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# The Transforming Growth Factor-β1 (TGF-β1) Gene Polymorphisms (TGF-β1 T869C and TGF-β1 T29C) and Susceptibility to Postmenopausal Osteoporosis

## *A Meta-Analysis*

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**Abstract:** The aim of the present study was to integrate all the eligible studies and investigate whether the transforming growth factor-β1 (TGF-β1) gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C) are correlated with postmenopausal osteoporosis (PMOP) risk.

PMOP is a common skeletal disease and several genetic factors play an important role in the development and progression of PMOP. Significant associations between TGF-β1 gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C) and PMOP risk have been reported; however, some of these results are controversial.

A systematic online search was performed using PubMed, EMBASE, Web of Science, and the Cochrane Library to identify case–control studies investigating the relationship between TGF-β1 T869C and TGF-β1 T29C polymorphisms and the susceptibility of PMOP. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated to assess the associations, and subgroup meta-analyses were performed according to the ethnicity of the study populations.

Eight studies involving 1851 cases and 2247 controls met the inclusion criteria after assessment by 2 reviewers. Overall, there were significant associations between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP (TGF-β1 T869C—C vs T: OR = 1.18, 95% CI = 1.02–1.36, $P = 0.030$; CC vs TT: OR = 1.38, 95% CI = 1.01–1.88, $P = 0.042$; CC vs CT/TT: OR = 1.39, 95% CI = 1.09–1.76, $P = 0.008$; TGF-β1 T29C—CT vs TT: OR = 1.25, 95% CI = 1.02–1.53, $P = 0.032$; CT/CC vs TT: OR = 1.37, 95% CI = 1.02–1.84, $P = 0.035$). In the subgroup analysis of ethnicity, significant association was observed between TGF-β1 T869C polymorphism and PMOP risk in Asian population (C vs T: OR = 1.18, 95% CI = 1.01–1.38, $P = 0.043$; CC vs TT: OR = 1.41, 95% CI = 1.01–1.97, $P = 0.047$; CT/CC vs TT: OR = 1.31, 95% CI = 1.03–1.66, $P = 0.026$; CC vs CT/TT: OR = 1.35, 95% CI = 1.03–1.75, $P = 0.028$); however, there was no significant association between TGF-β1 T869C polymorphism and PMOP risk in Caucasian population. With regard to TGF-β1 T29C polymorphism, significant association was also observed in Asian population (CT vs TT: OR = 1.37, 95% CI = 1.07–1.75, $P = 0.013$; CT/CC vs TT: OR = 1.54, 95% CI = 1.16–2.05, $P = 0.003$), while there was no significant association in Caucasian population.

The TGF-β1 T869C and TGF-β1 T29C polymorphisms may be involved in susceptibility to PMOP, particular in Asian patients.

(*Medicine* 94(4):e461)

**Abbreviations**: BMD = bone mineral density, HWE = Hardy–Weinberg equilibrium, PMOP = postmenopausal osteoporosis.

## INTRODUCTION

Postmenopausal osteoporosis (PMOP) is the most common bone disease, and features bone loss and susceptibility to fragility fractures that are associated with a low bone mineral density (BMD).[1] PMOP is among the most prevalent metabolic bone diseases in postmenopausal women.[2,3] Although PMOP has been described decades ago, its exact mechanisms remain poorly understood.[4] Genetic or acquired disorders can compromise gains in bone quantity and quality leading to osteoporosis early in life.[5] Previous studies indicated that low BMD was a major risk factor for PMOP and was highly heritable.[6,7] Besides, many association studies have shown that genes and genetic factors might be involved in the pathogenesis of PMOP.[8–10]

Recently, many studies deduced that transforming growth factor superfamily catalyzed enzymes for osteoporosis. Transforming growth factor-β1 (TGF-β1), a member of the transforming growth factor superfamily, is abundant in bone and has been implicated as an important regulator of both bone formation and resorption,[11] which can stimulate proliferation or differentiation of preosteoblasts as well as inhibit mature osteoclasts and proliferation of mononuclear osteoclast precursors in vitro.[12] Molecular biological evidence showed that polymorphisms in the TGF-β result in a Leu → Pro substitution at amino acid 10, which includes a T → C transition at nucleotide 29 and a T → C transition at nucleotide 869 in the region encoding the signal sequence.[13,14] This change influenced the bone remodeling, indicating that genetic polymorphisms of the T29C and T869C genes might be associated with increased risk for osteoporosis. Recently, significant association has been found between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP in several studies. But the results of these studies are complex and even opposite.[13,15–21] Furthermore, no consolidated reports have been conducted to investigate the associations between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP. Therefore, we performed this

Editor: James Franklin Kellam.
Received: December 6, 2014; revised: December 19, 2014; accepted: December 22, 2014.
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This research was funded by Natural Science Foundation of China (81171689) and Jiangsu Provincial Special Program of Medical Science, China (BL2012004).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000461

meta-analysis to make contribution to obtain a more exact evaluation of the associations between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP risk.

