Systematic Review and Meta-Analysis

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The association of OPG polymorphisms with risk of osteoporotic fractures

A systematic review and meta-analysis

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Abstract

Background: Subjects with low bone mineral density and osteoporosis are more likely to suffer osteoporotic fractures during their lifetime. Polymorphisms in osteoprotegerin (OPG) gene are found to be associated with low bone mineral density and osteoporosis risk but their association with fracture risk is inconclusive. Here, we performed a meta-analysis to investigate the relationship between OPG polymorphisms with susceptibility to osteoporotic fractures.

Methods: Eligible studies investigating the association between common OPG polymorphisms (A164G, T245G, T950C, and G1181C) and risk of osteoporotic fracture were retrieved from PubMed, EMBASE, Web of Science, and the Cochrane Library. Odds ratio (OR) and the 95% confidence interval (CI) were calculated in the allelic, dominant, recessive, and homozygous model. Subgroup analyses of vertebral fractures, Caucasians, and postmenopausal women were also performed.

Results: A total of 14 studies comprising 5459 fracture cases and 9860 non-fracture controls were included. A163G was associated with fracture risk in dominant (OR = 1.29, 95%CI 1.11–1.50), recessive (OR = 1.64, 95%CI 1.10–2.44), and homozygous model (OR = 1.73, 95%CI 1.16–2.59). T245G was significantly correlated with susceptibility to fractures in all genetic models. Subjects with CC genotype of T950C had a reduced risk of fracture compared to those with CT or TT genotypes (OR = 0.81, 95%CI 0.70–0.94, $P = .004$). Subgroup analysis showed that A163G and T245G but not T950C and G1181C were associated with vertebral fracture risk.

Conclusion: OPG A163G and T245G polymorphisms were risk factors of osteoporotic fractures while T950C had a protective role. These polymorphisms can be used as predictive markers of fractures.

Abbreviations: 95%CI = 95% confidence interval, BMD = bone mineral density, NOS = Newcastle–Ottawa Scale, OPG = osteoprotegerin, OR = odds ratio, RANK = receptor activator of NF-κB.

Keywords: meta-analysis, osteoporosis, osteoporotic fracture, osteoprotegerin, polymorphism

1. Introduction

Osteoporotic fracture, also known as low- or non-trauma fracture or fragility fracture, occurs mostly in women and the elderly, especially in postmenopausal women who had a high risk of low bone mineral density (BMD) and osteoporosis.[1] The fractures are associated with an increasing rate of morbidity and mortality, and impair the self-care ability of affected individuals,[2] thus causing tremendous economic burden to families and the healthcare systems.[3,4] Markers predicting osteoporotic fractures will help identify high-risk populations and make a strategy to prevent the occurrence of fractures.

Numerous factors, including female sex, old age, low BMD, and genetic determinants, may confer risk to fractures.[5] Recent genome-wide association studies and meta-analysis of genome-wide association studies have identified multiple susceptibility loci to vertebral fracture or all osteoporotic fractures, including osteoprotegerin (OPG), lipoprotein-receptor-related protein 5 (LRP5), MDS and EVI1 complex locus, rs10190845 on chromosome 2q13 and SVIL (supervillin).[6–12]

OPG (also termed TNFRSF11B), encoding a soluble receptor for RANK (receptor activator of NF-κB), inhibits osteoclast formation and bone resorption by interrupting the interaction between RANK and RANKL.[13] Four polymorphisms of OPG, including A164G, T245G, and T950C in the promoter region and G1181C (Lys3Asn) in exon 1, were widely investigated for association with bone-related traits.[14,15] These polymorphisms have been found in association with BMD in postmenopausal women[16] and the risk of osteoporosis.[17,18] Although subjects

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JD and CZ contributed equally to this work.

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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with low BMD and osteoporosis are prone to fractures, the association between these OPG polymorphisms and susceptibility to osteoporotic fractures is still inconclusive.[19–21] The inconsistent results may be caused by differences in sample size, population, study design, and fracture location. Therefore, we performed a meta-analysis to comprehensively investigate the genetic association of these 4 common OPG polymorphisms with osteoporotic fracture risk.

