Associations between ERα/β gene polymorphisms and osteoporosis susceptibility and bone mineral density in postmenopausal women: a systematic review and meta-analysis

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Abstract

Background: Many studies have reported associations between estrogen receptor (ER) gene polymorphisms and postmenopausal osteoporosis (PMOP) risk and bone mineral density (BMD), but the results are controversial. The aim of the present meta-analysis is to verify the association between ERα and ERβ gene polymorphisms and osteoporosis susceptibility and BMD in postmenopausal women.

Methods: PubMed, EMBASE, Web of Science, the Cochrane Library and China WeiPu Library were searched. OR and WMD with 95% CI were calculated to assess the association.

Results: Overall, no significant association was observed between ERα XbaI, ERα PvuII and PMOP susceptibility in either overall, Caucasian or Asian populations. ERα G2014A was significantly associated with a decreased risk of PMOP in Caucasian populations. There was a significant association between ERβ RsaI and PMOP risk in both overall and Asian populations. Caucasian PMOP women with ERα XbaI XX and Xx genotypes had a higher LS Z value than women with xx genotype. ERα XbaI XX genotype was associated with increased FN BMD in overall and Caucasian populations, an increased FN Z value in Asians, and a decreased FN Z value in Caucasians. There was also a significant association between ERα XbaI Xx genotype and an increased FN Z value in either Asians or Caucasians.

Conclusion: Each ERα and ERβ gene polymorphism might have different impact on PMOP risk and BMD in various ethnicities.

Keywords: Estrogen receptor, Postmenopausal osteoporosis, Gene polymorphism, Meta-analysis

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Background
Postmenopausal osteoporosis (PMOP) is a common metabolic bone disorder characterized by low bone mineral density (BMD) and increased fracture risks [1–3]. It is estimated that osteoporosis affects approximately 10 million American adults, with another 34 million being at high risk due to low bone mass [4].

The pathophysiology of PMOP is considered as a disorder or negative imbalance of bone metabolism and remodeling, with bone resorption outpacing bone formation [3], suggesting that vitamin D and parathyroid hormone (PTH) and other factors related to bone resorption and formation may play a key role in the underlying mechanism and pathophysiology of PMOP [5–8]. Furthermore, genetic factors including genes and gene polymorphisms may also play an important role in the development of PMOP [9].

Estrogen is another important hormone that plays an important role in the pathogenesis of PMOP, knowing that reduced ovarian production of estrogen after menopause is a cause for the initial phase of rapid bone loss and osteoporosis in women [3]. Estrogen is known as an important regulator of bone metabolism, and estrogen deficiency is believed to be the cause of BMD loss, increased mechanical loading–induced bone remodeling, and the development of PMOP [10]. Knowing that the action of estrogen is predominantly mediated by estrogen receptor (ER), including ERα and ERβ by binding to different ligands to mediate various biological effects [3,10], more attention has been paid to the relationship between ERs and PMOP risk and BMD in postmenopausal women [11–38]. However, the results of studies currently available about this issue are controversial.

Previous meta-analyses have been performed to assess the pooled effects of ER gene polymorphisms on BMD and fracture risk [39–41]. WANG et al. [39] showed that the ERα Xbal (rs9340799) polymorphism was associated with BMD at diverse skeletal sites, and ERα PvuII (rs2234693) PP genotype played a role in protecting the lumbar spine but on the other hand might be a risk factor for the femoral neck fracture. However, to the best of our knowledge, no meta-analysis has been performed to explore the relationships between ER gene [ERα Xbal (rs9340799), ERα PvuII (rs2234693) and ERα G2014A (rs2228480)] and ERβ gene [ERβ AluI (rs4986938) and ERβ Rsal (rs1256049)] polymorphisms and PMOP susceptibility and BMD of the lumbar spine and femoral neck in postmenopausal women. To address these issues, we performed a meta-analysis of all currently available studies relating ER gene [ERα Xbal (rs9340799), ERα PvuII (rs2234693) and ERα G2014A (rs2228480)] and ERβ gene [ERβ AluI (rs4986938) and ERβ Rsal (rs1256049)] polymorphisms with PMOP risk and BMD.

Methods
Data sources and searches
We searched PubMed, EMBASE, Web of Science, the Cochrane Library and China WeiPu Library to identify case-control studies that investigated the associations between ERα gene polymorphisms [ERα Xbal (rs9340799), ERα PvuII (rs2234693) and ERα G2014A (rs2228480)] ERβ gene polymorphisms [ERβ AluI (rs4986938) and ERβ Rsal (rs1256049)] and osteoporosis susceptibility and BMD in postmenopausal women by using the following search terms (‘PMOP’ OR ‘Postmenopausal osteoporosis’ OR ‘Postmenopausal’) AND (‘Estrogen Receptor’ OR ‘ER’) AND (‘polymorphism’ OR ‘single nucleotide polymorphism’ OR ‘SNP’ OR ‘variation’). To analyze the pooled effects of ER gene polymorphisms on BMD, the following search terms were used: (PMOP’ OR ‘Postmenopausal osteoporosis’ OR ‘Postmenopausal’) AND (‘Estrogen Receptor’ OR ‘ER’) AND (‘polymorphism’ OR ‘single nucleotide polymorphism’ OR ‘SNP’ OR ‘variation’) AND (‘BMD’ OR ‘bone mineral density’). Then, one-by-one screening was performed by two authors according to the inclusion and exclusion criteria. No language restrictions were applied. Secondary searches of eligible studies were conducted by searching the reference lists of the selected studies, reviews or comments.

Inclusion and exclusion criteria
The inclusion criteria of our meta-analysis are as follows: (1) case-control studies; (2) studies on BMD and fracture risks in postmenopausal women with PMOP due to estrogen deficiency using postmenopausal women without PMOP or healthy volunteers as control; (3) studies reporting alleles and genotypes of at least one of the ER gene polymorphisms in women with or without PMOP: ERα Xbal (rs9340799), ERα PvuII (rs2234693), ERα G2014A (rs2228480), ERβ AluI (rs4986938) and ERβ Rsal (rs1256049); (3) studies reporting the sample size, mean and standard deviation (SD) of BMD (g/cm²) or BMD Z value in PMOP women with at least one of the ER genotypes; and (4) studies with sufficient data. The exclusion criteria were: (1) reviews or case reports without controls, and (2) studies with no availability of current data; and (3) duplicated reports.

Data extraction
Data from the eligible studies were extracted according to the inclusion and exclusion criteria by two authors, and a consensus was reached by discussion. In the study of associations between ER gene polymorphisms and PMOP risk, the following data were collected: author list, year of publication, ethnicity, sample size, alleles, genotype of each gene polymorphism and Hardy-Weinberg equilibrium (HWE). The following data were collected for analysis of differences in BMD in PMOP
women with various ER genotypes: author list, year of publication, ethnicity, the number of cases and mean and SD of BMD (g/cm²) and BMD Z value.

Data synthesis and statistical analysis

We calculated odds ratios (OR) and 95% confidence interval (CI) to evaluate the association between ER gene polymorphisms and PMOP risk (osteoporosis occurred in postmenopausal women due to estrogen deficiency as represented by low BMD and increased fracture risks). The strength of association between ER gene polymorphisms and PMOP susceptibility was evaluated by OR and 95% CI under the allele contrast model, heterozygote model, homozygote model, dominant model and recessive model. HWE was calculated in the control population to evaluate the quality of the data by using chisquare test. Regarding the associations between BMD and ER gene polymorphisms, we compared BMD (g/cm²) and BMD Z value in PMOP women under the heterozygote and homozygote model respectively using the weight mean difference (WMD) and 95% CI. Heterogeneity of the included studies was examined by a chisquared-based Q statistical test and quantified by I² metric value. If I² value was > 50% or P < 0.10, ORs and WMD were pooled by the random effect model; otherwise, the fixed effect model was used. Power analysis was performed using the Power and Precision V4 software (Biostat Inc., Englewood, USA). Sensitivity analysis was performed to assess the impact of each study on the combined effect of the present meta-analysis. Besides, subgroup analysis was also performed according to the ethnicity of the study populations. Stata 12.0 software (StataCorp, College Station, TX, USA) was used and a P < 0.05 was considered as statistically significant.

