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Meta-analysis

Vitamin D receptor BsmI polymorphism may be associated with an decreased osteoporosis risk in South China

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Abstract: Although many epidemiology studies have evaluated the correlation between vitamin D receptor (VDR) BsmI polymorphism and osteoporosis, the current results remain inconclusive. This meta-analysis updated and reevaluated the possible association between VDR BsmI polymorphism and osteoporosis in Chinese populations. Studies were identified using PubMed and Chinese databases through December 2016. The associations were assessed with pooled odds ratios (ORs) and 95% confidence intervals (CIs). A total of nine studies with 688 osteoporosis cases and 730 controls were included in this meta-analysis. Overall, no significant association was found between VDR BsmI polymorphism and osteoporosis when all studies in Chinese populations were pooled into this meta-analysis. In subgroup analyses, significantly decreased risk was found in South China (bb vs. BB: OR = 0.22, 95% CI = 0.06-0.76; bb+Bb vs.BB: OR = 0.27, 95% CI = 0.09-0.81). This meta-analysis suggests that VDR BsmI polymorphism may have a protective role against the development of osteoporosis in South China.

Key words: Meta-analysis; Vitamin D receptor; Polymorphism; Osteoporosis.

Introduction

It is estimated that osteoporosis can affect 30% of women and 12% of men (1). Clinical manifestations include increased bone fragility, easy occurrence of bone fracture, and relatively high lethal and disability rates caused by hip and vertebral fractures, which results in heavy financial burden for the families of patients and society, and has become a serious health problem (1). The pathogenesis of osteoporosis is associated with environment and genetics (2-4). Notably, twin and family studies have shown that approximately 50–85% of heritability for bone mineral density in the general population may be attributed to genetic factors (5). These indicated that the genetic variations may play key functions in the pathogenesis of osteoporosis.

The vitamin D receptor (VDR) gene is polygenetic gene, and VDR polymorphisms could influence the expression and function of VDR protein, which are proved to influence the risk of bone mineral density and osteoporosis. Several VDR gene polymorphisms have been identified; of these the BsmI single nucleotide polymorphism has been extensively studied. Morrison et al. firstly investigated that VDR BsmI polymorphism could affect osteoporosis in Caucasian women in 1992 (6). Since then, a number of studies were conducted to investigate the association between VDR BsmI polymorphism and osteoporosis in different ethnic groups. But these studies reported conflicting results. Differences in results may be related to the racial and regional differences in patients who have been studied, as well as a limited number of patients in each study. In order to reduce the influence of the diverse genetic backgrounds, we performed a meta-analysis based on Chinese population to assess the relationship between VDR BsmI polymorphism and osteoporosis risk.

Materials and Methods

Search strategy and selection criteria

We searched for studies examining the relationship between VDR BsmI polymorphism and osteoporosis in PubMed and Chinese databases. The keywords were (VDR or vitamin D receptor) and osteoporosis and (Chinese or China). The last search was updated on December, 2016. Additional records were identified by manual searching.

Inclusion criteria: (1) case–control study, (2) the study assessed the association between VDR BsmI polymorphism and osteoporosis, (3) sufficient original data for calculating odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs), (4) all participants were Chinese people. Exclusion criteria: (1) not case-control studies that evaluated the association between VDR BsmI polymorphism and osteoporosis risk, (2) studies associated with VDR BsmI polymorphism and bone mineral density, (3) repeated literatures, (4) incomplete data, (5) case reports, letters, reviews, and editorial articles.

Data extraction

We conducted this meta-analysis in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (7). The data was independently extracted by two investigators from all eligible publications and the

results were reviewed by a third investigator. Discrepancies were resolved by a discussion between these reviewers. For each study, the following characteristics were collected: the first author's name, year of publication, source of controls, geographic area, sample size, and available genotype data for VDR BsmI. Hardy-Weinberg equilibrium (HWE) in controls were calculated from corresponding genotype distributions. Source of controls was stratified to population based [PB] and hospital based [HB]. In this meta-analysis, the quality of individual studies was assessed according to the nine-star Newcastle–Ottawa Scale (8).

Statistical analysis

The association betweenVDR BsmI polymorphism and osteoporosis was evaluated by calculating pooled ORs based on the individual ORs. Four comparisons were performed: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. The statistical heterogeneity between studies was tested using the Chi-squarebased Q-test (9). The fixed-effect model (Mantel-Haenszel) or random-effect model (Der-Simonian and Laird) was selected to summarize the combined ORs and their 95%Cis according to the results of the heterogeneity test. Subgroup analyses were performed according to source of controls, geographic area, and HWE. Sensitivity analysis was performed by comparing the results of fixed-effects model and random-effects model. Publication bias was assessed using Begg's funnel plot and Egger's linear regression test. All statistical analyses were conducted using the Stata, version 12 (StataCorp LP, College Station, TX). A P value less than 0.05 was considered to be statistically significant.