2. Materials and methods

2.1. Search strategy

The meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Candidate articles investigating the association between OPG polymorphisms and osteoporotic fracture risk were searched from PubMed, EMBASE, Web of Science, and the Cochrane Library from inception to April 30, 2021. The following searching terms were used: (osteoprotegerin or OPG or TNFRSF11B) and fracture. The language was restricted to English. Additional eligible studies were obtained from the reference lists of reviews, meta-analyses, and candidate articles. Since this was a meta-analysis synthesizing published data, ethical approval and patient consent were not required.

2.2. Inclusion/exclusion criteria

Eligible studies should meet the following criteria: (1) at least 1 of the 4 common OPG polymorphisms (A1635G, T245G, T950C, and G1181C) were investigated; (2) cases were diagnosed with an osteoporotic fracture, that is, non- or low-traumatic fracture, by radiographic methods; and (3) studies provided sufficient genotyping data to estimate the strength of genetic association. If 2 or more studies had overlapped samples, only the 1 with the largest sample size was included. Reviews, meta-analyses, case reports, and studies without sufficient genotype data to calculate the effect size were excluded.

2.3. Quality assessment and data extraction of eligible studies

We used the Newcastle–Ottawa Scale (NOS),[22] a quality assessment tool comprising selection, comparability, and exposure domains, to evaluate the quality of included studies. The total score of NOS is 9, and studies with $\leq$4, 5–6, and $\geq$7 scores were considered of low, moderate, and high quality, respectively.

We extracted the following information of each study: first author, publication year, country, ethnicity, fracture location, sample size and mean age of each group, source of control, percent of female, genotyping method, and genotype data of each polymorphism.

Two independent researchers performed literature search and filtering, quality assessment, and data extraction. For each procedure, an agreement was reached by further discussion if discrepancies occurred.

2.4. Statistical analysis

All the analyses were performed using STATA 11.0 (Stata Corporation, College Station, TX, USA). The between-study heterogeneity was assessed by I^2 and Q test. An $I^2 < 50\%$ and P value for Q test $>.10$ indicate low-to-moderate heterogeneity and the fixed effect model will be used for pooling analysis. Otherwise, the random effect model will be used. The strength of genetic association was estimated by calculating the odds ratio (OR) and the corresponding 95% confidence interval (CI). The association was evaluated under different genetic models: (1) allelic model, that is, variant allele vs wildtype allele; (2) dominant model, that is, heterozygous/homozygous variant genotype vs homozygous wildtype genotype; (3) recessive model, that is, homozygous variant genotype vs heterozygous/homozygous wildtype genotype; and (4) homozygous model, that is, homozygous variant genotype vs homozygous wildtype genotype.

Since fractures may occur in various locations including the spine, hip, and wrist, we analyzed the risk of total fractures and performed a separate analysis of vertebral fracture risk. Subgroup analysis regarding ethnicity, source of control and menopausal status, and sensitivity analysis assessing the stableness of pooled results by omitting 1 study each time were conducted. Publication bias was evaluated by viewing the symmetry of the funnel plot and Egger test. $P < .05$ was considered statistically significant.

3. Results

3.1. Overall description of eligible studies

According to the search strategy and filtering criteria (Fig. 1), a total of 14 studies comprising 5459 fracture cases and 9860 non-fracture controls were included in the final quantitative synthesis.[19–21,23–33] The associations of A163G, T245G, T950C, and G1181C with total fractures risk were investigated in 10, 7, 5, and 8 studies, respectively. Eight studied only recruited postmenopausal women, and 11 studies were performed in Caucasians. The controls were enrolled from populations and hospitals in 8 and 6 studies, respectively. In addition, 3 studies only reported vertebral fracture and 4 studies provided genotype data of vertebral fracture subgroup. Thus, 7 studies involving 991 cases and 7434 controls were eligible for quantitative analysis of vertebral fracture risk. All studies had 5 or more NOS scores and were considered of moderate-to-high