## MATERIALS AND METHODS

### Literature Search

Databases including PubMed, EMBASE, Web of Science, and the Cochrane Library were searched for the eligible case–control studies that examined the relationship between TGF-β1 polymorphisms (TGF-β1 T869C and TGF-β1 T29C) and the susceptibility to PMOP. The following search terms were used: (Postmenopausal osteoporosis OR PMOP) AND (Transforming growth factor-β1 OR TGF-β1 OR TGF-β1 T869C OR TGF-β1 T29C) AND (polymorphism OR single nucleotide polymorphism OR SNP OR variation). There were no language restrictions in our study selection. Secondary searches of unpublished literature were conducted by searching the reference lists of the selected studies and reviews.

### Inclusion and Exclusion Criteria

The inclusion criteria of our meta-analysis were as follows: case–control study; evaluation of PMOP risk and at least one of these identified TGF-β1 gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C); and sufficient data, including number or frequency of alleles and genotypes. The exclusion criteria were reviews or case reports that were not case–control studies, no available data reported, and duplicated reports.

### Data Extraction

Data from the eligible studies were extracted according to the inclusion and exclusion criteria by 2 authors, and a consensus was reached. For each study, the following data were collected: author list, year of publication, ethnicity, sample size, alleles, and genotypes of TGF-β1 T869C and TGF-β1 T29C polymorphisms. Furthermore, we also evaluated whether the genotype distributions of the control group followed the Hardy–Weinberg equilibrium (HWE).

### Data Synthesis and Statistical Analysis

Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the association between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP risk. Allele contrast (C vs T), heterozygote (CT vs TT), homozygote (CC vs TT), dominant (CT/CC vs TT), and recessive (CC vs CT/TT) models were used to evaluate the relationship between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP risk. The assumption that there was heterogeneity was verified by a $\chi^2$-based Q statistical test and quantified by $I^2$ metric value. If $I^2$ value is $>50\%$ or $P < 0.10$, suggesting that an obvious heterogeneity existed, ORs were pooled by random effect model; otherwise, the fixed effect model was used. Sensitivity analysis was performed to assess the impact of each study on the combined effect of the present meta-analysis and subgroup analysis was performed according to the ethnicity of the study populations. All meta-analyses were performed using Stata 12.0 software (StataCorp, College Station, TX) and a $P$ value below 0.05 was considered statistically significant. This is a systematic review about literatures, so ethical approval was not necessary for our research.

## RESULTS

### Study Characteristics

A total of 8 studies[13,15–21] involving 1851 cases and 2247 controls eventually satisfied the eligibility criteria (Figure 1). Three studies[15,17,18] reported both alleles and genotypes of