Results

Study selection and characteristics

A total of 28 studies [11–38] were finally recruited in our meta-analysis. The study selection and inclusion process is shown in Fig. 1. Fourteen studies [11–24]...
reported the association between ERα Xbal and PMOP risk, and the number of the included studies that reported the alleles and genotypes of ERα PvuII, ERα G2014A, ERβ AluI and ERβ Rsal was 16 [11–25, 32], 4 [26–29], 4 [17, 30–32] and 2 [30, 31], respectively. Ivanova et al. [20], Albagha et al. [33], Aerssens et al. [24], Kurt et al. [34], Ge et al. [36] and Pérez et al. [19] reported both the lumbar spine and femoral neck BMD (g/cm²). Jeedigunta et al. [15] and Kurabayashi et al. [35] were also recruited in the assessment of the lumbar spine BMD (g/cm²) in ERα Xbal genotypes. Ivanova et al. [20], Albagha et al. [33] and An et al. [38] reported both the lumbar spine and femoral neck Z values. Shang et al. [11] also studied the lumbar spine Z value in PMOP with ERα Xbal genotypes. Ten studies [15, 19, 20, 23, 24, 33–37] and 8 studies [19, 20, 23, 24, 33, 34, 36, 37] were recruited in the pooled analysis of differences in lumbar spine and femoral neck BMD (g/cm²) in PMOP women carrying ERα PvuII, respectively. With regard to differences in lumbar spine and femoral neck Z value in PMOP women with ERα PvuII, 4 studies [11, 20, 33, 38] and 3 studies [20, 33, 38] were included in our meta-analysis, respectively. In addition, all these studies complied with HWE. The characteristics of the included studies are shown in Tables 1, 2 and 3.

Power analysis
Before initiation of the meta-analysis, a power analysis was conducted by using the Power and Precision V4 software to verify whether the included studies could offer adequate power (>80%). The result showed that the statistical power in our study was sufficient to detect the associations between ER gene polymorphisms and PMOP risk.

Associations between ER gene polymorphisms and PMOP risk
Overall, we did not find any significant association between ERα Xbal and ERα PvuII polymorphisms and risk of PMOP in either overall, Caucasian or Asian populations (all P > 0.05) (Table 4). ERα G2014A polymorphism played a protective role in developing PMOP in Caucasian populations, while no significant association was observed in overall and Asian populations (both P > 0.05). All the data are shown in Table 4 and Fig. 2.

With regard to ERβ polymorphism, ERβ AluI was significantly associated with the risk of developing PMOP in Asian postmenopausal women under the recessive model; however, we did not observe any significant association between ERβ AluI and PMOP risk in overall and Caucasian populations (both P > 0.05) (Table 4 and Fig. 3). Furthermore, we also found that there was a remarkable association between ERβ Rsal polymorphism and decreased PMOP risk in overall and Asian populations (Table 4).

Associations between ER gene polymorphisms and BMD in PMOP women

**ERα Xbal and lumbar spine bone mineral density (BMD g/cm² and BMD Z value)**
In our meta-analysis, no significant difference in lumbar spine BMD (g/cm²) was observed between PMOP women with ERα Xbal XX, ERα Xbal Xx and ERα Xbal xx genotype in either overall, Caucasian or Asian populations (all P > 0.05) (Table 5). The lumbar spine BMD Z value in Caucasian PMOP women carrying ERα Xbal XX genotype was greater than that in those carrying xx genotype, while no significant difference was observed in overall and Asian populations (both P > 0.05). ERα Xbal Xx genotype was found to be significantly associated with high lumbar spine BMD Z value in either overall or Caucasian populations but not in Asian populations.

**ERα Xbal and femoral neck bone mineral density (BMD g/cm² and BMD Z value)**
Our pooled analyses indicated that the ERα Xbal XX genotype was significantly associated with increased femoral neck BMD in overall and Caucasian populations. In contrast, ERα Xbal Xx genotype did not play a key role in femoral neck BMD in Asian populations (Table 5 and Fig. 4). Interestingly, compared with PMOP women with xx genotype, Xx genotype was significantly associated with decreased femoral neck Z value in Caucasians, and increased femoral neck Z value in Asians (Table 5). However, no significant association was observed between XX genotype and the femoral neck Z value in overall populations. In addition, Caucasians and Asians carrying the ERα Xbal Xx genotype were at risk of a high femoral neck Z value, while no significant association was found in overall populations. We did not observe remarkable relationships between ERα Xbal Xx genotype and femoral neck BMD in either overall, Caucasian or Asian populations (all P > 0.05). All data are shown in Table 5.

**ERα PvuII and lumbar spine bone mineral density (BMD g/cm² and BMD Z value)**
With regard to ERα PvuII, the difference in the lumbar spine Z value between the PP and pp. genotypes was 0.07 (95% CI = −0.03 to −0.01, P = 0.031) in Caucasian PMOP women; however, no significant difference was observed in overall and Asian populations. For the Pp versus pp. genotype, the difference in lumbar spine BMD was −0.01 (95% CI = −0.02 to −0.00, P = 0.036) in overall populations, and the difference in the lumbar spine Z value was −0.16 (95% CI = −0.20 to −0.12, P < 0.001) in Caucasian populations.
| Author           | Year | Ethnicity | Sample Size | ERα Xba   | HWE |
|------------------|------|-----------|-------------|-----------|-----|
|                  |      |           | Case Control| X x XX Xx xx |     |
| Shang et al.     | 2016 | Asian     | 198 276     | 338 58 146 46 6 | 109 443 10 89 177 0.77 |
| Wang et al.      | 2015 | Asian     | 72 72       | 125 19 55 15 2 | 132 12 62 8 2 0.21 |
| Li et al.        | 2014 | Asian     | 440 791     | 254 626 31 192 217 | 404 1178 48 308 435 0.50 |
| Erdogan et al.   | 2011 | Caucasian | 50 30       | 41 59 7 27 16 | 28 32 6 16 8 0.70 |
| Jeedigunta et al.| 2010 | Asian     | 247 254     | 253 241 60 133 54 | 306 202 81 144 29 0.32 |
| Tannrøver et al. | 2010 | Caucasian | 50 50       | 48 52 5 38 7 | 54 46 12 30 8 0.14 |
| Harsløf et al.   | 2010 | Caucasian | 228 225     | 134 322 19 96 113 | 164 286 30 104 91 0.97 |
| Musumeci et al.  | 2009 | Caucasian | 100 200     | 130 70 35 60 5 | 155 245 13 129 58 0.26 |
| Pérez et al.     | 2008 | Caucasian | 64 68       | 48 80 9 30 25 | 46 90 5 36 27 0.13 |
| Ivanova et al.   | 2007 | Caucasian | 220 180     | 256 184 73 110 37 | 163 197 25 113 42 0.58 |
| Huang et al.     | 2006 | Asian     | 66 116      | 19 113 2 15 49 | 46 186 4 38 74 0.74 |
| Nam et al.       | 2005 | Asian     | 6 168       | 0 12 0 0 6 | 63 273 6 51 111 0.96 |
| Qin et al.       | 2004 | Asian     | 244 273     | 120 368 11 98 135 | 137 409 13 111 149 0.18 |
| Aerssens et al.  | 2000 | Caucasian | 135 239     | 92 178 14 64 57 | 175 303 32 111 96 0.99 |