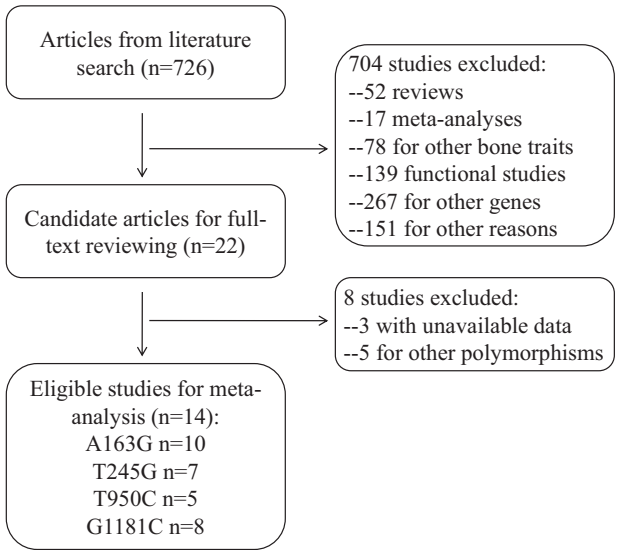

Figure 1. Flowchart of literature search.

Table 1

Characteristics of included studies in the meta-analysis.

Author	Publication year	Country	Fracture location	Sample size (case/control)	Source of control	Percent of female (%)	Genotyping method	Polymorphism
Langdahl et al	2002	Denmark	Vertebral	268/289	PB	79.3	PCR-RFLP	A163G, T245G, T950C, G1181C
Brandstrom et al	2004	Sweden	Hip, wrist, vertebral	361/497	PB	100	PCR-RFLP	T950C
Jorgensen et al	2004	Denmark	Lower forearm, hip	107/206	PB	100	PCR-RFLP	A163G
Ueland et al	2007	Australia	NA	259/1074	HB	100	MALDI-TOF	A163G, T950C, G1181C
Moffett et al	2008	United States	Hip, wrist, vertebral	2572/3565	PB	100	AS-PCR	G1181C
Dincel et al	2008	Turkey	Hip	21/21	HB	NA	AS-PCR	T245G
Piedra et al	2011	Spain	NA	73/225	HB	15.1	Sequencing	A163G, T245G, G1181C
Wang et al	2012	China	Hip, wrist, vertebral	1094/2386	PB	100	MALDI-TOF	T950C
Boronova et al	2015	Slovakia	Vertebral, non-vertebral	48/279	HB	100	TaqMan	A163G, T245G, G1181C
Bonfa et al	2015	Brazil	Vertebral	64/147	HB	100	TaqMan	A163G, T245G, G1181C
Krajcovicova et al	2015	Slovakia	Vertebral, radius	80/204	PB	100	PCR-RFLP	A163G
Pereira et al	2016	Brazil	Vertebral	262/538	PB	62.1	TaqMan	A163G, T245G, G1181C
Sheng et al	2017	China	NA	125/291	PB	100	TaqMan	A163G, G1181C, T950C
Wu et al	2019	China	NA	125/138	HB	80.2	PCR-RFLP	A163G, T245G

AS-PCR = allele-specific PCR, HB = hospital-based, MALDI-TOF = matrix-assisted laser desorption ionization-time of flight, NA = data not available, PB = population-based, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.

quality. The control groups of all studies conformed to Hardy–Weinberg equilibrium. The characteristics of all eligible studies were summarized in Table 1.

3.2. Total fractures

As shown in Table 2, A163G and T245G were significantly associated with the risk of total fractures. A163G polymorphism was associated with fracture risk in dominant (OR = 1.29, 95%CI: 1.11–1.50, $P = .001$), recessive (OR = 1.64, 95%CI: 1.10–2.44, $P = .016$), and homozygous models (OR = 1.73, 95%CI: 1.16–2.59, $P = .007$), respectively (Fig. 2). Meanwhile, the G allele or GG genotype of T245G polymorphism conferred higher fracture risk in all genetic models (OR: 1.67–3.55, $P < .05$, Fig. 3).

We found a protective role of T950C in the recessive model that CC genotype reduced the fracture risk when compared to CC/TT genotype (OR = 0.81, 95%CI: 0.70–0.94, $P = .004$), but not in the other models. As for G1181C, there was no significant association observed in any genetic model ($P > .05$).

3.3. Vertebral fracture

Similar to those of total fractures, we found positive associations between A163G and T245G polymorphisms with risk of vertebral fracture using fixed-effect model (Table 3). Carriers of the variant alleles or genotypes of both polymorphisms were more likely to develop vertebral fracture with ORs ranging from 1.30 to 1.85 for A163G and 1.51 to 3.07 for T245G. However,

Table 2

Association between OPG polymorphisms and risk of total fractures.