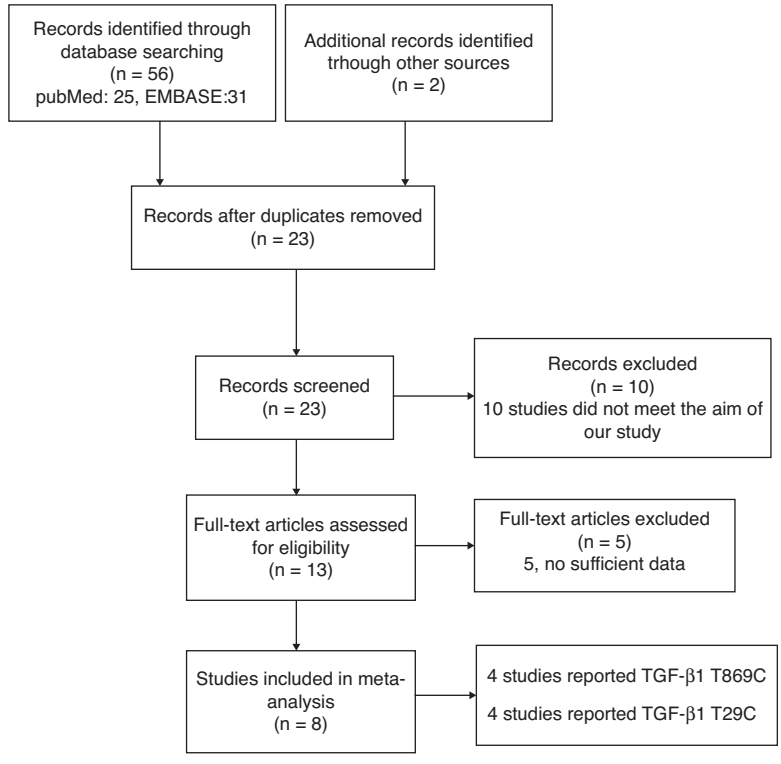


**FIGURE 1.** The study selection and inclusion process.

**TABLE 1.** General Characteristics of Studies Included in the Meta-Analysis

| | | | Sample Size | | TGF-β1 T869C Case | | TGF-β1 T869C Control | | TGF-β1 T29C Case | | TGF-β1 T29C Control | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Author** | **Year** | **Ethnicity** | **Case** | **Control** | **C/T** | **CC/TC/TT** | **C/T** | **CC/TC/TT** | **C/T** | **CC/TC/TT** | **C/T** | **CC/TC/TT** |
| Tural et al | 2013 | Caucasian | 146 | 97 | 167/125 | 50/67/29 | 104/90 | 24/56/17 | | | | |
| Yamada et al | 2001 | Asian | 288 | 625 | 276/300 | 58/160/70 | 536/714 | 93/350/182 | | | | |
| Edith Ming Chu Lau et al | 2004 | Asian | 151 | 439 | 181/121 | 56/69/26 | 506/372 | 141/224/74 | | | | |
| Utennam et al | 2012 | Asian | 275 | 93 | | 204/71 | | 56/37 | | | | |
| Yamada et al | 2000 | Asian | 213 | 323 | | | | | 198/228 | 42/114/57 | 248/398 | 32/184/107 |
| Yamada et al | 1998 | Asian | 285 | 130 | | | | | 189/381 | 21/147/117 | 92/168 | 24/44/62 |
| Lau et al | 2004 | Asian | 237 | 237 | | | | | 272/202 | 94/84/59 | 178/296 | 37/104/96 |
| Langdahl et al | 2003 | Caucasian | 256 | 303 | | | | | 172/340 | 30/112/114 | 204/402 | 37/130/136 |

TGF-β1 = transforming growth factor-β1.

