Vitamin D receptor BsmI polymorphism and osteoporosis risk in post-menopausal women

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Abstract

Introduction: Many studies have suggested that the vitamin D receptor polymorphism BsmI might be associated with the risk of osteoporosis development in post-menopausal women. However, the results have been inconsistent. The aim of this meta-analysis was to derive a more precise evaluation of the relationship.
Material and methods: Published literature from PubMed, EMBASE and the CNKI database was searched. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of any association.
Results: Ten case-control studies were included with a total of 1,403 osteoporosis cases and 2,144 healthy controls. In the overall analysis, no significant association was found between BsmI polymorphism and osteoporosis risk (BB vs. bb: OR = 0.76, 95% CI = 0.39–1.48; BB vs. Bb: OR = 0.90, 95% CI = 0.71–1.15; dominant model: OR = 1.20, 95% CI = 0.74–1.93; recessive model: OR = 0.83, 95% CI = 0.53–1.30). In the subgroup analysis by ethnicity, the results showed similar result that BsmI polymorphism m had no association with osteoporosis.
Conclusions: Results from the current meta-analysis suggest that vitamin D receptor BsmI polymorphism may not be a risk factor for osteoporosis in post-menopausal women.

Key words: vitamin D receptor, BsmI polymorphism, osteoporosis, meta-analysis.

Introduction

Osteoporosis is a common complex genetic disease in postmenopausal women, characterized by decreased bone mineral density (BMD), increased bone fragility and fracture risk. It is a major public health issue [1]. The World Health Organization estimates that 200 million women and men suffer from osteoporosis worldwide [2]. In the United States and the European Union, approximately 30% of all postmenopausal women have osteoporosis, and it has been predicted that more than 40% of them will suffer one or more fragility fractures during their remaining lifetime [3]. Many environmental factors have been identified as risk factors of osteoporosis, including exercise and calcium intake [4]. In addition, twin and family studies have shown that approximately 50–85% of heritability for BMD in the general population may be attributed to genetic factors [5]. Genetic factors may also play a role in the development of osteoporosis [6].

Vitamin D plays a crucial role in calcium and phosphate homeostasis and skeletal metabolism. Furthermore, the vitamin D receptor (VDR) plays an important role in cellular differentiation and the control of proliferation in a variety of cell types. The VDR gene located on the long arm of chromosome 12 (12q13.11) is a member of the nuclear receptor superfamily, and many studies have shown that VDR gene polymorphisms play an important role in the pathogenesis of osteoporosis [7]. VDR polymorphisms include VDR TaqI (rs17880019), VDR BsmI (rs1544410), VDR FokI (rs17881966), and VDR ApaI (rs17879735) [8, 9].

BsmI gene polymorphism is an important subtype of VDR gene polymorphisms, with genotypes BB, Bb, or bb by polymerase chain reactions based on polymorphism at the BsmI restriction site. Since 1996 when Berg *et al.* first reported that VDR BsmI polymorphism could affect osteoporosis in postmenopausal women [10], to date, a great number of studies regarding the association between BsmI gene polymorphism and osteoporosis in postmenopausal women have been published. However, the results remain controversial. The aim of this study was to investigate the association between BsmI gene polymorphism and osteoporosis risk in postmenopausal women by conducting a meta-analysis from all eligible case-control studies published.

Material and methods

Search strategy

The study retrieval was conducted using PubMed, EMBASE and the China National Knowledge Infrastructure (CNKI) databases with the following keywords: "BsmI polymorphism", "vitamin D receptor", and "osteoporosis" dating up until July of 2013. The references of the eligible articles or textbooks were also reviewed to check through manual searches to find other potential studies. When pertinent data were not included, or data that were presented were unclear, the authors were contacted directly. Any disagreement was resolved by discussion between the authors.

Selection criteria

The resulting reports were filtered using the following inclusion criteria: (i) case-control studies that addressed osteoporosis cases and healthy controls; (ii) studies on the association of VDR BsmI polymorphism and susceptibility to osteoporosis; (iii) studies that included sufficient genotype data for extraction. The following studies were excluded: (i) not case-control studies that evaluated the association between VDR BsmI polymorphism and osteoporosis risk; (ii) case reports, letters, reviews, and editorial articles; (iii) reports in which the number of null and wild genotypes could not be ascertained.

Data extraction

Two investigators (Bizeng Zhao and Wei Zhang) independently extracted the data with a standard protocol and the results were reviewed by a third investigator (Zubin Zhou). Discrepancies were resolved by discussion with our research team. For each study, the following characteristics were collected: the first author, year of publication, country of the study and ethnicity, genotype method, allele and genotype frequencies, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. Different ethnic descents were categorized as European and Asian that included subjects of more than one ethnicity.

