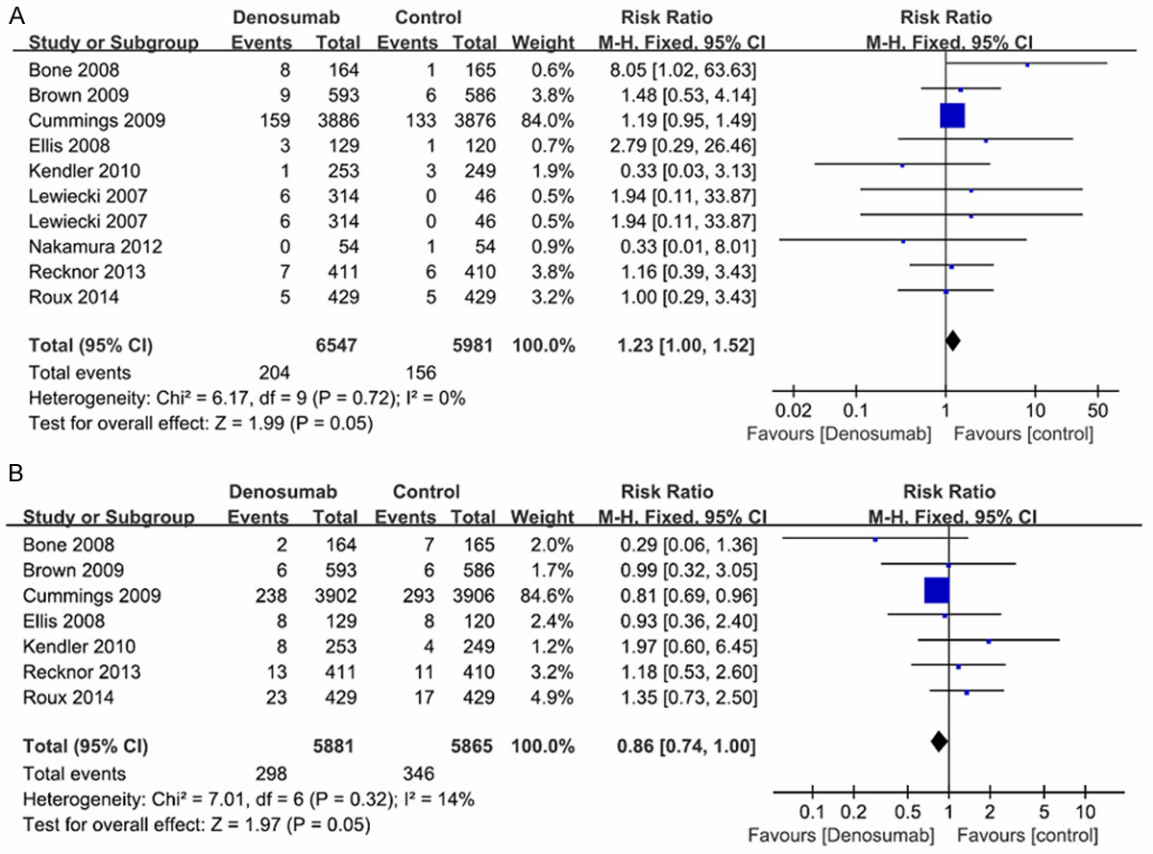


Figure 4. Forest plots of the risk of SAE related to infection and non-vertebral fracture. A: Forest plot of the risk of SAE related to infection, B: Forest plot of the risk of non-vertebral fracture.

were omitted from the remaining 31 literatures. The 20 literatures included three reviews, one animal study, four studies with the same population, six studies without related risk indicators, and seven studies lack of data about the comparison between the denosumab and control group. Finally, based on the included criteria and excluded criteria, 11 literatures [16-26] were included in this meta-analysis. The flow diagram of the search process is shown in **Figure 1**.

Characteristic of included studies

The characteristics of the included studies are summarized in **Table 1**. The included literatures were published from 2007 to 2014 in this meta-analysis. The 11 literatures contained 13 studies. The safety of denosumab was compared to placebo in seven [16, 17, 19-21, 24, 25] out of the thirteen studies with 4390 patients in placebo group and comparison between bisphosphonates and denosumab was shown in the other six studies [18, 20, 22-24, 26] with 4390 patients in bisphosphonates group. Among the patients in all studies, 6483 were assigned to the denosumab group. Length of the follow-up time was from 9 months to 3 years. All the included literatures were high quality studies with the Jadad scores from 3 to 5. Assessment of risk of bias is shown in **Figure 2**. There was no high risk of bias in the studies except the study of Kumagai et al. [19], Recknor et al. [22] and Roux et al. [23].