**TABLE 2.** Results of Genetic Models for TGF-β1 T869C and TGF-β1 T29C Polymorphisms and Postmenopausal Osteoporosis

| | | Test of Association | | | | Test of Heterogeneity | |
|---|---|---|---|---|---|---|---|
| **Comparison** | **N** | **OR** | **95% CI** | ***P* Value** | **Model** | ***P* Value** | **$I^2$, %** |
| T869C T/C | | | | | | | |
| Overall | 4 | | | | | | |
| C versus T | | 1.18 | 1.02–1.36 | 0.03 | F | 0.81 | 0 |
| TC versus TT | | 1.02 | 0.79–1.33 | 0.32 | F | 0.33 | 10.9 |
| CC versus TT | | 1.38 | 1.01–1.88 | 0.04 | F | 0.56 | 0 |
| TC/CC versus TT | | 1.25 | 1.00–1.56 | 0.05 | F | 0.17 | 39.8 |
| CC versus TC/TT | | 1.39 | 1.09–1.76 | 0.008 | F | 0.76 | 0 |
| Caucasian | 1 | | | | | | |
| C versus T | | 1.16 | 0.80–1.67 | 0.44 | F | 1 | 0 |
| TC versus TT | | 0.70 | 0.35–1.41 | 0.32 | F | 1 | 0 |
| CC versus TT | | 1.22 | 0.56–2.64 | 0.61 | F | 1 | 0 |
| TC/CC versus TT | | 0.86 | 0.44–1.66 | 0.65 | F | 1 | 0 |
| CC versus TC/TT | | 1.58 | 0.89–2.81 | 0.12 | F | | |
| Asian | 3 | | | | | | |
| C versus T | | 1.18 | 1.01–1.38 | 0.04 | F | 0.52 | 0 |
| TC versus TT | | 1.09 | 0.82–1.44 | 0.55 | F | 0.34 | 0 |
| CC versus TT | | 1.41 | 1.01–1.97 | 0.047 | F | 0.31 | 4.2 |
| TC/CC versus TT | | 1.31 | 1.03–1.66 | 0.03 | F | 0.17 | 44 |
| CC versus TC/TT | | 1.35 | 1.03–1.75 | 0.03 | F | 0.59 | 0 |
| T29C T/C | | | | | | | |
| Overall | 4 | | | | | | |
| C versus T | | 1.30 | 0.88–1.93 | *0.19* | R | <0.0010.31 | 88.7 |
| TC versus TT | | 1.25 | 1.02–1.53 | *0.03* | F | <0.001 | 16.2 |
| CC versus TT | | 1.48 | 0.59–3.75 | 0.41 | R | 0.07 | 90.8 |
| TC/CC versus TT | | 1.37 | 1.02–1.84 | *0.04* | R | <0.001 | 58.4 |
| CC versus TC/TT | | 1.30 | 0.51–3.34 | 0.59 | R | | 92.7 |
| Caucasian | 1 | | | | | 1 | |
| C versus T | | 1.00 | 0.78–1.28 | 0.98 | R | 1 | 0 |
| TC versus TT | | 1.03 | 0.72–1.47 | 0.88 | F | 1 | 0 |
| CC versus TT | | 0.97 | 0.56–1.66 | 0.90 | R | 1 | 0 |
| TC/CC versus TT | | 1.01 | 0.73–1.42 | 0.90 | R | 1 | 0 |
| CC versus TC/TT | | 0.95 | 0.57–1.59 | 0.86 | R | | 0 |
| Asian | 3 | | | | | <0.001 | |
| C versus T | | 1.42 | 0.87–2.32 | *0.19* | R | 0.39 | 89.8 |
| TC versus TT | | 1.37 | 1.07–1.75 | *0.01* | F | <0.001 | 0 |
| CC versus TT | | 1.70 | 0.50–5.77 | 0.39 | R | 0.21 | 92.7 |
| TC/CC versus TT | | 1.54 | 1.16–2.05 | *0.003* | R | <0.001 | 35.0 |
| CC versus TC/TT | | 1.43 | 0.41–5.06 | 0.58 | R | | 92.7 |

CI = confidence interval, F = fixed effect model, OR = odds ratio, R = random effect model, TGF-β1 = transforming growth factor-β1.

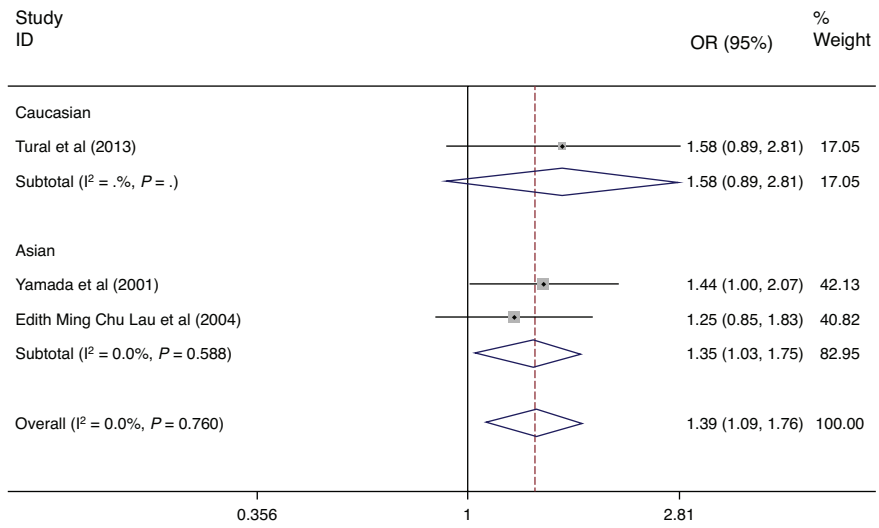


**FIGURE 2.** Forest plot describing the meta-analysis under recessive model for the association between TGF-β1 T869C polymorphism and the risk of postmenopausal osteoporosis. CI = confidence interval, OR = odds ratio, TGF-β1 = transforming growth factor-β1.

