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*Original Article*

# Association of osteopontin polymorphism with cancer risk: a meta-analysis

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**Abstract:** To investigate the association of osteopontin gene -443 C>T, -156 G>GG, and -1748 A>G polymorphisms with cancer risk. The Medline, PubMed, PUBMED, EMBASE and Web of Science databases were searched. Meta-analyses were conducted using RevMan 5.2 software. After searching and evaluating the included papers, total 10 documents involved in -443 C>T, 8 papers involved in four articles involved in -156 G>GG and -1748 A>G were included into this meta analysis. There were no significant differences in genotype osteopontin -443 C>T distribution between cancer cases and control (OR=0.98, 95% CI=0.68-1.40, P=0.90; OR=0.90, 95% CI=0.60-1.35, P=0.62; OR=0.98, 95% CI=0.59-1.64, P=0.94; OR=0.87, 95% CI=0.60-1.25, P=0.44, respectively). Meanwhile, no association between osteopontin -1748 A>G polymorphism and tumors under all genetic models. (OR=0.73, 95% CI=0.54-1.00, P=0.05; OR=0.95, 95% CI=0.82-1.10, P=0.48; OR=1.31, 95% CI=0.95-1.81, P=0.10; OR=0.90, 95% CI=0.77-1.06, P=0.20, respectively). However, osteopontin -156 G>GG polymorphism is only partly related to the tumor risk. (GGGG+GGG vs GG model, OR=1.21, 95% CI=1.01-1.46, P=0.04; GGG vs GG model: OR=1.19, 95% CI=1.05-1.35, P=0.008, respectively) osteopontin gene polymorphisms, -443 C>T and -1748 A>G was not associated with cancer risk, but partly associated to tumor risk for -156 G>GG gene polymorphism.

**Keywords:** Osteopontin, gene, polymorphism, tumor, risk, meta

## Introduction

Osteopontin (OPN), also known as early secreted phosphoprotein 1 (SPP1) or T-cell activation gene 1 (Eta-1), is a secreted protein involved in a wide variety of different functions such as immunoregulatory responses, inflammation, stress response and wound healing [1]. Increased data shown that OPN has played an important role in cancer progression and prognosis in multiple tumor types [2], such as colorectal cancer [3], hepatocellular carcinoma [4], lung cancer [5] and breast cancer [6]. Moreover, recently some meta analysis results revealed that there is a association of osteopontin expression with some tumors, including glioma [7] and ovarian neoplasm [8]. The osteopontin expression level in serum has also potential usefulness as a diagnostic and prognostic factor for gastric cancer [9].

Osteopontin gene polymorphism included -443 C>T, -156 G>GG and -1748 A>G may affect gene expression, and it has been associated with various tumor, such as gastric cancer [10], glioma [11] and lung cancer [12]. However, Wang et al. [13] reported there was no association of osteopontin gene polymorphism with tumor risk.

In here, we performed a meta analysis to evaluated the association of osteopontin gene polymorphisms, -443 C>T, -156 G>GG and -1748 A>G with risk of cancer.

## Methods

### *Study selection*

A Medline, PubMed, PUBMED, EMBASE and Web of Science databases search was performed on all studies between January 2000 and December 2014. The following English keywords were used: “osteopontin or OPN”, “neoplasms” or “carcinoma” or “tumor” and “polymorphism”. Only studies on human and in English were considered for inclusion. This

**Table 1.** Main characteristics of all eligible studies

| First author | Publication year | Race | Tumor style | Study design | Outcomes |
|---|---|---|---|---|---|
| Chen er al., | 2010 | China | glioma | cohort study | -443T>C; -156G>GG |
| Chen et al., | 2013 | China | lung cancer | cohort study | -443T>C; -156G>GG |
| Chiu et al., | 2010 | China | oral carcinogenesis | cohort study | -443T>C; -156G>GG |
| Golledge et al., | 2007 | Australia | abdominal aortic aneurysm | cohort study | -443T>C; -1748A>G |
| Lee et al., | 2013 | China | Gastric Cancer | cohort study | -443T>C; -156G>isnGG; -1748A>G |
| Mu et al., | 2013 | China | Papillary Thyroid Cancer | cohort study | -443T>C; -156G>GG |
| Wang et al., | 2014a | China | nasopharyngeal carcinoma | case-control study | -443T>C; -1748A>G |
| Wang et al., | 2014b | China | nasopharyngeal carcinoma | case-control study | -1748A>G |
| Xu et al., | 2011 | China | cervical cancer | cohort study | -443T>C; -156G>GG |
| Zhao et al., | 2012 | China | gastric cancer | cohort study | -443T>C; -156G>GG |
| Shen et al., | 2014 | China | Gliomas | case-control study | -443T>C; -156G>GG |

search was supplemented by manual research and a review of reference lists. We were not blind to author, institutions, journals while we selected trials or extracted the data.