Comparison of safety

For the six risk indicators, no significant heterogeneity ($p>0.05$, $I^2<50\%$) was detected among the included studies. A fixed-effects model was

Table 2. Summary of subgroup analysis and sensitivity analysis

Outcomes	Overall effect	Sensitivity analysis		Subgroup analysis	
		Method 1	Method 2	Denosumab vs. placebo	Denosumab vs. bisphosphonates
AAE	0.99 (0.98, 1.01)	0.99 (0.96, 1.02)	0.99 (0.98, 1.01)	1.00 (0.99, 1.01)	0.98 (0.95, 1.02)
SAE	1.05 (0.98, 1.13)	1.15 (0.94, 1.41)	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)	1.06 (0.84, 1.34)
SAE related to infection	1.23 (1.00, 1.52)	1.45 (0.87, 2.41)	1.23 (1.00, 1.51)	1.25 (1.00, 1.56)	1.13 (0.63, 2.03)
Neoplasm (Cancer)	1.14 (0.95, 1.37)	1.20 (0.80, 1.81)	1.14 (0.95, 1.38)	1.13 (0.93, 1.38)	1.17 (0.73, 1.87)
Non-vertebral fracture	0.86 (0.74, 1.00)	1.12 (0.78, 1.61)	0.86 (0.74, 1.00)	0.80 (0.68, 0.95)	1.31 (0.87, 1.98)
Deaths	0.77 (0.57, 1.04)	0.72 (0.24, 2.13)	0.78 (0.58, 1.05)	0.77 (0.57, 1.05)	0.72 (0.20, 2.59)

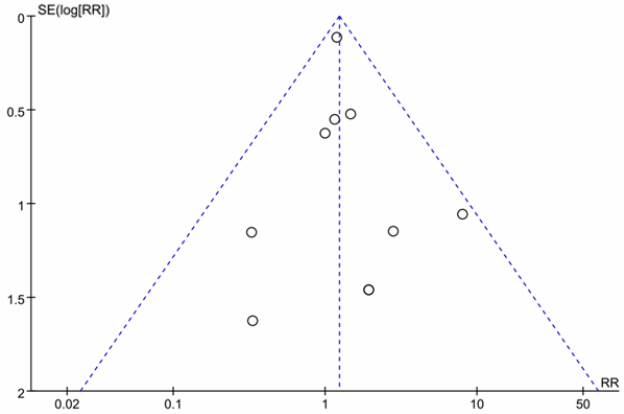


Figure 5. Funnel plot of detection of publication bias.

used to calculate RR and 95% CI. Relevant forest plots are presented in **Figures 3**, **4**. No significant difference between denosumab and control group was demonstrated in AAE (RR=0.99, 95% CI=0.98-1.01, p=0.29), SAE (RR=1.05, 95% CI=0.98-1.13, p=0.18), neoplasm/cancer (RR=1.14, 95% CI=0.95-1.37, p=0.16) and deaths (RR=0.77, 95% CI=0.57-1.04, p=0.09) (**Figure 3**). Subjects assigned to denosumab demonstrated evidence of significant risk of SAE related to infection (RR=1.23, 95% CI=1.00-1.52, p=0.05) when compared to controls. Denosumab treatment significantly decreased the risk of non-vertebral fracture (RR=0.86, 95% CI=0.74-1.00, p=0.05) in the postmenopausal women with osteoporosis or low BMD (**Figure 4**).

Subgroup analysis

In subgroup analysis, the pooled data (AAE: RR=1.00, 95% CI=0.99-1.01; SAE: RR=1.05, 95% CI=0.97-1.13; SAE related to infection: RR=1.25, 95% CI=1.00-1.56; non-vertebral fracture: RR=0.80, 95% CI=0.68-0.95; neoplasm/cancer: RR=1.13, 95% CI=0.93-1.38; deaths: RR=0.77, 95% CI=0.57-1.05) of denosumab vs. placebo showed the consistent results with the overall analysis. The results of denosumab vs. bisphosphonates indicated that there was no evidence to prove the significant differences between denosumab and bisphosphonates group in all the risk indicators (AAE: RR=0.98, 95% CI=0.95-1.02; SAE: RR=1.06, 95% CI=0.84-1.34; SAE related to infection: RR=1.13, 95% CI=0.63-2.03; neoplasm/cancer: RR=1.17, 95% CI=0.73-1.87; non-vertebral fracture: RR=1.31, 95% CI=0.87-1.98; deaths: RR=0.72, 95% CI=0.20-2.59) (**Table 2**).