TGF-β1 T869C polymorphism and only 1 study[20] reported the TT and CT/CC in both case and control groups. With regard to TGF-β1 T29C polymorphism, there were 4 studies[13,16,19,21] reporting both alleles and genotypes of this gene polymorphism. Furthermore, 6 studies[13,15,16,18–20] were performed in Asian populations and another 2 studies[17,21] were performed in Caucasian patients. The general demographic characteristics of studies included in this meta-analysis are summarized in Table 1. The genotype distribution in the control subjects in all studies was consistent with HWE, except for 3 studies.[13,15,16]

## Meta-Analysis Results

Overall, our meta-analysis suggested that there was significant association between TGF-β1 T869C polymorphism and PMOP (C vs T: OR = 1.18, 95% CI = 1.02–1.36, $P = 0.030$; CC vs TT: OR = 1.38, 95% CI = 1.01–1.88, $P = 0.042$; CC vs CT/TT: OR = 1.39, 95% CI = 1.09–1.76, $P = 0.008$), as shown in Table 2 and Figures 2 and 3. Furthermore, subgroup analysis showed significant association in Asian populations (C vs T: OR = 1.18, 95% CI = 1.01–1.38, $P = 0.043$; CC vs TT: OR = 1.41, 95% CI = 1.01–1.97, $P = 0.047$; CT/CC vs TT: OR = 1.31, 95% CI = 1.03–1.66, $P = 0.026$; CC vs CT/TT: OR = 1.35, 95% CI = 1.03–1.75, $P = 0.028$), but not in Caucasian populations (Table 2; Figures 2 and 3).

With regard to TGF-β1 T29C polymorphism, significant association was also observed (TGF-β1 T29C—CT vs TT: OR = 1.25, 95% CI = 1.02–1.53, $P = 0.032$; CT/CC vs TT: OR = 1.37, 95% CI = 1.02–1.84, $P = 0.035$), as shown in Table 2 and Figures 4 and 5. In the subgroup analysis, significant association was also observed in Asian population (CT vs TT: OR = 1.37, 95% CI = 1.07–1.75, $P = 0.013$; CT/CC vs TT: OR = 1.54, 95% CI = 1.16–2.05, $P = 0.003$), while there was

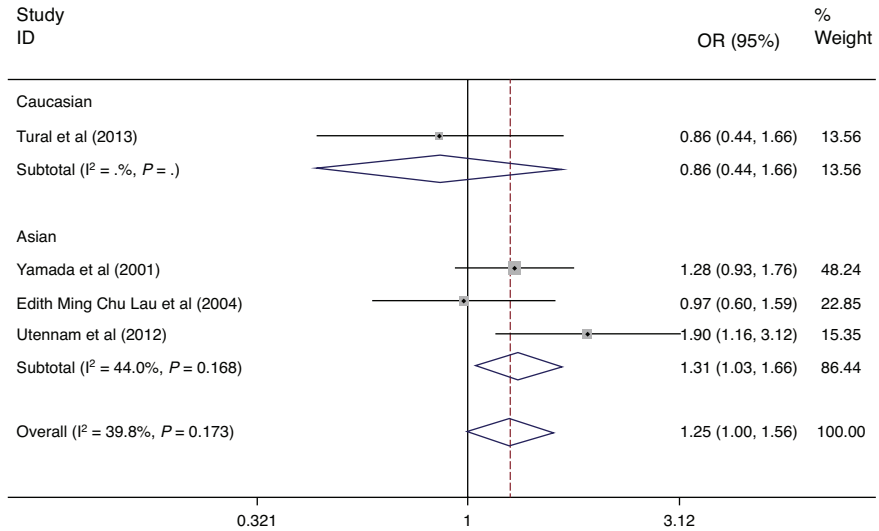


**FIGURE 3.** Forest plot describing the meta-analysis under dominant model for the association between TGF-β1 T869C polymorphism and the risk of postmenopausal osteoporosis. CI = confidence interval, OR = odds ratio, TGF-β1 = transforming growth factor-β1.