| Author           | Year | Ethnicity | Sample Size | ERα PvuII | HWE |
|------------------|------|-----------|-------------|-----------|-----|
|                  |      |           | Case Control| P p PP Pp pp |     |
| Shang et al.     | 2016 | Asian     | 198 276     | 156 240 28 100 | 70 386 166 138 110 28 0.38 |
| Wang et al.      | 2015 | Asian     | 60 60       | 30 90 3 24 33 | 32 88 3 26 31 0.40 |
| Li et al.        | 2014 | Asian     | 440 791     | 368 512 65 238 137 | 498 1084 69 360 362 0.12 |
| Sonoda et al.    | 2012 | Asian     | 114 171     | 118 110 24 70 | 20 137 205 31 75 65 0.26 |
| Erdogan et al.   | 2011 | Caucasian | 50 30       | 42 58 8 26 16 | 38 22 10 18 2 0.11 |
| Jeedigunta et al.| 2010 | Asian     | 247 254     | 181 313 50 81 116 | 232 276 60 112 82 0.08 |
| Tannrøver et al. | 2010 | Caucasian | 50 50       | 39 61 7 25 18 | 48 52 14 20 16 0.79 |
| Harsløf et al.   | 2010 | Caucasian | 228 224     | 198 258 46 106 76 | 233 215 63 107 54 0.52 |
| Musumeci et al.  | 2009 | Caucasian | 100 200     | 120 80 30 60 10 | 186 214 31 124 45 0.53 |
| Pérez et al.     | 2008 | Caucasian | 64 68       | 56 72 11 34 19 | 58 78 12 34 22 0.86 |
| Ivanova et al.   | 2007 | Caucasian | 220 180     | 226 214 58 110 52 | 148 212 21 106 53 0.37 |
| Morón et al.     | 2006 | Caucasian | 87 175      | 79 95 17 45 25 | 171 179 45 81 49 0.33 |
| Huang et al.     | 2006 | Asian     | 66 116      | 79 53 23 33 10 | 68 164 11 46 59 0.64 |
| Nam et al.       | 2005 | Asian     | 6 168       | 2 10 1 0 5 | 130 206 25 80 63 0.96 |
| Qin et al.       | 2004 | Asian     | 244 273     | 193 295 40 113 91 | 223 323 43 137 93 0.52 |
| Aerssens et al.  | 2000 | Caucasian | 135 239     | 120 150 27 66 42 | 219 259 47 125 67 0.41 |

| Author           | Year | Ethnicity | Sample Size | ERα G2014A | HWE |
|------------------|------|-----------|-------------|-----------|-----|
|                  |      |           | Case Control| A A AA AA GA GA GG GG |     |
| Wajanavisit et al.| 2015 | Asian     | 99 113      | 94 104 33 28 38 | 179 47 72 35 6 0.53 |
| Gómez et al.     | 2007 | Caucasian | 70 500      | 30 110 2 26 42 | 303 697 40 223 237 0.21 |
| Ongphiphadhanakul et al. | 2003 | Asian     | 33 325      | 23 43 5 13 15 | 129 521 13 103 209 0.94 |
| Ongphiphadhanakul et al. | 2001 | Asian     | 106 122     | 56 156 8 40 58 | 37 207 2 33 87 0.57 |
populations; however, we did not find any significant difference in lumbar spine BMD in either Caucasians or Asians, and in the lumbar spine Z value in overall and Asian populations (Table 5 and Fig. 5). In addition, no significant difference in lumbar spine BMD was observed between PP and pp. genotypes ($P > 0.05$) (Table 5).

**Discussion**

**Associations between ERα gene polymorphisms and PMOP risk**

ERα XbaI and ERα PvuII are the two restriction fragment length polymorphisms of ERα gene located in Intron 1 [14]. Many studies [11–25, 32] have been performed to explore the relationships between ERα XbaI, ERα PvuII and PMOP risk; however, these studies have yielded inconsistent data [11–25, 32]. Overall, we did not observe any significant association between ERα XbaI and ERα PvuII polymorphisms and PMOP risk in either overall, Caucasian or Asian populations. In our opinion, the inadequate sample size, different ethnicities, various genotyping techniques, the presence of admixture in the population, gene-environment interactions, differences in age and measurement errors of different investigators might be important factors contributing to these controversial results. ERα XbaI and ERα PvuII have proven to play key roles in attainment and maintenance of peak bone mass during young adulthood, and it might be difficult to document their effects in a population of postmenopausal women [24]. In addition, PvuII and XbaI polymorphisms are located in a non-functional area of the ER gene [20], which might also contribute to our polled results. With regard to ERα G2014A, it is located on the exon region of chromosome 6p25.1, and may contribute via the epigenetic level for the efficiency of translation or receptor protein expression [26]. Our results showed that a significant association between ERα G2014A and PMOP risk was observed only in Caucasian populations but not in overall and Asian populations.

**Associations between ERβ gene polymorphisms and PMOP risk**

ERβ has been found to be more abundant than ERα in trabecular bone, and more potent than ERα in
Table 2  Characteristics of included studies of lumbar spine BMD, femoral neck BMD, lumbar spine Z value and femoral neck Z value in ERα XbaI genotypes

| ERα XbaI | Lumbar Spine BMD (g/cm²) |  | ERα XbaI | Femoral Neck BMD (g/cm²) |  |
|----------|--------------------------|---|----------|--------------------------|---|
|          | XX                       | Xx | xx       | XX                       | Xx | xx |
| Author   | Year                     | Ethnicity | N | Mean ± SD | N | Mean ± SD | N | Mean ± SD | N | Mean ± SD | N | Mean ± SD |
| Ivanova et al. | 2007 | Caucasian | 73 | 0.75 ± 0.17 | 110 | 0.81 ± 0.06 | 37 | 0.87 ± 0.07 |
| Albagha et al. | 2001 | Caucasian | 27 | 0.88 ± 0.03 | 89 | 0.88 ± 0.02 | 90 | 0.85 ± 0.02 |
| Aerssens et al. | 2000 | Caucasian | 14 | 0.94 ± 0.21 | 64 | 0.93 ± 0.22 | 57 | 0.88 ± 0.16 |
| Jeedigunta et al. | 2010 | Asian | 60 | 0.89 ± 0.15 | 133 | 0.86 ± 0.13 | 54 | 0.64 ± 0.16 |
| Kurt et al. | 2012 | Caucasian | 41 | 0.95 ± 0.12 | 94 | 0.92 ± 0.12 | 40 | 0.93 ± 0.10 |
| Kurabayashi et al. | 1999 | Asian | 1 | 1.18 ± 0.00 | 20 | 0.92 ± 0.04 | 61 | 0.92 ± 0.02 |
| Ge et al. | 2006 | Asian | 37 | 0.73 ± 0.08 | 134 | 0.74 ± 0.09 | 26 | 0.75 ± 0.13 |
| Pérez et al. | 2008 | Caucasian | 7 | 0.70 ± 0.02 | 31 | 0.67 ± 0.02 | 24 | 0.66 ± 0.02 |