Sensitivity analysis

Based on the characteristic of the included studies, two methods were used to do sensitivity analysis. First, the study of Cummings et al. [17] was eliminated because of great weight (66.3%~92.5%) (**Figures 3**, **4**). After eliminating the study of Cummings et al., the pooled data showed an inconsistent result with the result of the overall analysis in non-vertebral fracture (RR=1.12, 95% CI=0.78-1.61). The result indicated no significant difference between denosumab and control group. For the other risk indicators (AAE: RR=0.99, 95% CI=0.96-1.02; SAE: RR=1.15, 95% CI=0.94-1.41; SAE related to infection: RR=1.45, 95% CI=0.87-1.41; neoplasm/cancer: RR=1.20, 95% CI=0.80-1.81; deaths: RR=0.72, 95% CI=0.24-2.13), the results were similar with the results of the overall analysis. Second, the study of Kumagai et al. [19] and Lewiecki et al. [20] were omitted to detect the stability of the results. Because multiple doses of denosumab were used in the two studies, while single-dose (60 mg/6 month) was used in the other studies. After omitting the study of Kumagai et al. and Lewiecki et al., the similar results (AAE: RR=0.99, 95% CI=0.98-1.01; SAE: RR=1.05, 95% CI=0.97-1.13; SAE related to infection: RR=1.23, 95%

CI=1.00-1.51; non-vertebral fracture: RR=0.86, 95% CI=0.74-1.00; neoplasm/cancer: RR=1.14, 95% CI=0.95-1.38; deaths: RR=0.78, 95% CI=0.58-1.05) with overall analysis was obtained (**Table 2**).

Statistically similar results with overall analysis were obtained in sensitivity analysis. It evinced the stability of this meta-analysis.

Publication bias

In this meta-analysis, no evidence of publication bias was detected in the risk indicator of SAE related to infection by the funnel plot in **Figure 5**.

Discussion

In this meta-analysis, we pooled data from 11 studies. Based on the results of statistical analysis, we concluded that there was no significant difference in AAE, SAE, neoplasm/cancer and deaths between denosumab and control group. Compared to control group, denosumab treatment increased the risk of SAE related to infection but reduced the risk of non-vertebral fracture. Nevertheless, the increase in the risk of SAE related to infection and the reduction in the risk of non-vertebral fracture were not demonstrated in the results of denosumab vs. bisphosphonates in the subgroup analysis.

At present, the phase III studies of denosumab were carried on [27]. Although many studies reported that denosumab was well tolerated [28-30], there were many potential theoretical safety concerns. A concern regarding the long-term use of denosumab relates to its possible effects on the immune system, increasing the risk of infections and cancer [27, 31]. In this meta-analysis, the result showed the increase in the risk of SAE related to infection. However, no significant effect on the risk of cancer was found. Another theoretical safety concern was that over-suppression of bone remodeling might increase fracture [32]. However, the risk of non-vertebral fracture was reduced when patients were treated by denosumab in this meta-analysis. Further studies need to be done to verify the result of this meta-analysis and explain the reason that why the results were inconsistent with the theoretical speculation.

Bisphosphonates have been widely, efficiently, and safely used for the treatment of osteoporosis [33]. No difference was found between the safety of denosumab and bisphosphonates in this meta-analysis. Thus, denosumab was safe as bisphosphonates in treating osteoporosis.

Anastasilakis et al. [34] reported a similar meta-analysis in 2009. Compared to that one, there were basically three reasons that constitute the primary advantages of this meta-analysis. First, the included studies were updated. Eight studies [17-19, 21-24, 26] that published after 2009 were included. Second, the safety of denosumab was assessed by comparing with placebo in the study of Anastasilakis et al. However, in this meta-analysis, the safety of denosumab was assessed by comparing with placebo or bisphosphonates in the overall analysis, and subgroup-analysis by the type of drugs used in the control group was performed. Third, there was no heterogeneity among the included studies in this meta-analysis.

Some limitations of this meta-analysis should be paid attention to. First, the sample size in the included studies was small except the study of Cummings et al. Thus, the stability and reliability of the result in this meta-analysis need to be verified by large sample studies. Second, the efficacy of denosumab for increasing BMD did not analysis in this meta-analysis due to the limitation of the data in the included studies. The following study need to be done to perfect the study of denosumab.

In conclusion, compared to placebo, denosumab treatment significantly reduced the risk of non-vertebral fracture but increased the risk of SAE related to infection in the postmenopausal women with osteoporosis or low BMD. However, there was no difference between the safety of denosumab and bisphosphonates. Denosumab is a valuable new option for the treatment of postmenopausal osteoporosis in women and may be used as a first-line treatment in future. However, due to the existence of the unstable factors, furthermore studies need to be done to verify the result of this study.

Disclosure of conflict of interest

The authors have declared that no competing interests exist.

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