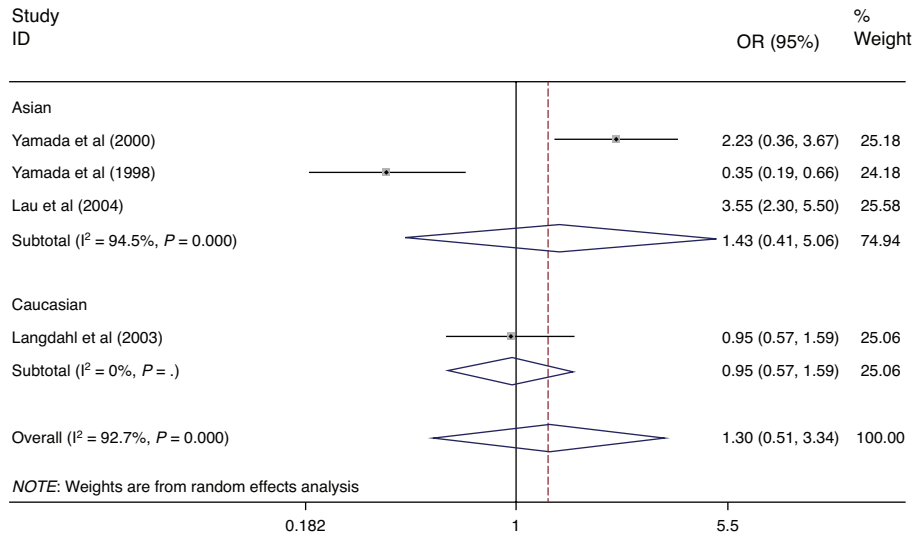


**FIGURE 4.** Forest plot describing the meta-analysis under recessive model for the association between TGF-β1 T29C polymorphism and the risk of postmenopausal osteoporosis. CI = confidence interval, OR = odds ratio, TGF-β1 = transforming growth factor-β1.

no significant association in Caucasian population (Table 2 and Figure 4).

## Sensitivity Analysis and Publication Bias

We eliminated the studies[13,15,16] that were not consistent with the HWE to estimate the sensitivity of our study and we found that the results of association between TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP were relatively stable and credible. Furthermore, we did not assess publication bias because the number of studies analyzed was less than 10.

## DISCUSSION

PMOP, an important health problem among postmenopausal women, is such a common skeletal disease characterized by skeletal fragility resulting in fractures from relatively minor trauma that several risk factors[22–26] may play an important role in the etiology and progression. Recently, PMOP is considered as an immune disease due to the fact that several cytokines and immune factors[8,10] have been observed in the etiology of PMOP, such as TGF-β,[17,18] IL-6,[27], IL-10,[17], IL-17,[26], etc. Among these genetic factors, TGF-β1 that plays an important role in the regulation of both bone formation and resorption, tissue recycling, and immune response has been widely studied in both Asian and Caucasian patients.[13,15–21] Utennam et al[20] evaluated the association of T869C, C-509T, and G915C of the TGF-β1 gene with BMD serum TGF-β1 levels in 278 postmenopausal female osteoporosis subjects and 95 postmenopausal female control subjects and they concluded that T869C polymorphism of the TGF-β1 gene had an impact on decreased serum TGF-β1 levels and influenced susceptibility to

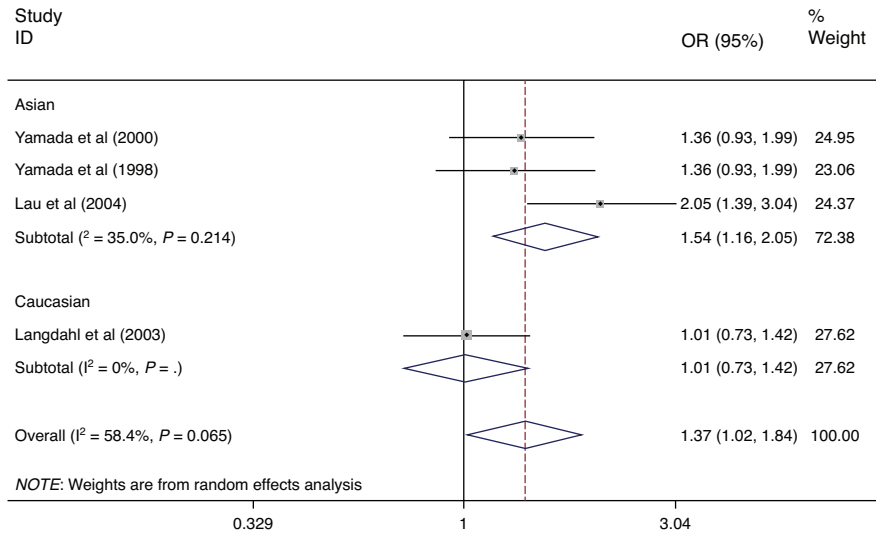


**FIGURE 5.** Forest plot describing the meta-analysis under dominant model for the association between TGF-β1 T29C polymorphism and the risk of postmenopausal osteoporosis. CI = confidence interval, OR = odds TGF-β1 = transforming growth factor-β1.

