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Original Article

Association between osteoprotegerin gene A163G polymorphism and osteoporosis risk: a pooled analysis based on different populations

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Abstract: Background: Many studies have analyzed the association between osteoprotegerin (OPG) gene A163G polymorphism and osteoporosis risk, however, the results have been inconsistent. This meta-analysis updates and reevaluates possible associations between OPG A163G polymorphism and susceptibility to osteoporosis based on different populations. Methods: Five databases involving PubMed, Embase, Web of Science, the Cochrane Library, and CNKI were used for literature searching up to April 2018. The association between OPG A163G polymorphism and osteoporosis was evaluated by calculating pooled odds ratios (ORs) and 95% confidence intervals (CIs). Results: A total of eleven studies including 1476 osteoporosis cases and 1672 controls were screened out. In the overall population, the A163G polymorphism was associated with an increased risk of osteoporosis in the dominant model (GG+AG vs. AA: OR = 1.41, 95% CI: 1.11-1.80). Further subgroup analyses based on ethnicity and subject type suggested that the A163G polymorphism was associated with an increased osteoporosis risk in Caucasians and postmenopausal women. Conclusions: Our study provides additional evidence supporting the hypothesis that the OPG A163G polymorphism increases osteoporosis risk, especially in Caucasians and postmenopausal women.

Keywords: Meta-analysis, osteoprotegerin (OPG) gene, polymorphism, osteoporosis

Introduction

Osteoporosis is characterized by a combination of low bone mass and deteriorated microarchitecture of the bone [1]. It affects hundreds of millions of patients around the world and is becoming a major economic burden on families and societies [2]. According to statistics, the risk of osteoporosis for an individual increases with age and is higher in women than in men, with 30% of women and 12% of men suffering from osteoporosis at some point during their lifetime [3]. Bone mass is determined by interaction of genetic, metabolic, and environmental factors. Genetic factors have been shown to be responsible for 40-75% of the inter-individual variation [4]. One of the most widely studied candidate genes for osteoporosis, the osteoprotegerin (OPG) gene, also named tumor necrosis factor receptor superfamily, member 11b (TNFRSF11B), is the gene encoding OPG and spans 29 kb on chromosome 8q24.2 [5]. Functional studies have shown that the polymorphisms of the OPG gene are associated with the biomechanical properties of bone [6].

Among OPG genetic polymorphisms, A163G (rs3102735) was the most studied loci in relation to osteoporosis risk. Langdahl et al. reported that rare alleles of A163G were significantly more common among patients with vertebral fractures. Subsequently, a large number of epidemiological studies have been carried out to evaluate the association between OPG-A163G polymorphisms and individual susceptibility to osteoporosis in different populations. However, the relationship is still poorly understood. These different results might have been caused by racial and regional differences in the studied patients, as well as by the limitation of the number of patients per study. Whether the association differs between populations from different ethnic backgrounds remains unknown. We therefore undertook a meta-analysis to quantitatively clarify the relationship between OPG-A163G and osteoporosis risk based on different populations.

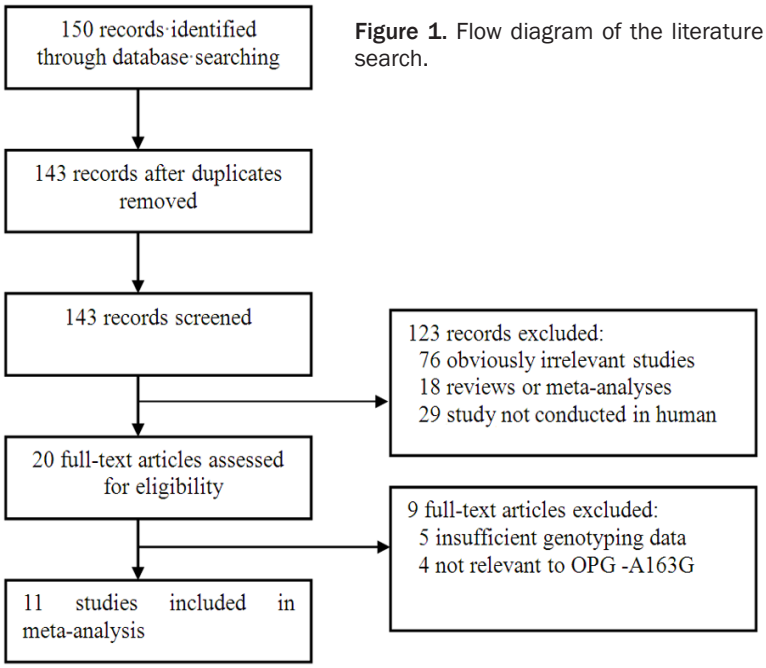

Figure 1. Flow diagram of the literature search.