Statistical analysis

We calculated the odds ratio (OR) and corresponding 95% confidence interval (CI) to evaluate the association between the VDR BsmI polymorphism and osteoporosis risk under a homozygote comparison (BB vs. bb), a heterozygote comparison (BB vs. Bb), a dominant model (bb + Bb vs. BB) and a recessive mode (BB + Bb vs. bb) between groups. We quantified the effect of heterogeneity by using the I^2 test, which ranges from 0 to 100% and represents the proportion of inter-study variability that can be contributed to heterogeneity rather than chance [11, 12]. When $I^2 > 50\%$ indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used. Subgroup analysis was performed according to ethnicity. The different ethnicities were categorized as Asians and Europeans. To test for robustness of the summary effects, sensitivity analysis was performed by comparison of random effect model values to the fixed effect to ensure the stability of the findings. All analyses were conducted using Stata 12.0 (Stata-Corp LP, College Station, TX, USA).

Results

Studies and data included

According to the inclusion criteria, 10 studies were included [10, 13–20]. The flow chart of the study selection is shown in Figure 1. The total osteoporosis cases and healthy controls numbered 1403 and 2144 respectively, in the 10 case-control studies that evaluated the relationship between BsmI polymorphism and the risk of osteoporosis. The publication year of the involved studies ranged from 1996 to 2009. Of the 10 included studies, 9 used the restriction fragment length polymorphism (PCR-RFLP) method and one used the TKM method [18]. Meta-analysis of the relationship between VDR gene BsmI polymorphism and oste-