osteopenia/osteoporosis in Thai women, which was consistent with the results of studies by Yamada et al[13,15] and Lau et al.[19] Tural et al[17] investigated the association between osteoporosis and TGF-β1 polymorphism in 146 osteoporotic and 97 healthy control women. However, they did not found any difference between the groups regarding TGF-β1 genotype distribution and allele frequencies. Due to these conflicting results, it is necessary to conduct a comprehensive study to determine whether the polymorphisms of TGF-β1 gene (TGF-β1 T869C and TGF-β1 T29C polymorphisms) are associated with the susceptibility to PMOP.

In our meta-analysis, significant association was observed between TGF-β1 T869C polymorphism and PMOP risk, which was consistent with 2 studies[15,20]; however, another 2 studies[17,18] reported opposite results. In our opinion, 2 factors may be contributed to these controversial results. First, the genotype distribution in the control subjects in the study by Yamada et al[15] was not consistent with HWE, which might have an effect on the overall results. Second, different sampling methods and environmental factors might also result in the overall results and the difference between overall results and individual results. Furthermore, in the subgroup analysis of ethnicity, there was significant association between TGF-β1 T869C polymorphism and PMOP risk in Asian populations, while no association was observed in Caucasian patients. We believe that 2 things may have contributed to this difference: first, genetic factors may vary from different ethnicities, suggesting that ancestral genetic factors may increase the risk of developing PMOP. Second, only 1 study[17] reported the association in Caucasian population, suggesting that no sufficient sample size and statistical power could be based on which to assess the relationship between TGF-β1 T869C polymorphism and PMOP risk in Caucasians. Besides, different methods of genotype analysis and the source of control individuals may be important contributors to these contradictory results.

With regard to TGF-β1 T29C polymorphism, significant association was also observed in our study and when stratified by ethnicity, significant association was also observed in Asian population, while there was no significant association in Caucasian population. However, Langdahl et al[21] studied the TGF-β1 T29C polymorphism using restriction fragment length polymorphism and sequencing in 296 osteoporotic patients with vertebral fractures and 330 normal individuals and the results suggested that TGF-β1 T29C polymorphism was not differently distributed among osteoporotic patients and normal controls. Therefore, they made the conclusion that TGF-β1 T29C polymorphism might not be a risk in the etiology of PMOP, which was inconsistent with our results. Sampling methods and the publication bias might be contributors to this significant difference. Langdahl et al[21] conducted their studies in Caucasian populations, in which no association was observed, while other studies[13,16,19] were performed in Asian populations and their results suggested that TGF-β1 T29C polymorphism was significantly associated with PMOP. Different ethnicity, sample size, and sampling methods might play an important role in this difference.

Despite a comprehensive analysis of the association between TGF-β1 gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C), and the risk of developing PMOP, there are some limitations that should be addressed. First, the number of studies that were included in this analysis described a total of 1851 cases and 2247 controls, which could not provide sufficient statistical power to detect all possible effects of TGF-β1 gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C) on PMOP. Second, small sample size of the study by Tural et al[17] and 3 studies[13,15,16] that was not consistent with HWE might contribute to the contrasting results and influence the conclusions drawn. Third, only 2 studies[17,21] were performed in Caucasian population, which may indicate a race-specific effect. Therefore, larger-scale and better-designed studies are necessary to determine the association between TGF-β1 gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C) and the risk of PMOP.

## CONCLUSION

In conclusion, in this meta-analysis we pooled all the available data related to TGF-β1 T869C and TGF-β1 T29C polymorphisms and PMOP risk, and found that the TGF-β1 T869C and TGF-β1 T29C polymorphisms may be involved in the susceptibility to PMOP, especially in Asian patients. Therefore, more studies are required to overcome the aforementioned limitations to further assess the association of TGF-β1 T869C and TGF-β1 T29C polymorphisms with increased susceptibility to PMOP.

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