| ERα XbaI | Lumbar Spine Z value |  | ERα XbaI | Femoral Neck Z value |  |
|----------|---------------------|---|----------|---------------------|---|
|          | XX                  | Xx | xx      | XX                  | Xx | xx |
| Author   | Year                | Ethnicity | N | Mean ± SD | N | Mean ± SD | N | Mean ± SD | N | Mean ± SD |
| Shang et al. | 2016 | Asian | 146 | -1.98 ± 0.91 | 146 | -1.65 ± 0.02 | 6 | -0.35 ± 2.19 |
| Ivanova et al. | 2007 | Caucasian | 73 | -2.10 ± 0.00 | 110 | -0.6 ± 0.00 | 37 | -0.1 ± 0.00 |
| Albagha et al. | 2001 | Caucasian | 27 | -0.34 ± 0.20 | 89 | -0.29 ± 0.11 | 90 | -0.47 ± 0.11 |
| An et al. | 2000 | Asian | 10 | 0.48 ± 0.49 | 84 | 0.12 ± 0.85 | 152 | -0.26 ± 0.58 |
| Author       | Year | Ethnicity | N  | Mean ± SD | N  | Mean ± SD | N  | Mean ± SD |
|--------------|------|-----------|----|-----------|----|-----------|----|-----------|
| Ivanova et al. | 2007 | Caucasian | 58 | 0.70 ± 0.09 | 110 | 0.71 ± 0.10 | 52 | 0.77 ± 0.06 |
| Albagha et al. | 2001 | Caucasian | 37 | 0.87 ± 0.03 | 102 | 0.86 ± 0.02 | 67 | 0.88 ± 0.02 |
| Aerssens et al. | 2000 | Caucasian | 27 | 0.93 ± 0.18 | 66 | 0.91 ± 0.22 | 42 | 0.89 ± 0.17 |
| Jeedigunta et al. | 2010 | Asian | 50 | 0.92 ± 0.18 | 81 | 0.89 ± 0.11 | 116 | 0.81 ± 0.14 |
| Kurt et al. | 2012 | Caucasian | 44 | 0.93 ± 0.13 | 104 | 0.93 ± 0.11 | 46 | 0.93 ± 0.09 |
| Kurabayashi et al. | 1999 | Asian | 19 | 0.99 ± 0.04 | 27 | 0.89 ± 0.03 | 36 | 0.91 ± 0.02 |
| Ge et al. | 2006 | Asian | 38 | 0.73 ± 0.10 | 93 | 0.74 ± 0.09 | 67 | 0.75 ± 0.10 |
| Ge et al. | 2006 | Asian | 38 | 0.73 ± 0.10 | 92 | 0.74 ± 0.09 | 67 | 0.75 ± 0.10 |
| Qin et al. | 2004 | Asian | 40 | 0.70 ± 0.01 | 113 | 0.70 ± 0.01 | 91 | 0.72 ± 0.01 |
| Pérez et al. | 2008 | Caucasian | 11 | 0.73 ± 0.03 | 34 | 0.66 ± 0.02 | 17 | 0.65 ± 0.02 |

| Author       | Year | Ethnicity | N  | Mean ± SD | N  | Mean ± SD | N  | Mean ± SD |
|--------------|------|-----------|----|-----------|----|-----------|----|-----------|
| Shang et al. | 2016 | Asian | 28 | −1.54 ± 0.35 | 100 | −1.67 ± 0.91 | 70 | −2.79 ± 1.46 |
| Ivanova et al. | 2007 | Caucasian | 58 | −2.40 ± 0.00 | 110 | −2.10 ± 0.00 | 52 | −1.50 ± 0.00 |
| Ivanova et al. | 2007 | Caucasian | 58 | −2.40 ± 0.00 | 110 | −2.10 ± 0.00 | 52 | −1.50 ± 0.00 |
| Albagha et al. | 2001 | Caucasian | 37 | −0.35 ± 0.16 | 102 | −0.44 ± 0.10 | 67 | −0.28 ± 0.14 |
| An et al. | 2000 | Asian | 53 | −0.53 ± 0.16 | 128 | −0.21 ± 0.99 | 65 | 0.22 ± 0.46 |
**Table 4** Results of genetic models for ERα XbaI, ERα PvuII, ERα G2014A, ERβ AluI and ERβ RsaI polymorphisms and osteoporosis susceptibility in postmenopausal women

| Comparison       | N  | Test of association | Model | Test of heterogeneity | Begg's test | Egger's test |
|------------------|----|---------------------|-------|-----------------------|-------------|--------------|
|                  |    | OR                  | 95% CI | P value               | I² (%)      | P value      | P value |
| **ERα XbaI**     |    |                     |       |                       |             |              |         |
| Overall          | 14 |                     |       |                       |             |              |         |
| X vs. x          | 1.21 | 0.73–2.00       | 0.455 | R < 0.001             | 96.4        | 0.584        | 0.955   |
| XX vs. xx        | 1.84 | 0.71–4.75        | 0.206 | R < 0.001             | 93.7        | 0.443        | 0.465   |
| Xx/XX vs. xx     | 1.19 | 0.83–1.70        | 0.357 | R < 0.001             | 80.1        | 0.511        | 0.610   |
| Xx vs. Xx/xx     | 1.34 | 0.82–2.18        | 0.240 | R < 0.001             | 90.4        | 0.661        | 0.545   |
| XX vs. Xx/xx     | 1.50 | 0.70–3.24        | 0.296 | R < 0.001             | 93.4        | 0.443        | 0.875   |
| **Caucasian**    |    |                     |       |                       |             |              |         |
| X vs. x          | 1.15 | 0.76–1.74        | 0.510 | R < 0.001             | 88.0        |              |         |
| XX vs. xx        | 1.56 | 0.56–4.39        | 0.399 | R < 0.001             | 88.9        |              |         |
| Xx vs. xx        | 1.13 | 0.76–1.67        | 0.540 | R < 0.001             | 59.8        |              |         |
| Xx/XX vs. xx     | 1.24 | 0.76–2.01        | 0.387 | R < 0.001             | 76.2        |              |         |
| XX vs. Xx/xx     | 1.30 | 0.56–3.03        | 0.536 | R < 0.001             | 88.2        |              |         |
| **Asian**        |    |                     |       |                       |             |              |         |
| X vs. x          | 1.23 | 0.47–3.25        | 0.668 | R < 0.001             | 98.0        |              |         |
| XX vs. xx        | 2.18 | 0.37–12.73       | 0.388 | R < 0.001             | 98.1        |              |         |
| Xx vs. xx        | 1.22 | 0.63–2.36        | 0.553 | R < 0.001             | 88.0        |              |         |
| Xx/XX vs. xx     | 1.39 | 0.56–3.46        | 0.481 | R < 0.001             | 94.6        |              |         |
| XX vs. Xx/xx     | 1.77 | 0.44–7.14        | 0.424 | R < 0.001             | 96.0        |              |         |
| **ERα PvuII**    |    |                     |       |                       |             |              |         |
| Overall          | 16 |                     |       |                       |             |              |         |
| P vs. p          | 0.96 | 0.71–1.29        | 0.769 | R < 0.001             | 92.3        | 0.753        | 0.616   |
| PP vs. pp        | 0.99 | 0.55–1.78        | 0.961 | R < 0.001             | 90.8        | 1.000        | 0.886   |
| Pp vs. pp        | 1.01 | 0.72–1.41        | 0.956 | R < 0.001             | 82.3        | 0.753        | 0.501   |
| PP/Pp vs. pp     | 0.97 | 0.65–1.43        | 0.868 | R < 0.001             | 88.7        | 0.893        | 0.539   |
| PP vs. Pp/pp     | 0.99 | 0.65–1.53        | 0.977 | R < 0.001             | 87.3        | 0.893        | 0.976   |
| **Caucasian**    |    |                     |       |                       |             |              |         |
| P vs. p          | 0.95 | 0.71–1.26        | 0.716 | R < 0.001             | 79.2        |              |         |
| PP vs. pp        | 0.93 | 0.49–1.79        | 0.831 | R < 0.001             | 81.4        |              |         |
| Pp vs. pp        | 0.98 | 0.73–1.31        | 0.877 | R < 0.001             | 40.0        |              |         |
| PP/Pp vs. pp     | 0.97 | 0.67–1.39        | 0.861 | R < 0.001             | 63.5        |              |         |
| PP vs. Pp/pp     | 0.97 | 0.59–1.58        | 0.895 | R < 0.001             | 78.2        |              |         |
| **Asian**        |    |                     |       |                       |             |              |         |
| P vs. p          | 0.97 | 0.57–1.66        | 0.919 | R < 0.001             | 95.6        |              |         |
| PP vs. pp        | 1.08 | 0.40–2.96        | 0.877 | R < 0.001             | 94.4        |              |         |
| Pp vs. pp        | 1.04 | 0.58–1.88        | 0.889 | R < 0.001             | 90.2        |              |         |
| PP/Pp vs. pp     | 0.98 | 0.50–1.95        | 0.962 | R < 0.001             | 93.8        |              |         |
| PP vs. Pp/pp     | 1.05 | 0.50–2.20        | 0.891 | R < 0.001             | 91.8        |              |         |
| **ERα G2014A**   |    |                     |       |                       |             |              |         |
| Overall          | 4  |                     |       |                       |             |              |         |
| A vs. G          | 0.89 | 0.32–2.51        | 0.825 | R < 0.001             | 95.1        | 0.308        | 0.237   |
Table 4 Results of genetic models for ERα XbaI, ERα PvuII, ERα G2014A, ERβ AluI and ERβ RsaI polymorphisms and osteoporosis susceptibility in postmenopausal women (Continued)