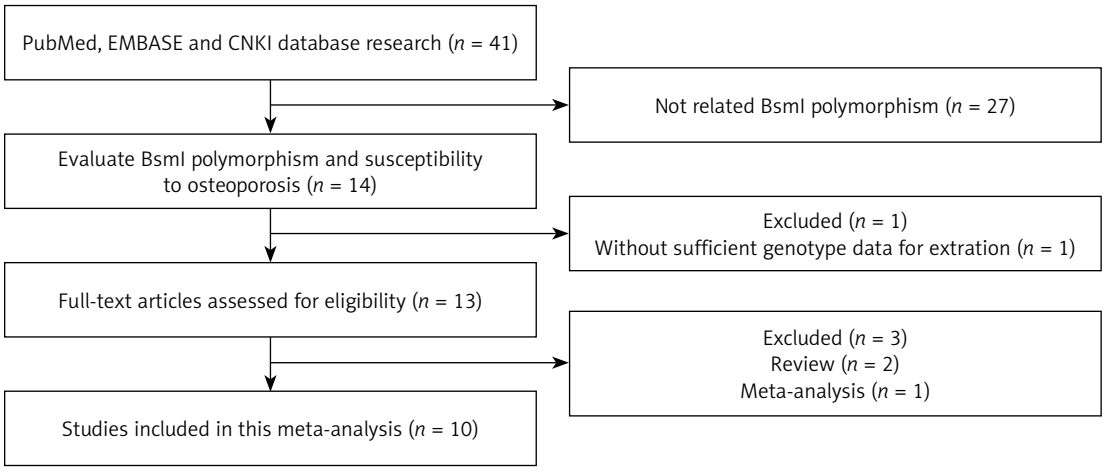

Figure 1. Flow chart showing study selection procedure

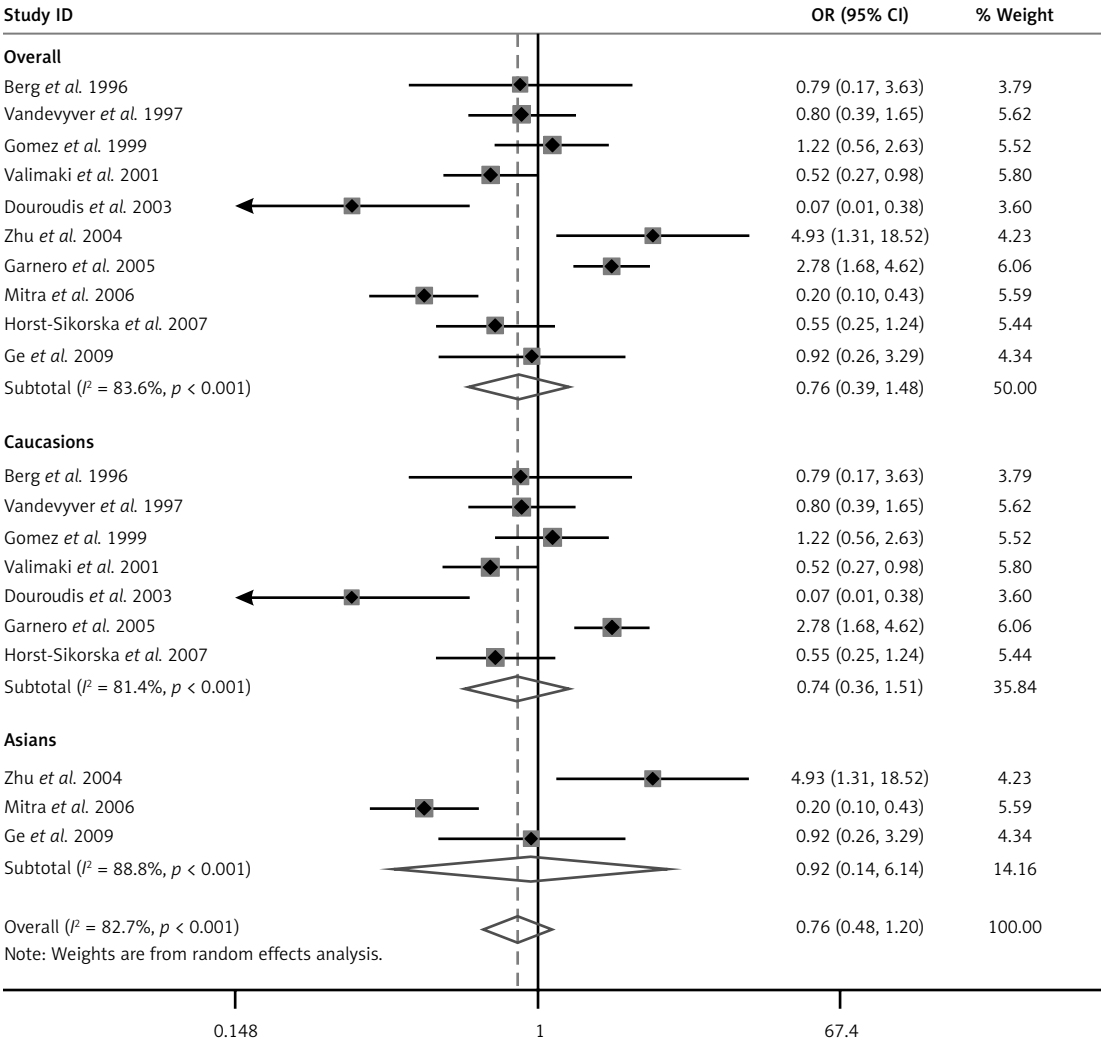

Figure 2. Meta-analysis of the relationship between VDR gene BsmI polymorphism and osteoporosis risk using BB vs. bb model

oporosis risk using BB vs. bb model (Figure 2). The HWE test was performed on the genotype distribution of the controls in all included studies. All of them were in HWE except those of Douroudis *et al.*, Zhu *et al.* and Ge *et al.* The main characteristics of included studies are listed in Table I. Of these studies, 7 reported on Europeans, and 3 reported on Asians.

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

First author	Year	Country	Ethnicity	Genotyping method	Genotypes for cases			Genotypes for controls			HWE test
					BB	Bb	bb	BB	Bb	bb	
Berg	1996	Norway	European	RFLP	4	8	7	8	11	11	0.16
Vandevyver	1997	Belgium	European	RFLP	12	50	24	127	368	203	0.08
Gomez	1999	Spain	European	RFLP	13	38	25	38	109	89	0.63
Valimaki	2001	Finland	European	RFLP	44	175	153	20	55	36	0.90
Douroudis	2003	Greece	European	RFLP	3	12	20	10	29	5	0.03
Garnero	2005	France	European	RFLP	50	124	66	40	162	147	0.64
Horst-Sikorska	2007	Poland	European	RFLP	10	35	40	33	85	73	0.34
Zhu	2004	China	Asian	RFLP	6	26	8	7	105	46	0.00
Mitra	2006	India	Asian	TKM method	19	38	40	51	46	22	0.05
Ge	2009	China	Asian	RFLP	6	33	314	4	12	192	0.00

RFLP – Restriction fragment length polymorphism.

Table II. Summary ORs and 95%CI of BsmI gene polymorphism with bone mineral density risk