Polymorphism	No. of study	Heterogeneity		Effect size		
		I^2 (%)	*P*	OR	95%CI	*P*
A163G (rs3102735)						
G vs A	9	44.3	.073	1.19	0.99–1.43	.060
GG/GA vs AA	9	16.2	.298	1.29	1.11–1.50	.001
GG vs GA/AA	8	0	.630	1.64	1.10–2.44	.016
GG vs AA	8	0	.580	1.73	1.16–2.59	.007
T245G (rs3134069)						
G vs T	6	67.5	.009	1.67	1.04–2.70	.035
GG/GT vs TT	6	52.0	.064	1.69	1.17–2.44	.006
GG vs GT/TT	6	40.1	.138	2.15	1.02–4.55	.045
GG vs TT	5	8.3	.359	3.55	1.53–8.22	.003
T950C (rs2073617)						
C vs T	5	0	.701	1.03	0.96–1.12	.381
CC/CT vs TT	4	57.9	.068	1.15	0.93–1.43	.196
CC vs CT/TT	4	31.5	.223	0.81	0.70–0.94	.004
CC vs TT	4	0	.964	0.93	0.79–1.10	.399
G1181C (rs2073618)						
C vs G	7	20.8	.271	1.02	0.96–1.08	.508
CC/CG vs GG	7	0	.792	0.98	0.88–1.08	.649
CC vs CG/GG	6	59.6	.030	0.97	0.78–1.22	.800
CC vs GG	6	0	.914	1.05	0.93–1.19	.428

CI = 95% confidence interval, OR = odds ratio, OPG = osteoprotegerin.