*Data extraction and quality assessment*

Data were extracted by two independent reviewers using standard forms. The recorded data included first author, year of publication, country or district, tumor type, gene type. All relevant text, tables and figures were reviewed for data extraction. Discrepancies between the two reviews were resolved by discussion and consensus. The quality of all selected studies was ranked in accordance with the score of the non-randomized controlled clinical trial quality evaluation standard.

*Statistical methods*

Related-data from the comparative groups was compared using $X^2$ test for categorical data, a significant difference was considered when P was less than 0.05; the meta-analysis was performed using the Review Manager (RevMan) software, version 5.2. We analyzed dichotomous variables using estimation of odds ratios(OR) with a 95% confidence interval (95% CI). Heterogeneity was evaluated by $X^2$ and $I^2$. We considered heterogeneity to be present if the $I^2$ statistic was >50%, P<0.05 was considered significant.

## Results

*Study characteristics*

After searching and evaluating the included papers, total 10 documents [10-12, 14-20] involved in -443 C>T, 8 papers [10-12, 14, 16, 17, 19, 20] involved in four articles [10, 15, 13, 18] involved in -156 G>GG and -1748 A>G were included into this meta analysis. The publication year of involved studies ranged from 2000 to 2014. Other details could be find in **Table 1**.

*No association between osteopontin -443 C>T polymorphism and all tumors*

In here, there were 10 documents shown that osteopontin -443 C>T gene polymorphism involved in the risk of cancer. As shown in **Figure 1**, there were no significant differences in genotype osteopontin -443 C>T distribution between cancer cases and control (OR=0.98, 95% CI=0.68-1.40, P=0.90; OR=0.90, 95% CI=0.60-1.35, P=0.62; OR=0.98, 95% CI=0.59-1.64, P=0.94; OR=0.87, 95% CI=0.60-1.25, P=0.44, respectively).

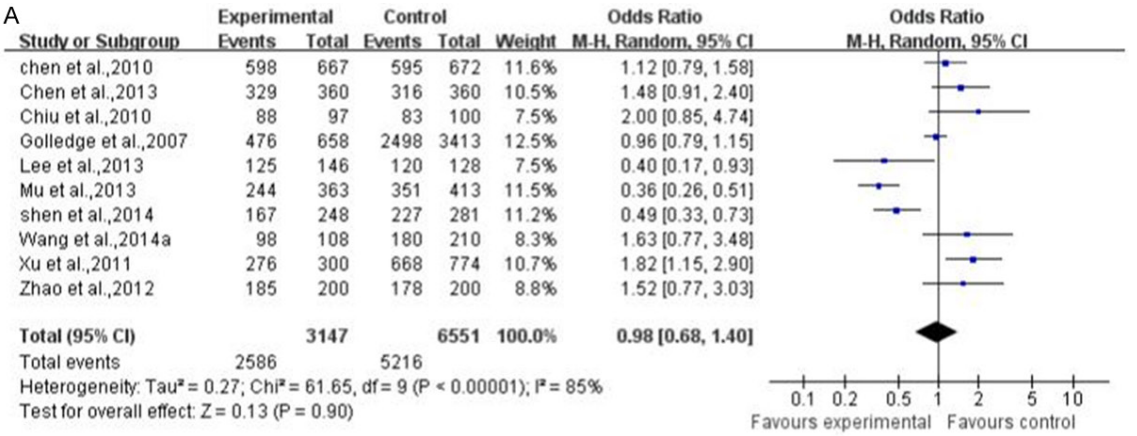
*Association between osteopontin -156 G>GG polymorphism and tumors*

As shown in **Figure 2A** and **2C**, there were no significant differences on association of osteopontin -156 G>GG gene polymorphism with cancer risk between patients and control groups. (GGGG vs GGG+GG model, OR=0.83, 95% CI=0.66-1.04, P=0.10; GGGG vs GG model: OR=1.31, 95% CI=0.98-1.74, P=0.07, respectively). However, there were different results in other genetic models (GGGG+GGG vs GG model, OR=1.21, 95% CI=1.01-1.46, P=0.04; GGG vs GG model: OR=1.19, 95% CI=1.05-1.35, P=0.008, respectively) (**Figure 2B** and **2D**).