| Comparison        | N  | Test of association | Model | Test of heterogeneity | Begg’s test | Egger’s test |
|-------------------|----|---------------------|-------|-----------------------|-------------|--------------|
|                   |    | OR                  | 95% CI | P value               | I² (%)      |               |
|                   |    |                     |       |                       | P value     |               |
|                   |    |                     |       |                       | P value     |               |
|                   |    |                     |       |                       | P value     |               |
| AA vs. GG         | 0.88 | 0.08–9.19          | 0.912 | < 0.001               | 92.9        | 0.734        | 0.419        |
| GA vs. GG         | 0.76 | 0.28–2.03          | 0.581 | < 0.001               | 88.1        | 0.734        | 0.530        |
| GA/AA vs. GG      | 0.73 | 0.22–2.41          | 0.601 | < 0.001               | 92.8        | 0.734        | 0.530        |
| AA vs. GA/GG      | 1.13 | 0.23–5.72          | 0.878 | < 0.001               | 88.6        | 0.734        | 0.299        |
| Caucasian         | 1   | A vs. G             | 0.63  | 0.41–0.96             | 0.032       | R – –        |
|                   |     | AA vs. GG           | 0.28  | 0.07–1.21             | 0.089       | R – –        |
|                   |     | GA vs. GG           | 0.66  | 0.39–1.11             | 0.116       | R – –        |
|                   |     | GA/AA vs. GG        | 0.60  | 0.36–1.00             | 0.050       | R – –        |
|                   |     | AA vs. GA/GG        | 0.34  | 0.08–1.43             | 0.141       | R – –        |
| Asian             | 3   | A vs. G             | 1.00  | 0.23–4.46             | 0.996       | R < 0.001    | 96.6         |
|                   |     | AA vs. GG           | 1.28  | 0.05–30.10            | 0.878       | R < 0.001    | 95.2         |
|                   |     | GA vs. GG           | 0.77  | 0.17–3.45             | 0.736       | R < 0.001    | 91.3         |
|                   |     | GA/AA vs. GG        | 0.76  | 0.12–4.62             | 0.765       | R < 0.001    | 94.8         |
|                   |     | AA vs. GA/GG        | 1.69  | 0.20–14.27            | 0.630       | R < 0.001    | 92.2         |
| ERβ AluI          |     | Overall             | 1.25  | 0.78–2.00             | 0.362       | R < 0.001    | 91.5         | 1.000        | 0.997        |
|                   |     | AA vs. GG           | 1.27  | 0.52–3.13             | 0.597       | R < 0.001    | 88.4         | 0.734        | 0.647        |
|                   |     | GA vs. GG           | 1.16  | 0.65–2.07             | 0.606       | R 0.001      | 81.0         | 0.734        | 0.408        |
|                   |     | GA/AA vs. GG        | 1.29  | 0.66–2.53             | 0.459       | R < 0.001    | 87.8         | 0.734        | 0.612        |
|                   |     | AA vs. GA/GG        | 1.21  | 0.65–2.24             | 0.553       | R < 0.001    | 85.7         | 0.497        | 0.646        |
| Caucasian         | 3   | A vs. G             | 1.23  | 0.58–2.57             | 0.590       | R < 0.001    | 94.3         |
|                   |     | AA vs. GG           | 1.28  | 0.34–4.84             | 0.717       | R < 0.001    | 92.2         |
|                   |     | GA vs. GG           | 1.30  | 0.60–2.78             | 0.504       | R 0.001      | 86.5         |
|                   |     | GA/AA vs. GG        | 1.36  | 0.55–3.39             | 0.507       | R < 0.001    | 91.8         |
|                   |     | AA vs. GA/GG        | 1.10  | 0.37–3.22             | 0.863       | R < 0.001    | 90.3         |
| Asian             | 1   | A vs. G             | 1.31  | 1.06–1.62             | 0.012       | R – –        |
|                   |     | AA vs. GG           | 1.24  | 0.72–2.13             | 0.441       | R – –        |
|                   |     | GA vs. GG           | 0.84  | 0.48–1.48             | 0.548       | R – –        |
|                   |     | GA/AA vs. GG        | 1.10  | 0.64–1.87             | 0.739       | R – –        |
|                   |     | AA vs. GA/GG        | 1.44  | 1.12–1.84             | 0.004       | R – –        |
| ERβ RsaI          |     | Overall             | 0.92  | 0.50–1.70             | 0.785       | R 0.010      | 85.0         |
|                   |     | AA vs. GG           | 0.49  | 0.34–0.70             | < 0.001     | F 0.261      | 20.9         |
|                   |     | GA vs. GG           | 0.87  | 0.41–1.84             | 0.722       | R < 0.001    | 85.9         |
|                   |     | GA/AA vs. GG        | 0.85  | 0.37–1.95             | 0.704       | R < 0.001    | 88.9         |
mediating estrogen-induced repression of TNF-α expression, which is considered an important contributor to PMOP [30]. ERβ AluI is one of the widely-studied ERβ gene polymorphisms, knowing that it could alter mRNA stability and protein levels, leading to reduced synthesis of ERβ [30]. In our study, ERβ AluI was found to be significantly associated with increased risk of PMOP in Asian populations, while no significant relationship was observed in overall and Caucasian populations. Thus, different genetic backgrounds, environmental effects and/or their internal interactions could explain the diverse results in various ethnicities. ERβ Rsal is another important polymorphism of ERβ. Our subgroup analysis revealed a significant association between ERβ Rsal and PMOP risk in overall populations, which is consistent with the studies of Shoukry et al. [30], and Huang et al. [31].