Sub-group	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Sensitivity analysis	
		Case	Control		I^2 (%)	Value of *p*	OR	95% CI	OR	95% CI
Overall	BB vs. bb	1403	2144	Random	83.6	< 0.001	0.76	0.39–1.48	0.87	0.68–1.11
	BB vs. Bb			Fixed	42.8	0.06	0.90	0.71–1.15	0.88	0.61–1.26
	Dominant model			Random	71	< 0.001	1.20	0.74–1.93	1.15	0.92–1.43
	Recessive model			Random	81.4	< 0.001	0.83	0.53–1.30	0.97	0.82–1.15
European	BB vs. bb	978	1692	Random	78.3	< 0.001	0.74	0.36–1.51	1.01	0.76–1.32
	BB vs. Bb			Fixed	8.3	0.37	0.96	0.74–1.26	0.93	0.68–1.28
	Dominant model			Random	59.8	0.02	1.14	0.75–1.74	1.01	0.80–1.29
	Recessive model			Random	81.5	< 0.001	0.77	0.48–1.26	0.98	0.81–1.18
Asian	BB vs. bb	490	485	Random	88.8	< 0.001	0.92	0.14–6.14	0.51	0.30–1.07
	BB vs. Bb			Random	77.5	0.01	0.92	0.25–3.38	0.70	0.41–1.19
	Dominant model			Random	85.8	< 0.001	1.03	0.22–4.73	1.73	1.07–2.82
	Recessive model			Random	86.8	< 0.001	0.91	0.31–2.68	0.85	0.60–1.21

Results of meta-analysis

A summary of the meta-analysis findings of the association between VDR BsmI polymorphism and osteoporosis risk is shown in Table II. Meta-analysis results showed that there was no association between BsmI polymorphism and the risk of osteoporosis (BB vs. bb: OR = 0.76, 95% CI: 0.39–1.48; BB vs. Bb: OR = 0.90, 95% CI; 0.71–1.15; dominant model: OR = 1.20, 95% CI: 0.74–1.93; recessive model: OR = 0.83, 95% CI: 0.53–1.30). In the subgroup analysis based on ethnicity, the included studies were divided into Asian and European populations, and the results also showed no significant association between BsmI polymorphism and susceptibility to osteoporosis in both Asian and European populations. Sensitivity analysis was performed by comparing random effect model values to the fixed effect, and the significance of pooled OR in all individual analyses and subgroup analyses was not influenced.

Publication bias

The publication bias of the meta-analysis of the association between VDR BsmI polymorphism and osteoporosis risk was detected by Begg's funnel plot. All graphical funnel plots of the included studies appeared to be symmetrical. There was no visual evidence of publication bias visually from the funnel plot, which implied that the publication bias was low in the present overall meta-analysis (BB

vs. bb: $p = 0.806$; BB vs. Bb: $p = 0.806$; dominant model: $p = 0.806$; recessive model: $p = 0.806$).

Discussion

Osteoporosis is a multifactorial disorder with a strong genetic component, and the VDR gene has been suggested as a candidate gene for osteoporosis [21]. The VDR gene has been widely studied due to its crucial role in the regulation of bone turnover and homeostasis. Active vitamin D as the ligand of VDR plays an important role in intestinal and renal calcium absorption, as well as subsequent, normal bone mineralization and remodeling [22]. 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. Zintzaras *et al.* performed a meta-analysis to study the relationship between VDR gene polymorphism and the risk of osteoporosis, and found that there was no evidence of a relationship between BsmI polymorphism and osteoporosis risk [23]. Post-menopausal women were regarded as a 'high-risk' population for low osteoporosis; therefore, we conducted a meta-analysis to evaluate the relationship between VDR BsmI gene polymorphism and susceptibility to osteoporosis. Our meta-analysis is the first to examine this relationship of VDR BsmI gene polymorphism with osteoporosis risk in post-menopausal women. Overall, the results showed that the VDR BsmI polymorphism may not be an osteoporosis susceptibility gene in post-menopausal women. Considering that the result may be affected by ethnicity, we performed a race-related subgroup analysis, and again no significant association was found between BsmI polymorphism and susceptibility to osteoporotic fracture in post-menopausal women in both Caucasian and Asian populations. Sensitivity analysis was performed by comparing random effect model values to the fixed effect, and the result revealed that this meta-analysis was realistic and believable. There was no evidence of publication bias in this meta-analysis (all $p > 0.05$). As the eligible study number was small in this meta-analysis, these results still need further investigation.

The potential function of BsmI polymorphism might be affected by gene-gene and gene-environment interactions. A previous study demonstrated that polymorphisms of both genes (BsmI polymorphism and estrogen receptor genotypes) increased osteoporosis risk and found that BsmI polymorphism alone did not increase the osteoporosis risk [8, 24]. In addition, obesity can mask the effects of the VDR genotypes on BMD as reported by Dawson-Hughes [25, 26]. As one study could not be included in our meta-analysis, further studies of gene-gene and gene-environment interactions should be taken into consideration.

The present study has some limitations. First, the number of studies included in the systematic review might have been too small to detect slight associations within ethnic groups. Second, heterogeneity exists between studies, possibly owing to covariates: age and years from onset, gender, fraction of patients among these studies, and so on.

In conclusion, our meta-analysis suggests no association between BsmI polymorphism and osteoporosis risk, both in Caucasian and Asian populations. Large-scale case-control and population-based association studies are warranted to validate the risk identified in the current meta-analysis.

Conflict of interest

All authors declared no conflict of interest.

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