Materials and methods

Identification and selection of studies

All eligible literatures that assessed the relation between OPG-A163G polymorphism and osteoporosis published before April 2018 were considered in this study. Five databases involving PubMed, Embase, Web of Science, the Cochrane Library, and CNKI were used for literature searching. A combination of keywords ("OPG" or "osteoprotegerin" or "TNFRSF11B") AND ("osteoporosis" or "bone loss" or "bone mineral density") AND ("genetic polymorphism" or "single-nucleotide polymorphism") was used. Additionally, attention was paid to the relevant references to acquire the most comprehensive studies.

Inclusion criteria: (1) studies using a case-control design describing the relation between OPG-A163G polymorphism and osteoporosis, (2) studies with sufficient genetypes data in participants, (3) all patients met the diagnostic criteria for osteoporosis. The exclusion criteria were defined as follows: (1) overlapped literatures, (2) unextractable data, (3) study design is not a case-control study, (4) abstract or reviews.

Data extraction

Two investigators screened the potentially relevant studies and extracted the following crucial data: first author's name, publication year, ethnicity, subject type, sample size, and available genotype information from OPG-A163G polymorphism. Subject type was stratified to 'men and women' or 'postmenopausal women'. The titles and abstracts were reviewed for each retrieved document and then the full articles were read if the titles and abstracts could not determine whether it is appropriate. Different data from the two investigators were judged with a discussion and then reached agreement.

Statistical analysis

The odds ratios (ORs) and 95% confidence intervals (CIs) were generated for OPG-A163G polymorphism and osteoporosis risk. The model of G versus A, GG versus AA, GG versus (AG+AA) and (GG+AG) versus AA were examined with the osteoporosis risk, respectively. Heterogeneity of pooled results as well as Hardy-Weinberg equilibrium (HWE) in controls was assessed by I-squared statistic based on Q-test. The random-effects model was applied to estimate the pooled ORs when $P_{heterogeneity} < 0.1$ or $I^2 > 50\%$; otherwise, the fixed-effects model was adopted. The statistical test of the whole calculated ORs was evaluated by Z-test. Both fixed-effects and random-effects model for each pooled ORs were computed to assess the sensitivity analysis results. Possible publication bias was evaluated by Egger's test. All statistical analysis was done with Stata version 12 (StataCorp LP, College Station, TX), and a statistical test with a *p*-value less than 0.05 was considered significant.

Results

Research characteristics

One hundred and fifty publications which assessed the relationship between OPG polymorphisms and osteoporosis were identified. In total, eleven studies [7-17] were used in this report, which met our inclusion criteria. The publication year of included studies ranged

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

References	Country	Ethnicity	Subject type	Case number	Control number	Cases			Controls			HWE	
						AA	AG	GG	AA	AG	GG	χ^2	P
Langdahl 2002	Denmark	Caucasian	Men and women	266	287	175	77	14	211	68	8	0.77	0.381
Wu 2006	China	Asian	Postmenopausal women	73	61	12	37	24	10	22	29	2.47	0.116
Hsu 2006	China	Asian	Men and women	285	290	216	65	4	206	71	13	4.25	0.039
Geng 2008	China	Asian	Postmenopausal women	186	214	18	66	102	34	102	78	0.00	0.946
Shui 2008	China	Asian	Men and women	104	208	64	12	28	143	23	42	105.03	0.000
Seremak 2009	Poland	Caucasian	Postmenopausal women	139	64	101	37	1	51	12	1	0.09	0.764
Brambila 2012	Mexico	Caucasian	Men and women	41	30	23	13	5	21	8	1	0.05	0.827
Hussien 2013	Egypt	African	Postmenopausal women	150	150	84	42	24	111	36	3	0.00	0.968
Cvijetic 2016	Croatia	Caucasian	Postmenopausal women	20	58	2	11	7	1	17	40	0.28	0.594
Mydlárová 2017	Slovakia	Caucasian	Postmenopausal women	105	104	68	37	0	77	24	3	0.44	0.506
Jørgensen 2004	Denmark	Caucasian	Postmenopausal women	107	206	69	38		158	48		-	-