Results

Description of included studies

Figure 1 illustrates the literature search process in the form of a flow chart. One hundred and eleven articles which examined the association between VDR polymorphisms and osteoporosis risk were identified. According to the inclusion and exclusion criteria, nine studies (10-18) were included and 102 articles were excluded. The publication year of involved studies ranged from 1998 to 2005. In total, 688 osteoporosis cases and 730 controls were included in this meta-analysis. The source of controls in five included studies was population-based. The characteristics of the included studies

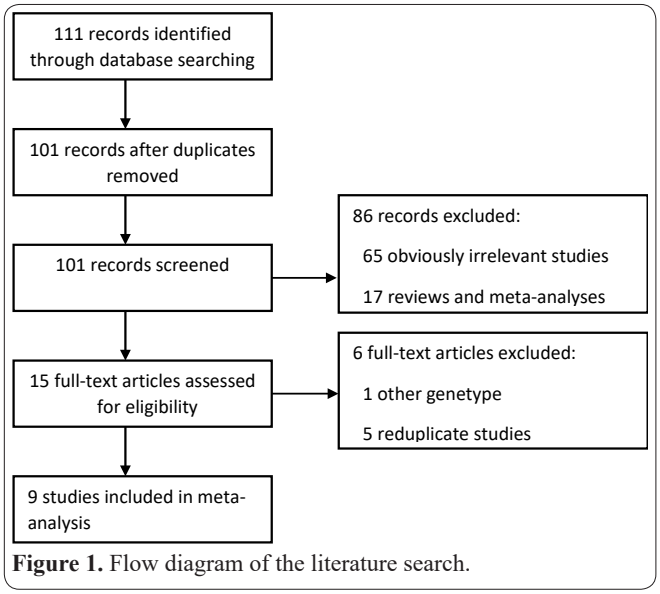

Figure 1. Flow diagram of the literature search.

are listed in Table 1.

Meta-analysis results

The main results of this meta-analysis and the heterogeneity test were shown in Table 2. In the total analyses, no significantly elevated osteoporosis risk was found in all analysis models (Table 2). However, there was significant heterogeneity between studies. Hence, we then performed subgroup analyses by source of controls, geographic area, and HWE. In the stratified analysis by source of controls and HWE, the results showed similar result that BsmI polymorphism had no association with osteoporosis. In the stratified analysis by geographic area, significantly decreased risk was found in the population from South China (bb vs. BB: OR = 0.22, 95% CI = 0.06-0.76; bb+Bb vs.BB: OR = 0.27, 95% CI = 0.09-0.81), was not found in the North.

Sensitivity analysis and publication bias diagnosis

We compared the pooled results between fixed- and random-effects models to evaluate the sensitivity of the meta-analysis. All the corresponding pooled ORs were not materially altered. 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 of literatures for VDR BsmI polymorphism and osteoporosis. As showed in Figure 3A, the shape of the funnel plot revealed some asymmetry. However, the Egger's test indicated that there was no evidence of ob-

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

References	Source of controls	Geographic area(s)	Case number	Control number	Cases			Controls			HWE		Quality score
					BB	Bb	bb	BB	Bb	bb	χ^2	*P*	
Wang 2007 (10)	HB	Heilongjiang	14	48	7	4	3	0	9	39	0.51	*0.474*	8
Xie 2005 (11)	PB	Beijing	372	45	7	2	363	2	1	42	27.96	*0.000*	8
Liu 2005 (12)	PB	Beijing	56	89	0	6	50	2	11	76	3.53	*0.060*	7
Zhang 1998 (13)	HB	Beijing	17	162	0	3	14	0	14	148	0.33	*0.565*	7
Chen 2003 (14)	HB	Chongqing	78	81	0	13	65	0	12	69	0.52	*0.472*	8
Lin 2003 (15)	HB	Zhejiang	59	71	0	1	58	0	9	62	0.33	*0.569*	7
Leng 2002 (16)	PB	Xinjiang	22	46	0	11	11	7	19	20	0.48	*0.488*	8
Zhu 2005 (17)	PB	Guangxi	40	158	6	26	8	7	105	46	27.26	*0.000*	8
Liang 2002 (18)	PB	Guangdong	30	30	1	1	28	0	0	30	—	—	7

Table 2. Association of the VDR BsmI polymorphism on osteoporosis susceptibility.