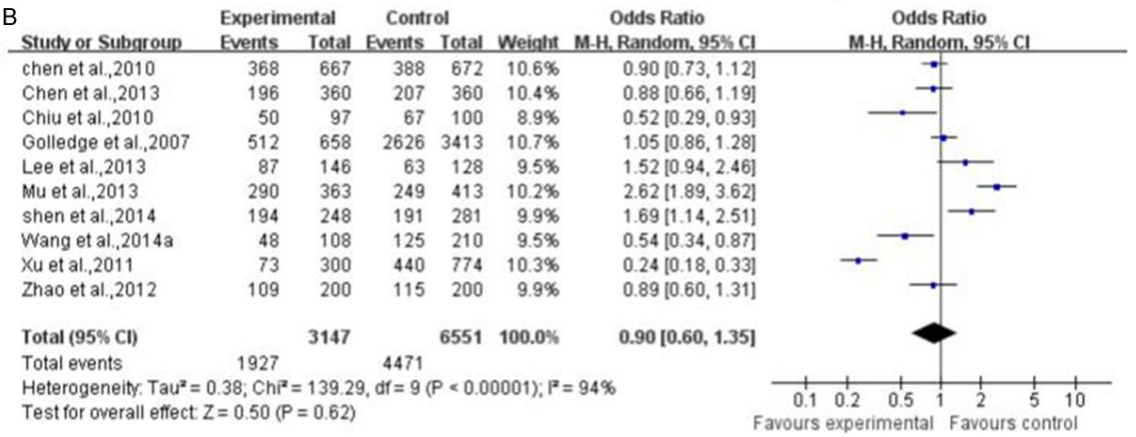
*No association between osteopontin -1748 A>G polymorphism and tumors*

In here, we investigated the association of osteopontin -1748 A>G gene polymorphism with tumor risk. As shown in **Figure 3**, no significant associations were observed under all genetic models. (OR=0.73, 95% CI=0.54-1.00,