Table 2. Association of the OPG-A163G polymorphism and osteoporosis susceptibility

Analysis model		n	OR_r (95% CI)	OR_f (95% CI)	P_h
G vs. A	Total analysis	10	1.16 (0.58-2.31)	1.59 (1.29-1.95)	0.000
	Asian	4	0.99 (0.45-2.18)	1.29 (1.00-1.65)	0.000
	Caucasian	5	0.66 (0.15-2.88)	1.30 (0.81-2.09)	0.001
	Men and women	4	1.30 (0.53-3.16)	1.28 (0.96-1.72)	0.000
	Postmenopausal women	6	0.89 (0.27-2.99)	1.97 (1.46-2.67)	0.000
GG vs. AA	Total analysis	10	1.26 (0.63-2.53)	1.59 (1.18-2.12)	0.000
	Asian	4	1.04 (0.47-2.31)	1.29 (0.90-1.83)	0.007
	Caucasian	5	0.79 (0.19-3.26)	1.30 (0.67-2.52)	0.060
	Men and women	4	1.26 (0.51-3.08)	1.28 (0.85-1..93)	0.027
	Postmenopausal women	6	1.06 (0.31-3.60)	1.97 (1.29-3.01)	0.001
GG vs. AA+AG	Total analysis	10	1.08 (0.56-2.09)	1.38 (1.09-1.75)	0.000
	Asian	4	0.94 (0.43-2.05)	1.31 (1.00-1.73)	0.000
	Caucasian	5	0.74 (0.20-2.70)	0.85 (0.49-1.49)	0.016
	Men and women	4	1.21 (0.52-2.81)	1.25 (0.83-1.88)	0.040
	Postmenopausal women	6	0.93 (0.31-2.79)	1.46 (1.09-1.95)	0.000
GG+AG vs. AA	Total analysis	11	1.41 (1.11-1.80)	1.38 (1.17-1.62)	0.048
	Asian	4	1.15 (0.77-1.71)	1.08 (0.83-1.39)	0.097
	Caucasian	6	1.53 (1.20-1.94)	1.52 (1.20-1.94)	0.559
	Men and women	4	1.20 (0.83-1.74)	1.16 (0.93-1.45)	0.074
	Postmenopausal women	7	1.68 (1.30-2.17)	1.69 (1.32-2.15)	0.377

OR_r: Odd ratio for random-effects model; OR_f: Odd ratio for fixed-effects model; P_h: *P* value for heterogeneity test.

from 2002 to 2017. The flowchart of **Figure 1** revealed detailed screening process of our analysis. At the end, 1476 osteoporosis cases and 1672 controls were included in the current study, which assessed the relation between OPG-A163G polymorphism and osteoporosis risk. The main characteristics of the 11 articles are listed in **Table 1**.

Meta-analysis results

A summary of the meta-analysis findings on the relationship between OPG A163G polymorphism and susceptibility to osteoporosis is provided in **Table 2**. Data from 11 case-control studies were pooled together for analysis of the A163G polymorphism. The meta-analysis results revealed that the A163G polymorphism may be associated with an increased risk of osteoporosis in dominant model (GG+AG vs. AA: OR = 1.41, 95% CI: 1.11-1.80), although this association was not significant under the other three models. Subgroup analysis by ethnicity showed that the magnitude of the effect was similar in Caucasians, but not in Asians (**Table 2**, **Figure 2**). Further subgroup analyses