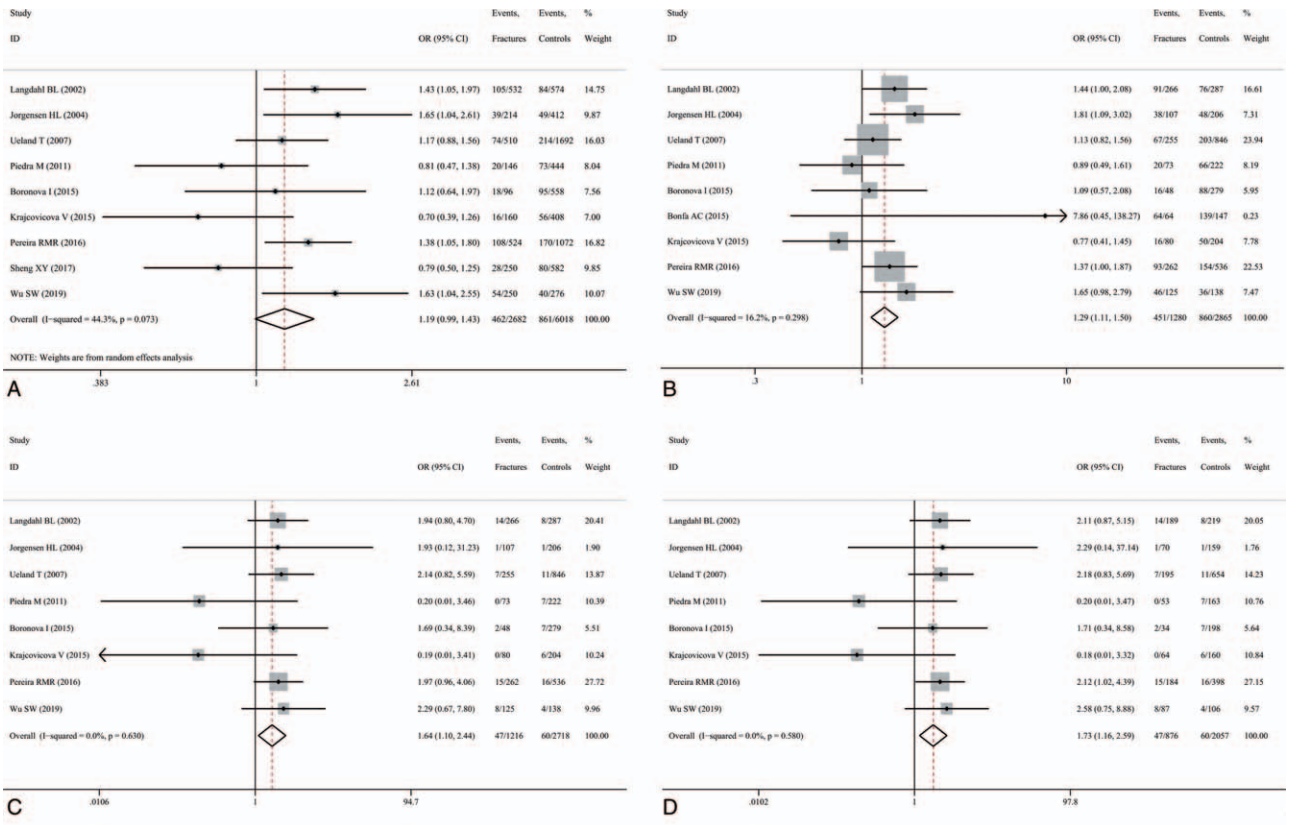

Figure 2. Forest plots of the meta-analysis of A163G in association with osteoporosis fracture risk in all genetic models. (A) Allelic model: G vs A; (B) dominant model: GG/GA vs AA; (C) recessive model: GG vs GA/AA; and (D) homozygous model: GG vs AA.