**Associations between ERα Xbal and lumbar spine and femoral neck BMD**

Our pooled results showed that there was no significant difference in lumbar spine BMD between PMOP women carrying XX, Xx, and xx genotype in either overall, Caucasian or Asian populations. However, WANG et al. [39] reported that the Xbal

### Table 4

| Comparison         | N | Test of association | Model | Test of heterogeneity | Begg’s test | Egger’s test |
|--------------------|---|---------------------|-------|-----------------------|-------------|--------------|
|                    |   | OR      | 95% CI | P value | I² (%) | P value | P value |
| AA vs. GA/GG       |   | 0.66    | 0.48–0.90 | 0.009 | F     | 0.408 | 0       |
| Caucasian          |   |          |        |         |        |        |         |
| A vs. G            | 1 | 1.30    | 0.83–2.04 | 0.245 | R     | –     | –       |
| AA vs. GG          | 1 | 1.92    | 0.17–21.41 | 0.596 | F     | –     | –       |
| GA vs. GG          | 1 | 1.32    | 0.80–2.15 | 0.273 | R     | –     | –       |
| GA/AA vs. GG       | 1 | 1.33    | 0.82–2.17 | 0.246 | R     | –     | –       |
| AA vs. GA/GG       | 1 | 1.81    | 0.16–20.11 | 0.630 | F     | –     | –       |
| Asian              |   |          |        |         |        |        |         |
| A vs. G            | 1 | 0.69    | 0.58–0.82 | <0.001 | R     | –     | –       |
| AA vs. GG          | 1 | 0.47    | 0.33–0.68 | <0.001 | F     | –     | –       |
| GA vs. GG          | 1 | 0.61    | 0.47–0.81 | <0.001 | R     | –     | –       |
| GA/AA vs. GG       | 1 | 0.57    | 0.44–0.74 | <0.001 | R     | –     | –       |
| AA vs. GA/GG       | 1 | 0.65    | 0.47–0.89 | 0.007 | F     | –     | –       |

*Random effect model

*Fixed effect model

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**Fig. 2** Forest plot describing the meta-analysis under the dominant model for the association between ERα G2014A polymorphism and the risk of PMOP (GA/AA vs. GG)
polymorphism was significantly associated with BMD of the lumbar spine, and XX had a protective effect in comparison with carriers of the x alleles, which is consistent with the report of Ioannidis et al. [41]. Both WANG and Ioannidis included all types of osteoporotic patients, not only postmenopausal women, which might be the most important reason for the difference between our results and theirs. As mentioned above, ERα XbaI might not play a key role in attainment and maintenance of peak bone mass in postmenopausal women [24], and therefore it could be easily understood why no significant association was observed between ERα XbaI and lumbar spine BMD. With regard to femoral neck BMD, our study indicated that the femoral neck BMD in PMOP women with XX genotype was significantly higher than that in women with xx genotype in overall and Caucasian populations, which highlights the theory that ERα gene is involved in the pathogenesis of PMOP. No significant difference of femoral neck BMD was observed between PMOP women with Xx and xx genotype in each subgroup. Although no significant association was observed between lumbar spine BMD and ERα XbaI, we found that the lumbar spine Z value in both PMOP women carrying XX and those carrying Xx genotype was significantly higher than that in Caucasians carrying xx genotype. We also observed that XX genotype was associated with a low femoral neck Z value in Caucasians and high femoral neck Z value in Asians. In addition, Caucasians and Asians carrying Xx genotype were at risk of a high femoral neck Z value. However, why ERα XbaI plays a contradictory role in BMD and Z value at the lumbar spine and femoral neck, and the mechanisms by which it is associated with BMD and Z value remains unclear and needs further investigation.

Associations between ERα PvuII and lumbar spine and femoral neck BMD

Although the molecular mechanism underlying the effect of ERα PvuII on bone mass is poorly understood, it is believed that ERα PvuII might play a key role in BMD as it is in linkage disequilibrium with the TA polymorphism in the ER promoter that is associated with altered gene transcription [20]. Our pooled analysis indicated that PMOP women with the Pp genotype had lower lumbar spine BMD than those with the pp genotype. We also found that there was no significant difference in lumbar spine BMD between women with the PP genotype and those with the pp genotype, which is consistent with the meta-analysis of Wang et al. [40]. Furthermore, we observed that the PP genotype was associated with decreased femoral neck BMD in Asians, while Pp might not play a key role in femoral neck BMD in all subgroups. Interestingly, WANG et al. [39] reported that PP play a role in protecting the lumbar spine but on the other hand it might be a risk factor for the femoral neck fracture. Wang CL [40] and WANG KJ [39] conducted their meta-analyses on osteoporotic women during menopause while our study included osteoporotic women post menopause, which might be the most important reason for the difference between our study and theirs. In addition, both PP and Pp genotypes were significantly associated with low lumbar spine Z value in Caucasians,
but not in overall and Asian populations, probably because of the different genetic backgrounds in various ethnicities and interactions between genetic and non-genetic factors. PMOP women with the PP and Pp genotypes had lower femoral neck Z value than those with the pp genotype in overall, Caucasian and Asian populations.

### Table 5

| ERα XbaI | XX vs. xx | Test of differences | Model | Test of heterogeneity | XX vs. xx | Test of differences | Model | Test of heterogeneity |
|----------|-----------|---------------------|-------|-----------------------|-----------|---------------------|-------|-----------------------|
|          | N         | WMD (95% CI)        | P value | I² (%) | N         | WMD (95% CI)        | P value | I² (%) |
| Lumbar Spine BMD (g/cm²) | | | | | | | | |
| Overall | 8         | 0.03 (--0.02, 0.08) | 0.198 R < 0.001 94.2 | 8         | 0.02 (--0.00, 0.05) | 0.086 R < 0.001 94.1 |
| Caucasian | 5         | 0.00 (--0.04, 0.04) | 0.917 R < 0.001 90.2 | 5         | 0.00 (--0.02, 0.02) | 0.862 R < 0.001 91.1 |
| Asian | 3         | 0.11 (--0.16, 0.38) | 0.414 R < 0.001 97.8 | 3         | 0.07 (--0.07, 0.20) | 0.326 R < 0.001 97.3 |
| Lumbar Spine Z value | | | | | | | | |
| Overall | 3         | 0.22 (--0.40, 0.83) | 0.495 R < 0.001 88.5 | 3         | 0.34 (0.00, 0.47) | 0.046 R 0.041 68.6 |
| Caucasian | 1         | 0.13 (0.05, 0.21) | 0.001 R -- -- | 1         | 0.18 (0.15, 0.21) | < 0.001 R -- -- |
| Asian | 2         | --0.28 (--2.58, 2.02) | 0.811 R < 0.001 85.2 | 2         | --0.33 (--1.81, 1.36) | 0.780 R 0.062 71.3 |
| Femoral Neck BMD (g/cm²) | | | | | | | | |
| Overall | 6         | 0.03 (0.01, 0.05) | 0.003 R 0.001 75.5 | 6         | 0.01 (--0.00, 0.03) | 0.057 R < 0.001 84.7 |
| Caucasian | 5         | 0.03 (0.01, 0.05) | 0.009 R < 0.001 80.4 | 5         | 0.01 (--0.00, 0.03) | 0.094 R < 0.001 87.7 |
| Asian | 1         | 0.03 (--0.01, 0.08) | 0.110 R -- -- | 1         | 0.01 (--0.02, 0.04) | 0.350 R -- -- |
| Femoral Neck Z value | | | | | | | | |
| Overall | 2         | --0.38 (--2.56, 1.80) | 0.733 R < 0.001 99.2 | 2         | 0.25 (--0.07, 0.58) | 0.130 R 0.011 91.6 |
| Caucasian | 1         | --1.48 (--1.57, --1.39) | < 0.001 R -- -- | 1         | 0.10 (0.07, 0.13) | < 0.001 R -- -- |
| Asian | 1         | 0.74 (0.37, 1.11) | < 0.001 R -- -- | 1         | 0.43 (0.24, 0.62) | < 0.001 R -- -- |