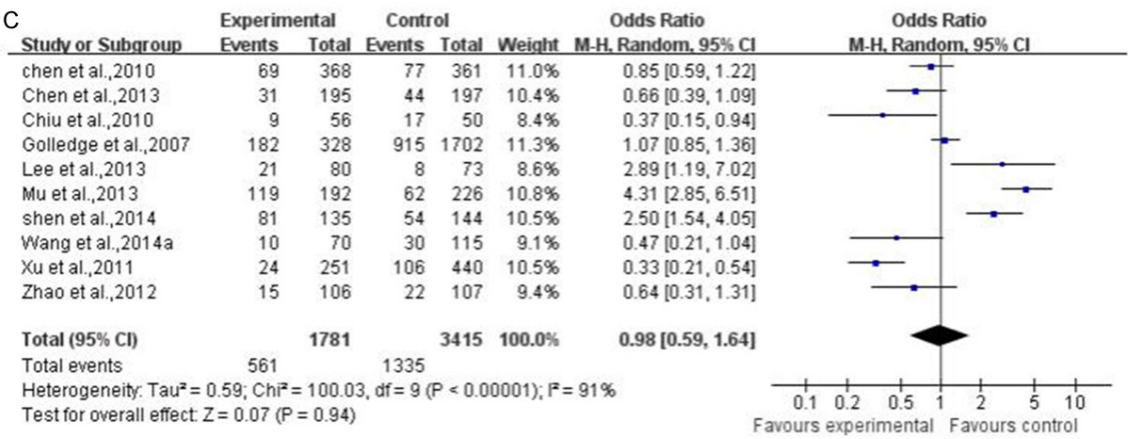
A


Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
chen et al.,2010 598 667 595 672 11.6% 1.12 [0.79, 1.58]
Chen et al.,2013 329 360 316 360 10.5% 1.48 [0.91, 2.40]
Chiu et al.,2010 88 97 83 100 7.5% 2.00 [0.85, 4.74]
Golledge et al.,2007 476 658 2498 3413 12.5% 0.96 [0.79, 1.15]
Lee et al.,2013 125 146 120 128 7.5% 0.40 [0.17, 0.93]
Mu et al.,2013 244 363 351 413 11.5% 0.36 [0.26, 0.51]
shen et al.,2014 167 248 227 281 11.2% 0.49 [0.33, 0.73]
Wang et al.,2014a 98 108 180 210 8.3% 1.63 [0.77, 3.48]
Xu et al.,2011 276 300 668 774 10.7% 1.82 [1.15, 2.90]
Zhao et al.,2012 185 200 178 200 8.8% 1.52 [0.77, 3.03]
Total (95% CI) 3147 6551 100.0% 0.98 [0.68, 1.40]
Total events 2586 5216
Heterogeneity: Tau² = 0.27; Chi² = 61.65, df = 9 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.13 (P = 0.90)
0.1 0.2 0.5 1 2 5 10
Favours experimental Favours control

B


Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
chen et al.,2010 368 667 388 672 10.6% 0.90 [0.73, 1.12]
Chen et al.,2013 196 360 207 360 10.4% 0.88 [0.66, 1.19]
Chiu et al.,2010 50 97 67 100 8.9% 0.52 [0.29, 0.93]
Golledge et al.,2007 512 658 2626 3413 10.7% 1.05 [0.86, 1.28]
Lee et al.,2013 87 146 63 128 9.5% 1.52 [0.94, 2.46]
Mu et al.,2013 290 363 249 413 10.2% 2.62 [1.89, 3.62]
shen et al.,2014 194 248 191 281 9.9% 1.69 [1.14, 2.51]
Wang et al.,2014a 48 108 125 210 9.5% 0.54 [0.34, 0.87]
Xu et al.,2011 73 300 440 774 10.3% 0.24 [0.18, 0.33]
Zhao et al.,2012 109 200 115 200 9.9% 0.89 [0.60, 1.31]
Total (95% CI) 3147 6551 100.0% 0.90 [0.60, 1.35]
Total events 1927 4471
Heterogeneity: Tau² = 0.38; Chi² = 139.29, df = 9 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.50 (P = 0.62)
0.1 0.2 0.5 1 2 5 10
Favours experimental Favours control

C


Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
chen et al.,2010 69 368 77 361 11.0% 0.85 [0.59, 1.22]
Chen et al.,2013 31 195 44 197 10.4% 0.66 [0.39, 1.09]
Chiu et al.,2010 9 56 17 50 8.4% 0.37 [0.15, 0.94]
Golledge et al.,2007 182 328 915 1702 11.3% 1.07 [0.85, 1.36]
Lee et al.,2013 21 80 8 73 8.6% 2.89 [1.19, 7.02]
Mu et al.,2013 119 192 62 226 10.8% 4.31 [2.85, 6.51]
shen et al.,2014 81 135 54 144 10.5% 2.50 [1.54, 4.05]
Wang et al.,2014a 10 70 30 115 9.1% 0.47 [0.21, 1.04]
Xu et al.,2011 24 251 106 440 10.5% 0.33 [0.21, 0.54]
Zhao et al.,2012 15 106 22 107 9.4% 0.64 [0.31, 1.31]
Total (95% CI) 1781 3415 100.0% 0.98 [0.59, 1.64]
Total events 561 1335
Heterogeneity: Tau² = 0.59; Chi² = 100.03, df = 9 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.07 (P = 0.94)
0.1 0.2 0.5 1 2 5 10
Favours experimental Favours control