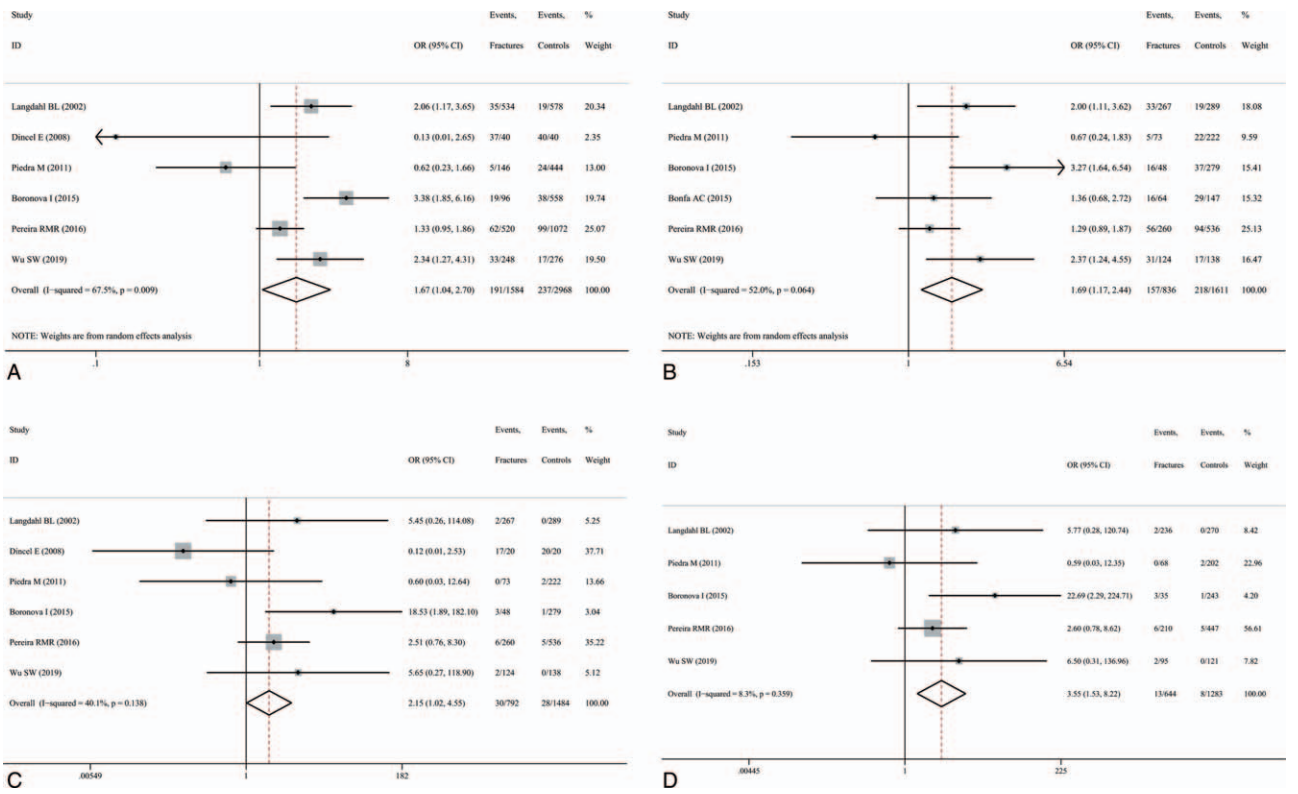

Figure 3. Forest plots of the meta-analysis of T245G in association with osteoporosis fracture risk in all genetic models. (A) Allelic model: G vs T; (B) dominant model: GG/GT vs TT; (C) recessive model: GG vs GT/TT; and (D) homozygous model: GG vs TT.

Table 3

Association between OPG polymorphisms and risk of vertebral fracture.

Polymorphism	No. of study	Heterogeneity		Effect size		
		I^2 (%)	*P*	OR	95%CI	*P*
A163G (rs3102735)						
G vs A	4	24.9	.262	1.30	1.08–1.58	.006
GG/GA vs AA	5	2.0	.395	1.33	1.07–1.65	.010
GG vs GA/AA	4	0	.485	1.74	1.03–2.92	.037
GG vs AA	4	0	.470	1.85	1.10–3.11	.021
T245G (rs3134069)						
G vs T	3	38.0	.199	1.56	1.18–2.05	.002
GG/GT vs TT	4	28.7	.240	1.51	1.15–2.00	.003
GG vs GT/TT	3	0	.895	2.88	1.02–8.13	.046
GG vs TT	3	0	.875	3.07	1.08–8.75	.036
T950C (rs2073617)						
C vs T	2	0	.388	0.89	0.72–1.11	.318
CC/CT vs TT	2	0	.952	1.06	0.74–1.53	.736
CC vs CT/TT	2	52.2	.148	0.50	0.13–1.90	.310
CC vs TT	2	33.8	.219	0.79	0.50–1.24	.306
G1181C (rs2073618)						
C vs G	4	0	.523	0.99	0.89–1.12	.967
CC/CG vs GG	5	0	.569	1.02	0.86–1.22	.793
CC vs CG/GG	4	67.3	.027	0.96	0.66–1.40	.835
CC vs GG	4	0	.617	1.03	0.82–1.29	.806

CI = 95% confidence interval, OR = odds ratio, OPG = osteoprotegerin.

no significant relationships of T950C or G1181C with vertebral fracture risk were observed.

3.4. Subgroups analysis

Subgroups with 3 or more eligible studies were analyzed and the results were shown in Table 4. In Caucasians, we found significant associations of A163G in all genetic models and T245G in dominant and homozygous models with fracture risk. In postmenopausal women, no significant associations were identified except G1181C, of which CC genotype conferred a higher risk of total fractures in comparison with GC/GG genotype (OR = 1.18, 95%CI: 1.06–1.30, $P = .002$).

3.5. Sensitivity analysis

Sensitivity analysis showed that the associations of T950C and G1181C with total fractures risk may be influenced by a single study. When we excluded the study from Wang et al,[19] CC genotype of T950C, compared to CC/CT genotype, was no longer associated with reduced fracture risk (OR = 0.91, 95%CI 0.75–1.10, $P = .344$, $I^2 = 0$). On the other side, the association between G1181C and total fractures risk became significant in

Table 4

Subgroup analysis of OPG polymorphisms associated with total fracture risk.