Analysis model		n	ORr(95%CI)	ORf(95%CI)	P_h
b vs. B	Total analysis	9	0.82 (0.38-1.79)	0.81 (0.61-1.07)	0.000
	Hospital-based	4	0.57 (0.10-3.28)	0.52 (0.32-0.84)	0.000
	Population-based	5	1.23 (0.62-2.43)	1.01 (0.71-1.44)	0.035
	North China	5	0.73 (0.19-2.85)	0.79 (0.52-1.20)	0.000
	South China	4	0.90 (0.39-2.09)	0.82 (0.55-1.21)	0.084
	In HWE	6	0.81 (0.26-2.57)	0.83 (0.57-1.20)	0.000
	Not in HWE	2	1.24 (0.32-4.82)	0.83 (0.53-1.30)	0.017
bb vs. BB	Total analysis	6	0.56 (0.09-3.50)	0.50 (0.26-0.98)	0.002
	Population-based	5	1.14 (0.24-5.38)	0.97 (0.44-2.15)	0.044
	North China	4	0.86 (0.05-16.17)	0.70 (0.31-1.55)	0.001
	South China	2	**0.22 (0.06-0.73)**	**0.22 (0.06-0.76)**	0.809
	In HWE	3	0.55 (0.01-47.77)	0.50 (0.21-1.20)	0.001
	Not in HWE	2	0.68 (0.06-7.85)	0.54 (0.18-1.56)	0.018
bb vs. BB+Bb	Total analysis	9	0.83 (0.40-1.71)	0.84 (0.58-1.21)	0.002
	Hospital-based	4	0.60 (0.12-2.98)	0.67 (0.39-1.16)	0.001
	Population-based	5	1.11 (0.60-2.07)	1.01 (0.62-1.64)	0.237
	North China	5	0.72 (0.23-2.30)	0.77 (0.46-1.28)	0.001
	South China	4	0.95 (0.36-2.50)	0.93 (0.55-1.56)	0.100
	In HWE	6	0.80 (0.30-2.10)	0.87 (0.57-1.35)	0.002
	Not in HWE	2	1.21 (0.26-5.59)	0.86 (0.42-1.75)	0.053
bb+Bb vs.BB	Total analysis	6	0.64 (0.12-3.37)	0.54 (0.28-1.02)	0.005
	Population-based	5	1.18 (0.27-5.16)	0.99 (0.46-2.13)	0.051
	North China	4	0.96 (0.06-14.84)	0.74 (0.34-1.64)	0.003
	South China	2	**0.27 (0.09-0.80)**	**0.27 (0.09-0.81)**	0.906
	In HWE	3	0.66 (0.01-41.34)	0.55 (0.23-1.31)	0.003
	Not in HWE	2	0.74 (0.08-6.52)	0.56 (0.21-1.50)	0.027

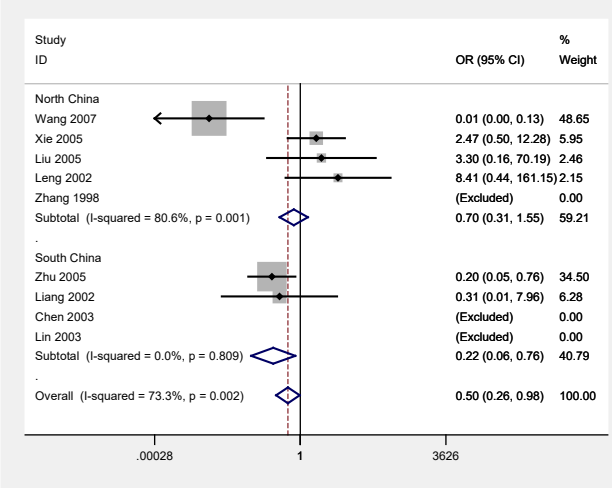

Figure 2. The forest plot on the association between VDR BsmI polymorphism on osteoporosis risk under homozygotes model.

vious publication bias in the reviewed studies (t=0.42, *p*=0.688). Due to the limited studies, we did not perform the publication bias assessment for subgroup analyses.