D

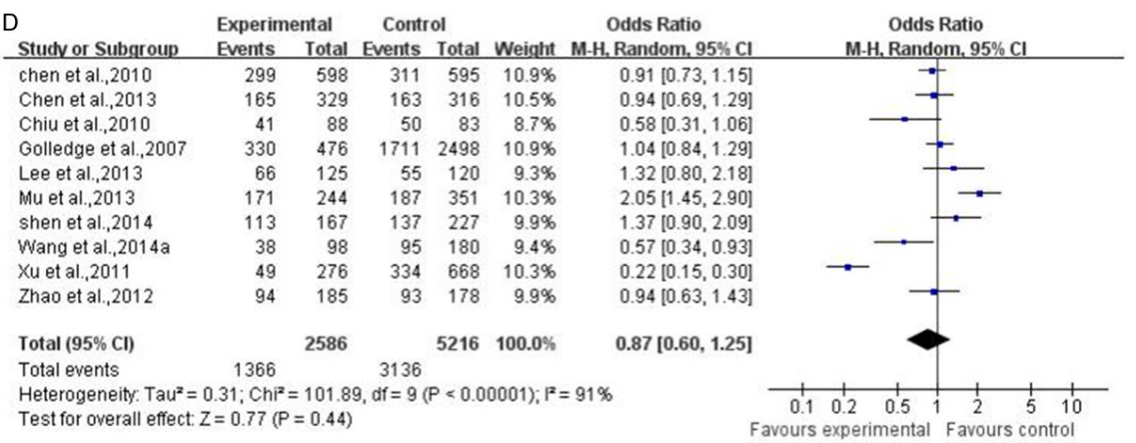

Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
chen et al.,2010 299 598 311 595 10.9% 0.91 [0.73, 1.15]
Chen et al.,2013 165 329 163 316 10.5% 0.94 [0.69, 1.29]
Chiu et al.,2010 41 88 50 83 8.7% 0.58 [0.31, 1.06]
Golledge et al.,2007 330 476 1711 2498 10.9% 1.04 [0.84, 1.29]
Lee et al.,2013 66 125 55 120 9.3% 1.32 [0.80, 2.18]
Mu et al.,2013 171 244 187 351 10.3% 2.05 [1.45, 2.90]
shen et al.,2014 113 167 137 227 9.9% 1.37 [0.90, 2.09]
Wang et al.,2014a 38 98 95 180 9.4% 0.57 [0.34, 0.93]
Xu et al.,2011 49 276 334 668 10.3% 0.22 [0.15, 0.30]
Zhao et al.,2012 94 185 93 178 9.9% 0.94 [0.63, 1.43]
Total (95% CI) 2586 5216 100.0% 0.87 [0.60, 1.25]
Total events 1366 3136
Heterogeneity: Tau² = 0.31; Chi² = 101.89, df = 9 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.77 (P = 0.44)
0.1 0.2 0.5 1 2 5 10
Favours experimental Favours control

**Figure 1.** Meta-analysis of the association between osteopontin gene -443 C>T polymorphism and susceptibility to cancer risk. A. Dominant model. B. Recessive model. C. TT vs CC. D. TC vs CC.