| ERα PvuII | PP vs. pp | Test of differences | Model | Test of heterogeneity | Pp vs. pp | Test of differences | Model | Test of heterogeneity |
|-----------|-----------|---------------------|-------|-----------------------|-----------|---------------------|-------|-----------------------|
|           | N         | WMD (95% CI)        | P value | I² (%) | N         | WMD (95% CI)        | P value | I² (%) |
| Lumbar Spine BMD (g/cm²) | | | | | | | | |
| Overall | 10        | 0.02 (--0.01, 0.04) | 0.216 R < 0.001 95.5 | 10        | --0.01 (--0.02, --0.00) | 0.036 R < 0.001 84.0 |
| Caucasian | 5        | 0.01 (--0.04, 0.06) | 0.793 R < 0.001 95.5 | 5         | --0.02 (--0.03, 0.00) | 0.106 R < 0.001 84.9 |
| Asian | 5        | 0.03 (--0.02, 0.08) | 0.288 R < 0.001 96.2 | 5         | --0.00 (--0.02, 0.02) | 0.912 R < 0.001 86.4 |
| Lumbar Spine Z value | | | | | | | | |
| Overall | 3         | 0.11 (--0.55, 0.78) | 0.742 R < 0.001 98.7 | 3         | 0.13 (--0.40, 0.67) | 0.623 R < 0.001 95.9 |
| Caucasian | 1         | --0.07 (--0.13, --0.01) | 0.031 R -- -- | 1         | --0.16 (--0.20, --0.12) | < 0.001 R -- -- |
| Asian | 2         | 0.24 (--1.72, 2.20) | 0.809 R < 0.001 99.0 | 2         | 0.34 (--1.18, 1.85) | 0.665 R < 0.001 97.9 |
| Femoral Neck BMD (g/cm²) | | | | | | | | |
| Overall | 8         | --0.04 (--0.09, 0.01) | 0.135 R < 0.001 99.3 | 8         | --0.02 (--0.04, 0.01) | 0.132 R < 0.001 98.2 |
| Caucasian | 5         | --0.06 (--0.16, 0.05) | 0.295 R < 0.001 99.6 | 5         | --0.03 (--0.05, 0.00) | 0.054 R < 0.001 95.2 |
| Asian | 3         | --0.01 (--0.02, --0.01) | 0.001 R 1.000 0.00 | 3         | --0.00 (--0.03, 0.02) | 0.768 R 0.009 78.7 |
| Femoral Neck Z value | | | | | | | | |
| Overall | 2         | --0.39 (--1.15, 0.37) | 0.315 R < 0.001 97.0 | 2         | --0.39 (--0.57, --0.20) | < 0.001 R 0.024 80.3 |
| Caucasian | 1         | --0.01 (--0.08, 0.05) | 0.718 R -- -- | 1         | --0.31 (--0.35, --0.27) | < 0.001 R -- -- |
| Asian | 1         | --0.79 (--1.05, --0.53) | < 0.001 R -- -- | 1         | --0.50 (--0.66, --0.34) | < 0.001 R -- -- |

*R Random effect model  
F Fixed effect model
Limitations

Although we performed a comprehensive analysis of the association between ERα, ERβ gene polymorphisms and PMOP risk and BMD in postmenopausal women, there are some limitations that should be addressed. First, high heterogeneity was observed in some of our pooled results, which might have negative impact on our conclusions. Second, PMOP is a disease whose etiology might be involved in several confounding factors, and other confounding factors such as age, years since menopause and estrogen therapy might interact with each other and play a key role in the etiology and progression of PMOP. However, no data available could be used in all recruited studies to detect the interactions between these confounding factors in PMOP patients. We should take all these confounding factors into consideration in our study rather than studying them separately, which is also a limitation of our meta-analysis. Third, we failed to perform a pooled analysis to detect whether ERα G2014A, ERβ AluI and ERβ Rsal were correlated with BMD in postmenopausal women as no sufficient data could be collected and analyzed. Therefore, larger-scale and better-designed studies are necessary to determine the association between ERα/β gene polymorphisms and PMOP risk and BMD in postmenopausal women.
Conclusion

ERα/β gene polymorphisms were significantly associated with PMOP risk and BMD in postmenopausal women, but each ERα/β gene polymorphism may have a distinct effect on PMOP risk and BMD in Asian and Caucasian populations.

Abbreviations

BMD: Bone mineral density; CI: Confidence interval; ER: Estrogen receptor; Lactase: LCT; OR: Odds ratios; PMOP: Postmenopausal Osteoporosis; PTH: Parathyroid Hormone; TGF-β: Transforming growth factor-β; WMD: Weight mean difference

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Authors’ contributions

HPZ and JNJ participated in the study design. QW and JZ made contributions to the data collection. LZ, YJX and TLM were responsible for the statistical analysis. HPZ and LYZ participated in the writing and LYZ was also responsible for the final proofing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

1. Gokosmanoglu F, Varim C, Atmaca A, Atmaca MH, Colak R. The effects of zolendronic acid treatment on depression and quality of life in women with postmenopausal osteoporosis: a clinical trial study. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2016;21:112.
2. Bandeira L, Bilezikian JP. Novel therapies for postmenopausal osteoporosis. Endocrinol Metab Clin N Am. 2017;46(1):207–19.
3. Eastell R, O’Neill TW, Hofbauer LC, Langdahl B, Reid IR, Gold DT, Cummings SR. Postmenopausal osteoporosis. Nature reviews Disease primers. 2016;2:16069.
4. Wensel TM, Iranikah MM, Wilborn TW. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. Pharmacotherapy. 2011;31(5):10–23.
5. Paschalis EP, Garnjaeger S, Hassler N, Fahrleitner-Pammer A, Dobnig H, Stepan JJ, Pavo I, Eriksen EF, Klaushofer K. Vitamin D and calcium supplementation for three years in postmenopausal osteoporosis significantly alters bone mineral and organic matrix quality. Bone. 2017;95:41–6.
6. Ebina K, Kashi M, Hiro M, Hashimoto J, Naguchi T, Koizumi K, Kitaguchi K, Matsuoka H, Iwahashi T, Tsukamoto Y, et al. Comparison of the effects of denosumab between a native vitamin D combination and an active vitamin D combination in patients with postmenopausal osteoporosis. J Bone Miner Metab. 2016;
7. Safer U, Safer VB, Demir SO, Yanikoglu I. Effects of bisphosphonates and calcium plus vitamin-D supplements on cognitive function in postmenopausal osteoporosis section sign. Endocrine, metabolic & immune disorders drug targets. 2016;16(1):56–60.
8. Gennari L, Rotatori S, Bianciardi S, Nitti R, Merlotti D. Treatment needs and current options for postmenopausal osteoporosis. Expert Opin Pharmacother. 2016;17(8):1141–52.
9. Xie W, Ji L, Zhao T, Gao P. Identification of transcriptional factors and key genes in primary osteoporosis by DNA microarray. Medical science monitor : international medical journal of experimental and clinical research. 2015;21:1333–44.
10. Macari S, Ajay Sharma L, Wyatt A, Knowles P, Szawka RE, Garlet GP, Gattan DR, Dias GJ, Silva TA. Osteoprotective effects of estrogen in the maxillary bone depend on ERalpha. J Dent Res. 2016;95(6):689–96.
11. Shang DP, Lian HY, Fu DP, Wu J, Hou SS, Lu JM. Relationship between estrogen receptor 1 gene polymorphisms and postmenopausal osteoporosis of the spine in Chinese women. Genetics and molecular research : GMR. 2016;15(2).
12. Wang ZR. Age difference of estrogen receptor gene polymorphisms in the elderly women with hip osteoporosis. Chin. J.of Tissue Engineering Res. 2015;19(7):991–5.
13. Hui L, Jishen X, Bingpu C, Hailing H, Jinhua W, Jianhui C, Xiaoyan F. Estrogen receptor- alpha gene Polymorphism, camellia oil and postmenopausal osteoporosis relevance in Guangxi Zhuang. Chinese. J Anat. 2014;37(5):581–4.
14. Erdogan MO, Yildiz H, Artan S, Solak M, Tascioglu F, Dundar U, Eser B, Colak E. Association of estrogen receptor alpha and collagen type I alpha 1 gene polymorphisms with bone mineral density in postmenopausal women. Osteoporos international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(4):1219–25.
15. Jeedigunta Y, Bhoomi Reddy PR, Kolla VK, Munshi A, Ananthapur V, Narasimulu G, Akka G. Association of estrogen receptor alpha gene polymorphisms with BMD and their affect on estradiol levels in pre- and postmenopausal women in south Indian population from Andhra Pradesh. Clin. Chim. Acta ; Int. J. of clin. Chem. 2010;411(7–8):597–600.
16. Durusu Tanriver M, Bora Tatar G, Uluturk TD, Dayangac Erdem D, Tanriver A, Kiliarcian A, Oz SG, Erdem Yurter H, Sozen T, Sain Guven G. Evaluation of the effects of vitamin D receptor and estrogen receptor 1 gene polymorphisms on bone mineral density in postmenopausal women. Clin Rheumatol. 2010;29(1):1285–93.
17. Hardt T, Husted LB, Carstens M, Stenkjaer L, Langdahl BL. Genotypes and haplotypes of the estrogen receptor genes, but not the retinoblastoma-interacting zinc finger protein 1 gene, are associated with osteoporosis. Calcif Tissue Int. 2010;86(1):25–35.