Discussion

Osteoporosis is a multifactorial disorder with a strong genetic component, and the VDR gene has been suggested as a candidate gene for osteoporosis. VDR BsmI gene polymorphism is one of the most important subtypes of VDR gene polymorphisms. To date, a variety of studies has been conducted to identify whether the VDR BsmI polymorphism was the genetic determiner of osteoporosis. However, conflicting results have been obtained. Therefore, we did this updated meta-analysis to estimate the relationship between VDR BsmI polymorphism and susceptibility to osteoporosis among Chinese populations only, in order to lessen the impact

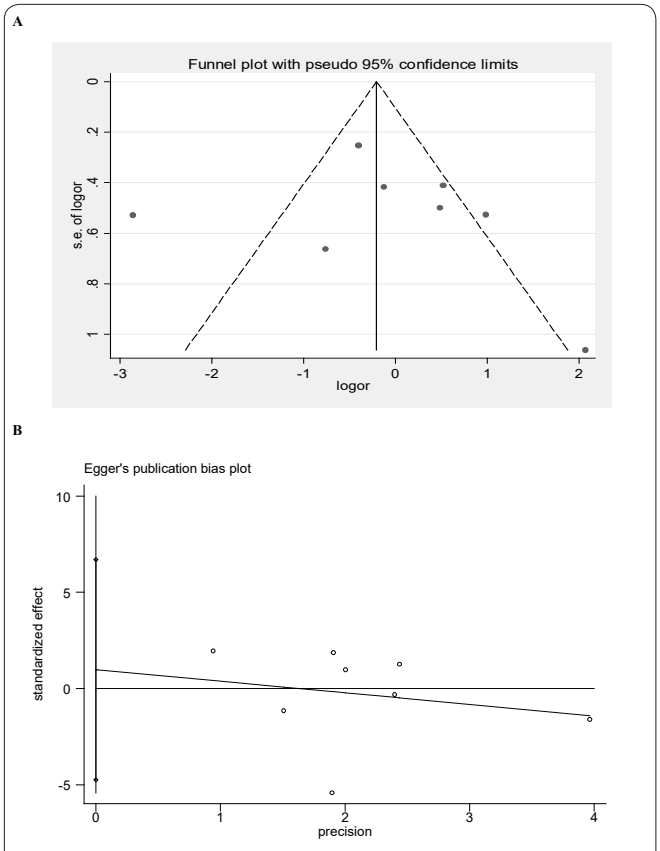

Figure 3. Publication bias assessment under allele model (A: Begg's funnel plot; B: Egger's linear regression).

of different genetic background. A total of 9 studies with 688 osteoporosis cases and 730 controls were included in this meta-analysis. The results of this meta-analysis show that VDR BsmI gene polymorphism was significantly associated with osteoporosis risk in South China

Till now, there are several published meta-analyses regarding VDR polymorphisms and osteoporosis risk

(19-22). In 2006, Zintzaras et al. (19) conducted a meta-analysis which involved 14 studies for BsmI polymorphism. Their results indicated that the relationship between the VDR polymorphisms and osteoporosis remains an unresolved issue and other probable genetic-environmental risk factors interacting with the above polymorphisms should be investigated (19). In 2013, two meta-analyses (20-21) were performed for the association between VDR BsmI polymorphism and osteoporosis; one suggested that VDR BsmI polymorphism may have a protective role against the development of osteoporosis (20), while another found no association of VDR BsmI B/b gene polymorphism and osteoporosis in overall populations, Caucasians, and Asians (21). In 2016, a meta-analysis (22) was performed among the Han Chinese population, and revealed no association between polymorphisms of vitamin D receptor genes and osteoporosis risk in the Han Chinese population. This current meta-analysis is strengthened by including all studies conducted in Chinese participants and subgroup analyses. Sensitivity analyses and publication bias test confirmed the reliability and stability of the meta-analysis. Therefore, our results indicated that VDR BsmI polymorphism may be associated with an decreased osteoporosis risk in South China.

Our meta-analysis has several strengths. First, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, our inclusion of non-English language reports, were important in minimizing a major potential threat to the validity of any meta-analysis-publication bias and the related threat of a language bias. Third, we investigated the influence of geographic area on the risk of periodontitis and VDR BsmI polymorphism. Fourth, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Several limitations should be also considered. First, this ethnic-specific meta-analysis only included data from a single ethnic group, and thus, our results are only applicable to this ethnic group. Second, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Third, the etiology of osteoporosis is complex and is mediated by the activities of multiple genes. The effect of any single gene or one single nucleotide polymorphism might have a limited impact on osteoporosis risk than have been anticipated so far. Finally, the small sample size in subgroup analyses was relatively small, and that may influence our conclusion.

In conclusion, this meta-analysis indicates a significant risk between VDR BsmI polymorphism and osteoporosis risk in South China. Ethnicity and geographic area seem to have a confounding effect on these studies. Due to the limited number of available studies, further study conducted in larger populations with multiple adjusted variables are required to obtain robust findings.