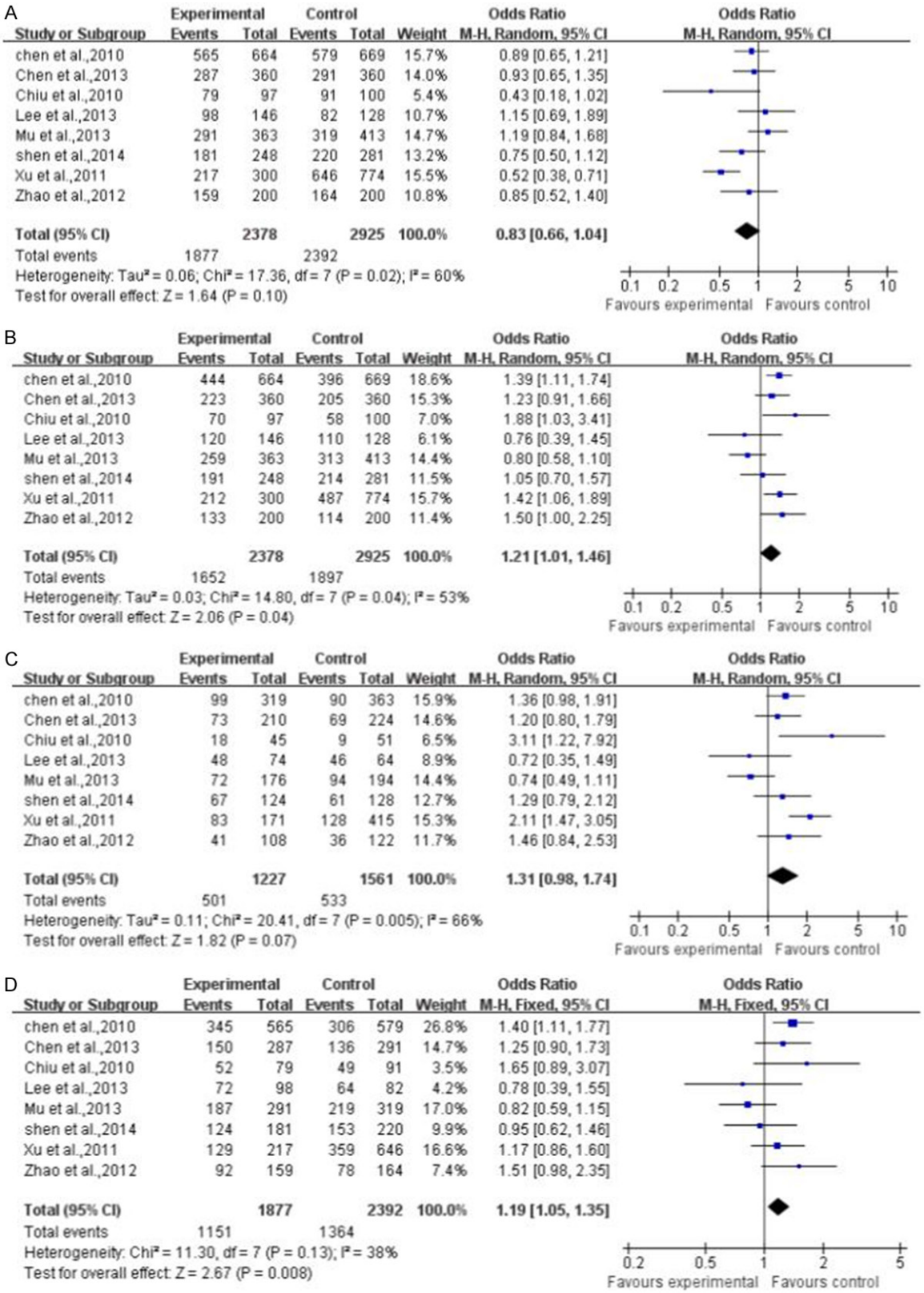


**Figure 2.** Meta-analysis of the association between osteopontin gene -156 G>GG and susceptibility to cancer risk. A. Dominant model. B. Recessive model. C. GGGG vs GG. D. GGG vs GG.