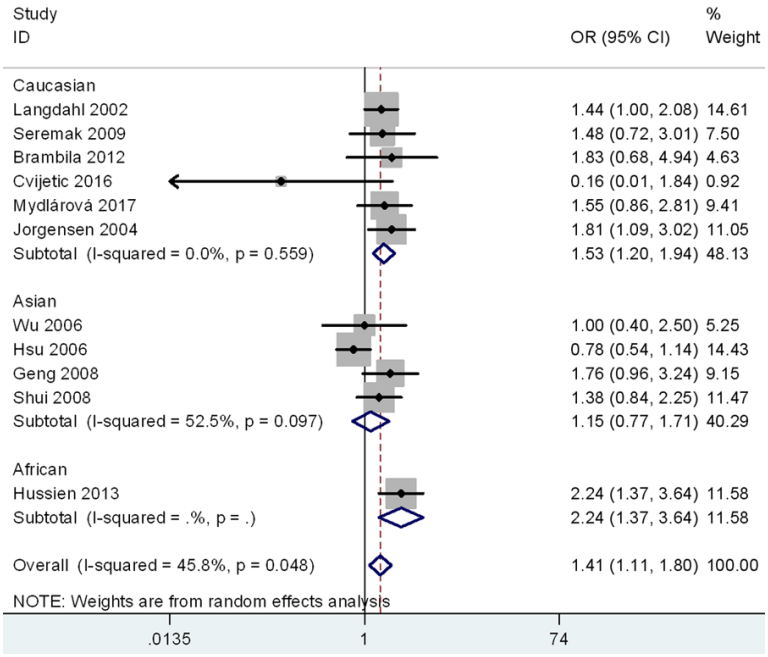

Figure 2. The forest plot on the association between OPG-A163G polymorphism and osteoporosis risk under dominant model.

based on subject type suggested that the A163G polymorphism was associated with an increased osteoporosis risk in the postmenopausal women subgroup for dominant model, while no evidence of any significant association was observed in the men and women subgroups (**Table 2**).

Sensitivity analysis and publication bias diagnosis

Pooled results were compared between fixed-effects model and random-effects model to evaluate the sensitivity of the meta-analysis. All the significant corresponding pooled ORs were not materially altered (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to assess the publication bias. As showed in **Figure 3**, the shape of the funnel plot did not reveal obvious asymmetry. Similarly, Egger's test indicated that there was no evidence of obvious publication bias in the 11 reviewed studies (t = -0.14, p = 0.892).

Discussion

Since OPG plays an important role as an inhibitor of osteoclast differentiation, polymorphisms in the gene coding for OPG might have an influence on the bone remodeling process [18]. Thus, the OPG gene is a candidate gene for identifying individuals at risk for developing osteoporosis. The G to A substitution at position 163 in the promoter region of the OPG gene has been well described [19]. Several investigations have reported that the OPG A163G polymorphism was associated with the onset of osteoporosis, however the previous results have yielded conflicting results. Regional and racial differences are likely reasons for the different results. Therefore, we conducted this meta-analysis based on different population individuals to assess the effect of OPG A163G polymorphism on risk for osteoporosis.

For this study, a broad selection of publications found in electronic databases were reviewed and included 11 studies in our meta-analysis. The A163G polymorphism may be associated with an increased risk of osteoporosis in Caucasians, but not in Asians. Subgroup analyses based on subject type suggested that the A163G polymorphism was associated with an increased osteoporosis risk in the postmenopausal women subgroup, while no evidence of any significant association was observed in the men and women subgroups. Begg's funnel plots and the Egger's linear regression test did not reveal any evidence of obvious asymmetry, which indicated the accuracy and consistency of the results. These findings suggest that the OPG A163G polymorphism may play a role in the pathogenesis of osteoporosis.