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References

1. Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, Muratore M and Casciaro S, Major osteoporotic fragility fractures: risk factor updates and societal impact. World J Orthop 2016, 7: 171-181.

2. Ralston SH and De Crombrugghe B, Genetic regulation of bone mass and susceptibility to osteoporosis. Genes Dev 2006, 20:2492–2506.

3. Wong PK, Christie JJ, Wark JD (2007). The effects of smoking on bone health. Clin Sci (Lond), 113:233–241.

4. Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA Jr, Malik R and Arnsten JH, Association between alcohol consumption and both osteoporotic fracture and bone density. Am J Med, 2008, 121:406–418.

5. Riggs BL, Vitamin D-receptor genotypes and bone density. New Engl J Med 1997, 337: 125-126.

6. Morrison NA, Yeoman R, Kelly PJ and Eisman JA, Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Natl Acad Sci U S A 1992,89:6665-6669.

7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009, 339: b2700. doi: 10.1136/bmj.b2700.

8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P, The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp]

9. Hoaglin DC, Assessment of heterogeneity in meta-analyses. JAMA 2014, 312:2286-2287.

10. Wang XL, Zhu XY, Nie YK and Li X, Analysis of relationship between vitamin D receptor gene polymorphism and osteoporotic fracture. Chin J Osteoporos 2007,13: 692-695. (article in Chinese)

11. Xie YM, Hu SN, Han H, Kou QA, Gao X and Du BJ, Single nucleotide polymorphisms of VDR I, VDR II -1 and VDR II -2 in primary osteoporosis in Fujian, Wuhan and Beijing. Chin J Osteoporos 2005,11: 54-57. (article in Chinese)

12. Liu J, Miao YD, He PY, Gou SQ, Zhang YQ, Chen LX and Bao H, Study on the relationship between vitamin D receptor gene polymorphism and bone mineral density in old men. Chin J Osteoporos 2005, 11: 159-162. (article in Chinese)

13. Zhang H, Tao G and Wu Q, Preliminary studies on the relationship between vitamin D receptor gene polymorphism and osteoporosis in Chinese women. Zhonghua Liu Xing Bing Xue Za Zhi 1998, 19:12-14. (article in Chinese)

14. Chen J, Li Y, Zhang L, Qiu J, Peng H, Deng Z, Wang Y and Yan Z, The relationship between vitamin D receptor gene polymorphism and bone mineral density in osteoporosis in Chongqing area. Chonqing Med 2003,32: 881-882. (article in Chinese)

15. Lin XJ, The relationship between the polymorphism of vitamin D receptor, estrogen receptor and osteoporosis in health menopause women. Doctor Thesis of Zhejiang University 2003. (article in Chinese)

16. Leng X, Chen R, A LY, Li H, Jiang Y, Tao G, Zhang H, Liu W and Gao Y,. Relationship between vitamin D receptor gene and bone mineral density in Urumqi area. Chin J Endocrinol Metab 2002, 18: 123. (article in Chinese)

17. Zhu MJ, Yan XD, Wang F, Chen YH and Huang Z, Relationship between vitamin D receptor genetypes and bone mineral density, bone metabolism in Guangxi Chuang and Han national postmenopausal women. Chin J Gerontol 2005, 25: 278-280. (article in

Chinese)
18. Liang W, Xiu L, Liang Y and Yu B, The association between Vitamin D receptor gene polymorphism and osteoporosis. Acad J Sun Yat-Sen Univ Med Sci 2002, 23:47-49. (article in Chinese)
19. Zintzaras E, Rodopoulou P and Koukoulis GN, BsmI, TaqI, ApaI and FokI polymorphisms in the vitamin D receptor (VDR) gene and the risk of osteoporosis: a meta-analysis. Dis Markers 2006, 22:317-326.
20. Jia F, Sun RF, Li QH, Wang DX, Zhao F, Li JM, Pu Q, Zhang ZZ, Jin Y, Liu BL and Xiong Y, Vitamin D receptor BsmI polymorphism and osteoporosis risk: a meta-analysis from 26 studies. Genet Test Mol Biomarkers 2013,17:30-34.
21. Qin G, Dong Z, Zeng P, Liu M and Liao X, Association of vitamin D receptor BsmI gene polymorphism with risk of osteoporosis: a meta-analysis of 41 studies. Mol Biol Rep 2013, 40:497-506.
22. Yu M, Chen GQ and Yu F, Lack of association between vitamin D receptor polymorphisms ApaI (rs7975232) and BsmI (rs1544410) and osteoporosis among the Han Chinese population: A meta-analysis. Kaohsiung J Med Sci 2016, 32:599-606.