Subgroup*	Allelic model		Dominant model		Recessive model		Homozygous model	
	I^2 (%)	OR (95%CI)	I^2 (%)	OR (95%CI)	I^2 (%)	OR (95%CI)	I^2 (%)	OR (95%CI)
Caucasians								
A163G	35.7	**1.24 (1.08–1.42)**	18.5	**1.26 (1.07–1.48)**	0	**1.57 (1.02–2.40)**	0	**1.64 (1.07–2.52)**
T245G	71.6	1.51 (0.84–2.72)	55.2	**1.58 (1.04–2.40)**	49.1	2.19 (0.50–9.57)	29.1	**3.30 (1.37–7.93)**
T950C	0	0.97 (0.87–1.09)	0	1.02 (0.84–1.24)	0	0.91 (0.75–1.10)	0	0.95 (0.75–1.20)
G1181C	0	1.03 (0.97–1.10)	0	0.98 (0.88–1.08)	59.6	0.97 (0.78–1.22)	0	1.05 (0.93–1.19)
Hospital-based								
A163G	23.4	1.18 (0.96–1.44)	6.1	1.20 (0.95–1.51)	0	1.61 (0.86–3.02)	0	1.68 (0.89–3.15)
T245G	74.4	1.50 (0.61–3.70)	61.6	1.75 (0.96–3.19)	61.9	1.89 (0.19–18.69)	45.6	**4.56 (1.25–16.66)**
G1181C	9.0	1.03 (0.88–1.21)	0	1.05 (0.82–1.34)	0	1.04 (0.80–1.34)	0	1.05 (0.76–1.44)
Population-based								
A163G	60.9	1.18 (0.89–1.57)	32.0	**1.36 (1.11–1.67)**	0	1.66 (0.99–2.78)	0	**1.77 (1.05–2.98)**
T950C	0	1.04 (0.96–1.13)	47.7	**1.31 (1.15–1.49)**	13.8	**0.77 (0.65–0.90)**	0	0.92 (0.77–1.11)
G1181C	59.2	0.91 (0.76–1.10)	0	0.96 (0.85–1.08)	82.3	0.87 (0.53–1.43)	0	1.05 (0.91–1.20)
Postmenopausal women								
A163G	46.7	1.09 (0.90–1.31)	34.7	1.17 (0.93–1.48)	0	1.42 (0.68–2.93)	0	1.44 (0.69–2.98)
T950C	0	1.05 (0.97–1.13)	68.9	1.16 (0.89–1.51)	53.0	0.85 (0.67–1.07)	0	0.94 (0.79–1.13)
G1181C	47.2	1.03 (0.97–1.10)	0	0.94 (0.84–1.06)	0	**1.18 (1.06–1.30)**	0	1.07 (0.94–1.22)

CI = 95% confidence interval, OR = odds ratio, OPG = osteoprotegerin.

* Subgroups with 3 or more eligible studies were analyzed. Pooled odds ratios with *P* value <.05 were in bold.

the recessive model (OR = 1.16, 95%CI 1.05–1.28, $P = .004$, $I^2 = 0$) after omitting Langdahl et al study.[21]

3.6. Publication bias

The funnel plots of A163G polymorphism in recessive and homozygous models were asymmetric, and Egger test suggested potential publication bias ($P = .040$ and .046, respectively). For the other comparisons, there was no obvious evidence of publication bias.

4. Discussion

The present meta-analysis, involving 14 studies with 5459 fracture cases and 9860 non-fracture controls, identified significant associations of A163G, T245G, and T950C, but not G1181C, of OPG with risk of osteoporotic fractures. We also found that A163G and T245G were potential markers for vertebral fracture risk.

The balance of bone absorption, which is mainly driven by osteoclast, is critical for bone remodeling. Aberrant bone absorption may lead to osteoporosis or osteopetrosis, 2 opposite phenotypes featured by abnormally reduced and increased BMD, respectively. The formation, survival, and activation of osteoclast are regulated by the interaction between RANK, expressed by osteoclast precursors, and its ligand RANKL expressed by osteoblast.[34,35] However, the interaction can be inhibited by a soluble decoy receptor, encoded by OPG, resulting in osteoclast deficiency and diminished bone absorption.[13] RANK knock-out or OPG over-expressing mice both develop osteopetrosis due to the absence of osteoclasts.[13,36] Therefore, the OPG/RANK/RANKL signaling, a pivotal pathway for osteoclastogenesis, may be involved in the biological mechanism of bone-related traits, including BMD, osteoporosis, and osteoporotic fractures.[5]

In the present meta-analysis, we found significant associations of A163G and T245G polymorphisms in the promoter region of the OPG gene with osteoporotic fracture risk. This is in line with previous findings that both polymorphisms were associated with susceptibility to osteoporosis, the main risk factor of non-trauma fracture.[18] Both A163G and T245G polymorphisms are located in the promoter region that may modulate the OPG expression. It was found that the transcript with the G allele of T245G had a decreased expression of OPG,[37] leading to enhanced bone absorption and development of osteoporosis.