Currently, there are two published meta-analyses regarding OPG A163G polymorphism and osteoporosis risk [20, 21]. The two meta-analyses were published in 2014, and they all included seven case-control studies with a total of 1078 osteoporosis cases and 1092 healthy controls respectively with OPG A163G polymorphism. Their results indicated that the G allele of the A163G polymorphism may be associated with an increased risk of osteoporosis, the magnitude of the effect was similar in Cau-

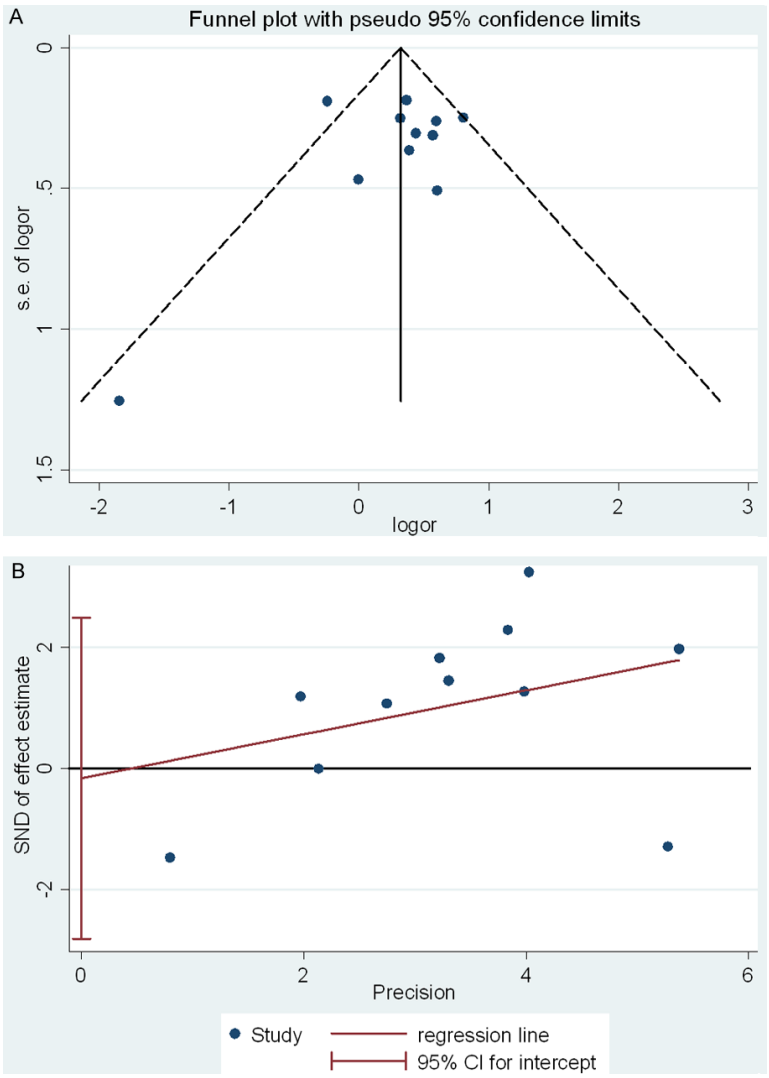

Figure 3. Publication bias assessment of OPG-A163G polymorphism and osteoporosis (A: Begg's funnel plot; B: Egger's linear regression).

casian and postmenopausal women subgroups. Our current meta-analysis is strengthened by including more studies than the previously published meta-analyses. Sensitivity analyses and publication bias test confirmed the reliability and stability of the meta-analysis. Therefore, our results indicate that OPG A163G polymorphism may be associated with osteoporosis, especially in Caucasians and postmenopausal women.

Several potential limitations of this study should be noted. First, there was significant between-study heterogeneity from studies in most comparisons, which may affect the results. Second, as with other complex traits, osteoporosis risk may be modulated by genetic markers besides the OPG gene. Thus, fully elucidating the pathogenesis of osteoporosis would demand an investigation into the association and combined interaction of many gene variants of genes with osteoporosis risk. Third, only English and Chinese databases were used for literature searching in this meta-analysis, other language articles/databases were not included. Therefore, further studies are needed to assess the association in other population. Finally, due to in-sufficient information, subgroup analyses stratified by other factors could not be conducted, such as gender, smoking status, and so on.

In conclusion, the current meta-analysis provides additional evidence supporting the hypothesis that the OPG A163G polymorphism increases osteoporosis risk, especially in Caucasians and postmenopausal women. Thus, the OPG A163G polymorphism could probably be used along with other genetic markers together to identify individuals at a high risk of osteoporosis.

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Disclosure of conflict of interest

None.

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