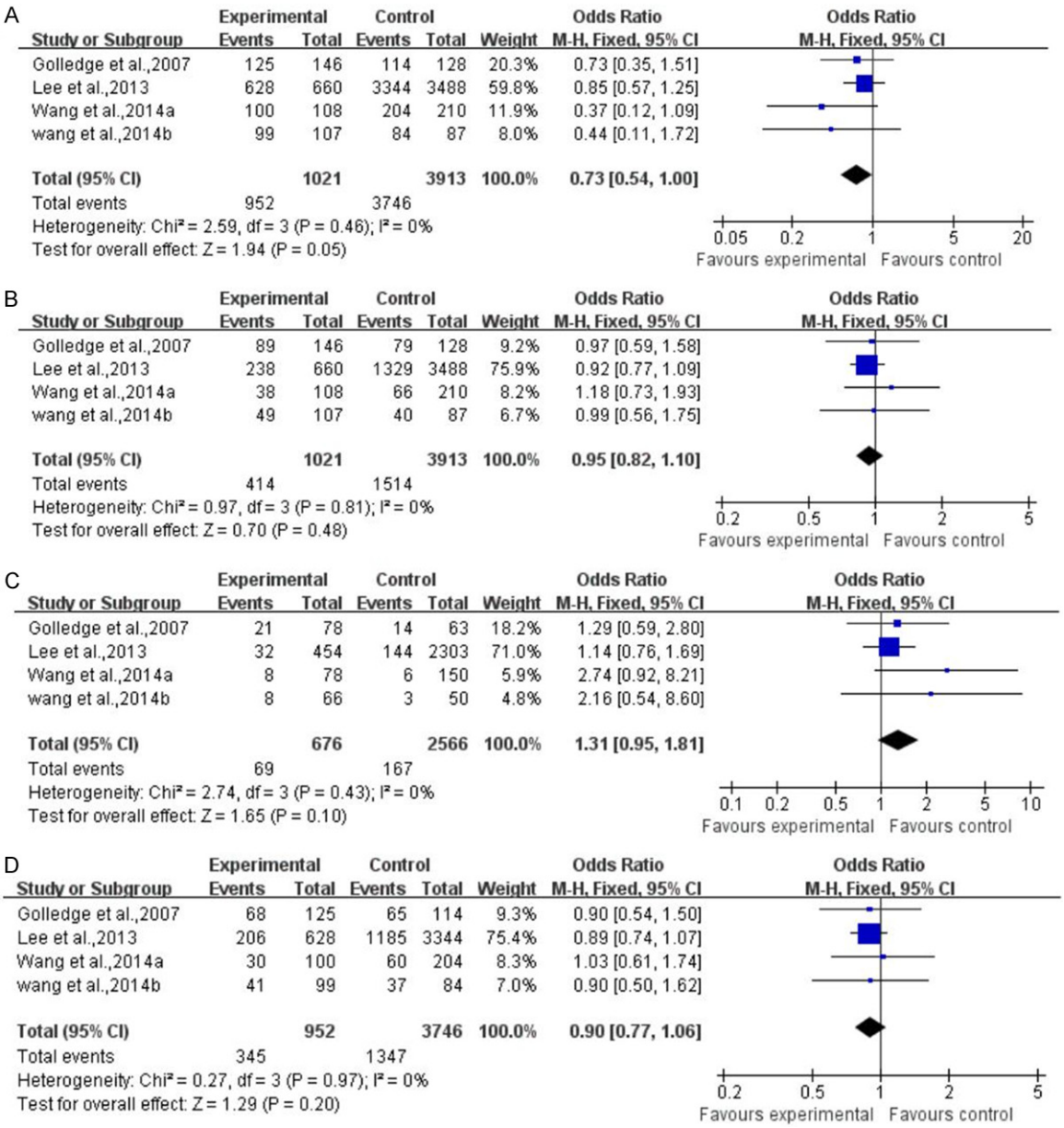



**Figure 3.** Meta-analysis of the association between osteopontin gene -1748 A>G and susceptibility to cancer risk. A. Dominant model. B. Recessive model. C. GG vs AA. D. AG vs AA.

P=0.05; OR=0.95, 95% CI=0.82-1.10, P=0.48; OR=1.31, 95% CI=0.95-1.81, P=0.10; OR=0.90, 95% CI=0.77-1.06, P=0.20, respectively).

## Discussion

To our knowledge, this is the first meta analysis which comprehensively assed the associations between osteopontin -443 C>T, -156 G>GG and -1748 A>G polymorphisms and tumor risk. In this study, we revealed that no significant associations were observed under all genetic models on osteopontin -443 C>T and -1748 A>G gene polymorphisms with tumor risk. However, there were only significant differences in two genetic models (GGGG+GGG vs GG and GGG vs GG models).

The OPN encoding genes mapped on human chromosome 4q21-q25 and polymorphisms in the OPN gene promoter may affect its transcriptional activity [21]. More than sixty gene polymorphisms have been identified in the human OPN encoding gene, however, of which three gene polymorphisms on the promoter region of OPN gene, namely, -443 C>T, -156 G>GG and -1748 A>G were the most studied [13, 15, 21]. Chiu et al. [14] revealed the -443 T>C gene polymorphisms was found to be more prevalent in oral squamous cell carcinoma patients. Mu et al. [17] found only -443 T>C gene polymorphism was significantly related to papillary thyroid cancer risk, but -156 G>GG gene polymorphism, which is not consistent with our meta analysis results. Therefore, more and high quality clinical studies should be included into this meta analysis in future.

In the present study, our results failed to detect the association of variant -1748 A>G, with tumor risk, which is consistent with previous study [15]. In contrast, several studies reported that this variant contributed to the risk of some other disease, such as Behcet's disease [22], suggesting that some gene polymorphism may interact with -1748 A>G variant and subsequently exert the effect on the pathogenesis of tumor, such as -443 C>T and/or -156 G>GG.

Some limitation in this meta analysis should be addressed. Firstly, a relatively small number of studies and sample size were included into this study, which may influence the statistical power of the analysis. Secondly, our meta analysis results were based on unadjusted estimates, while a more precise analysis could be conducted if individual data were available.

In conclusion, this study suggested that osteopontin gene polymorphisms, -443 C>T and -1748 A>G was not associated with cancer risk, but partly associated to tumor risk for -156 G>GG gene polymorphism.

## Disclosure of conflict of interest

None.

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