T950C, another promoter variant, may alter OPG expression that C allele had a higher expression level in vitro.[38,39] Previous meta-analyses demonstrated that CC genotype was associated with higher lumbar spine BMD in postmenopausal women[16] and decreased risk to develop osteoporosis in the Chinese population.[40] However, none of the included studies in the present study[19,21,24,31,33] reported a significant association with fracture risk. By pooling these studies together, we found carriers of CC genotype of T950C had a reduced risk of fracture (OR = 0.81, $P = .004$) compared to those of CT or TT genotypes. These results implied that CC genotype of T950C may be a protective factor for bone-related traits.

G1181C is located in the 1st exon of OPG and causes an amino acid substitution from lysine to asparagine. There were significant associations of CC genotype with higher BMD[41] and lower risk of osteoporosis.[18] Langdahl et al firstly reported a different genotype distribution of G1181C and a lower frequency of CC genotype in osteoporotic fracture individuals than normal controls.[21] Yet, this association was not successfully replicated in the other studies.[20,29,31] Our meta-analysis failed in finding associations of G1181C with fracture risk in the overall population, but observed an increased risk (OR = 1.18, 95%CI 1.06–1.30) in postmenopausal women carrying CC genotype. This result was similar to that of Sheng et al study, which reported C allele increasing fracture risk in postmenopausal women.[24] Nevertheless, the contradictory associations of G1181C with BMD, osteoporosis, and fracture need further investigation.

Vertebral fracture is the most common form of osteoporotic fracture, having an increasing incidence with age.[42] Thus, we performed a subgroup analysis focusing on vertebral fractures. Similar to the results with respect to total fractures, only A163G and T245G were found to be significantly associated with the risk of vertebral fracture. Another subgroup analysis showed that A163G and T245G were susceptibility loci of fractures in Caucasians, while no enough studies from the Asians were available for pooling analysis. In the analysis of postmenopausal at high risk of osteoporosis and fractures, we surprisingly found no association between A163G and fracture risk.

Our analysis demonstrated that A163G and T245G polymorphisms were risk factors of osteoporotic fractures while T950C exerted a protected role in preventing the occurrence of fractures. These polymorphisms may help identify high-risk subjects suffering fractures by whom early preventive measures are needed. However, the association between OPG polymorphisms and fracture risk is discordant with that between serum levels of circulating OPG and fracture risk. In a prospective study with 8-year follow-ups, males in the highest quantile of serum OPG levels had 2-fold or more risk than those in lower quantiles.[43] In elderly women, high OPG levels were linked to higher hip fracture risk.[44,45] Cell line experiments demonstrated that risk alleles of A163G and T245G had reduced OPG expression and protective allele of T950C had increased expression, which is in line with the biological role of OPG.[37–39] Whereas, the predictive role of serum OPG levels is contradictory with the biological role. It was assumed that the increased levels of serum OPG were not a reflection of endogenous expression but secondary to the response to the decay of bone structure compromising bone strength.[43] Taken together, the predictive role of OPG polymorphisms, alone or together with circulating OPG levels, needs verification in large-scale, prospective-designed cohort studies in the future.

Our meta-analysis has some limitations. Firstly, fractures occur in multiple locations, which may influence the genetic associations. We only analyzed the susceptibility to total and vertebral fractures, but not to hip and forearm fractures. Secondly, the studies included in our analysis were mostly from Caucasians, and subgroup analysis was impossible for the other populations. Therefore, more studies reporting different fracture locations or from various populations are needed in the future.

5. Conclusions

Overall, the present meta-analysis demonstrated that the OPG protomer polymorphisms (A163G, T245G, and T950C) are associated with fracture risk and can be promising biomarkers of osteoporotic fractures.

Author contributions

Conceptualization: Jianfeng Ding.

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Formal analysis: Chongyang Zhang, Yuning Guo, Jianfeng Ding.
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Supervision: Jianfeng Ding.
Writing – orginal draft: Jianfeng Ding, Chongyang Zhang.
Writing – review & editing: Chongyang Zhang, Yuning Guo, Jianfeng Ding.

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