18. Musneci M, Vadala G, Tringali G, Insinello E, Roccazzello AM, Simpore J, Musneci S. Genetic and environmental factors in human osteoporosis from sub-Saharan to Mediterranean areas. J Bone Miner Metab. 2009;27(4):424–34.

19. Perez A, Ulla M, Garcia B, Lavezzi M, Elias E, Binci M, Rivoira M, Centeno V, Aliso A, Tolosa de Talamoni N. Genotypes and clinical aspects associated with bone mineral density in Argentine postmenopausal women. J Bone Miner Metab. 2008;26(4):359–65.

20. Ivanova JT, Doukova PB, Boyanov MA, Popivanov PR, Puvill and Xbal polymorphisms of the estrogen receptor gene and bone mineral density in a Bulgarian population sample. Hormones (Athens, Greece). 2007;6(1):36–43.

21. Wang W, Fu SJ, Wang XS, Zhang YP, Wang SW, Zhong B. The relationship between ER gene polymorphisms and postmenopausal osteoporosis of spine in southern Chinese women. Jurnal of Clinical Orthopedics. 2006;9(6):562–5.

22. Nam HS, Shin MH, Kweon SS, Park KS, Sohn SJ, Rhee JA, Choi JS, Son MH. Association of estrogen receptor-alpha gene polymorphisms with bone mineral density in postmenopausal Korean women. J Bone Miner Metab. 2005;23(1):84–9.

23. Qin YJ, Zhang ZL, Huang QH, He JW, Zhou Q, Hu YQ, Li M, Liu YJ. Association of ER alpha gene PvuII and Xbal polymorphisms and related factors with osteoporosis in postmenopausal women: a case-control study. Chin J Geriatr. 2004;23(6):380–3.

24. Aerssens J, Dequeker J, Peeters J, Breemans S, Broos P, Boonen S. Association of estrogen receptor-alpha gene polymorphisms with bone mineral density in postmenopausal Korean women. J Bone Miner Metab. 2005;23(1):84–9.

25. Sonoda T, Takada J, Ika K, Asakura S, Yamashita T, Mori M. Interaction between ER genes and environmental factors in osteoporotic hip fracture in elderly postmenopausal women. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2000;11(7):583–91.

26. Wajanavisit W, Suppachokmongkorn S, Woratanarat P, Ongphiphadhanakul B, Tawonsawatruk T. The association of bone mineral density and G2014A polymorphism of the estrogen receptor gene in osteoporotic hip fracture in Thai population. Journal of the Medical Association of Thailand = Chomthamthai thangphaet. 2015;98(Suppl 8):S82–7.

27. Gomez R, Magana JJ, Cisneros B, Perez-Salazar E, Faugeron S, Castro E, Magana JJ. Association of bone mineral density and G2014A polymorphism of the estrogen receptor gene with postmenopausal osteoporosis in the Mexican population. Clin Genet. 2007;71(6):574–81.

28. Ongphiphadhanakul B, Chanprasertyothin S, Payattikul P, Saetung P, Rajatanavin R. The implication of assessing a polymorphism in estrogen receptor alpha gene in the risk assessment of osteoporosis using a screening tool for osteoporosis in Asians. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2007;18(3):295–301.

29. Ongphiphadhanakul B, Chanprasertyothin S, Payattikul P, Saetung P, Rajatanavin R, Aerssens J, Dequeker J, Peeters J, Breemans S, Broos P, Boonen S. Association of estrogen receptor-alpha gene polymorphisms with bone mineral density in postmenopausal osteoporosis. Mol Cell Biochrem. 2015;405(2):23–31.

30. Shoukry A, Shalaby SM, Ewaa RL, Ahmed HS, Abdelrahman HM. Association of estrogen receptor beta and estrogen-related receptor alpha gene polymorphisms with bone mineral density in postmenopausal women. Mol Cell Biochrem. 2015;405(2):23–31.

31. Huang HL, Tan HH, Chen BP, Li H, Xie JS, Zhao QZ. Correlation of polymorphism of estrogen receptor-beta and camellia oil with postmenopausal osteoporosis in Zhuang women of Guangxi. Chinese Journal of Anatomy. 2015;33(3):323–325,343.

32. Moron FJ, Mendoza N, Vazquez F, Molero E, Queveda F, Salinas A, Fontes J, Martinez-Astorquiza T, Sanchez-Borrego R, Ruiz A. Multic locus analysis of estrogen-related genes in Spanish postmenopausal women suggests an interactive role of ERα, ERβ and NRIP1 genes in the pathogenesis of osteoporosis. Bone. 2006;39(1):213–21.

33. Albagha OM, FE MG, Reid DM, Ralston SH. Estrogen receptor alpha gene polymorphisms and bone mineral density: haplo type analysis in women from the United Kingdom. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2001;16(1):28–34.

34. Kurt O, Yilmaz-Aydoglan H, Uyar M, Isbir T, Seyhan MF, Can A. Evaluation of ERalpha and VDR gene polymorphisms in relation to bone mineral density in Turkish postmenopausal women. Mol Biol Rep. 2012;39(6):6723–30.

35. Kurabayashi T, Tomita M, Matsuhashi H, Yahata T, Honda A, Takakuwa K, Tanaka K. Association of vitamin D and estrogen receptor gene polymorphism with the effect of hormone replacement therapy on bone mineral density in Japanese women. Am J Obstet Gynecol. 1999;180(5):1115–20.

36. Ge JR, Zhu XX, Chen K. Effect of estrogen receptor gene Pvu haplotype on bone mineral density in female postmenopausal osteoporosis. Chin J Geriatr. 2006;24(6):416–9.

37. Ge JR, Wang HM, Zhu XX, Chen K. Effect of PvuII polymorphisms of estrogen receptor gene on filtering risk factors in postmenopausal osteoporosis. Chin J Osteoporo. 2006;12(1):38–40.

38. An SJ, Li F, Tong XX, Liu K, Zhao JS. Study on relationship between estrogen receptor gene polymorphism and syndrome differentiation typing of female postmenopausal osteoporosis in traditional Chinese medicine. Chinese Journal of Integrated Traditional and Western Medicine. 2000;20(12):607–10.

39. Wang KJ, Shi DQ, Sun LS, Jiang X, Lu YY, Dai J, Chen DY, Xu ZH, Jiang Q. Association of estrogen receptor alpha gene polymorphisms with bone mineral density: a meta-analysis. Chin Med J. 2012;125(14):2589–97.

40. Wang CL, Tang XY, Chen WQ, Su YX, Zhang CX, Chen YM. Association of estrogen receptor alpha gene polymorphisms with bone mineral density in Chinese women: a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2007;18(3):295–305.

41. Ioannidis JP, Stavrou I, Trikalinos TA, Zois C, Brandi ML, Gennari L, Albagha O, Ralston SH, Tsatsoulis A. Association of polymorphisms of the estrogen receptor alpha gene with bone mineral density and fracture risk in women: a meta-analysis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2002;17(11):2048–60.