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*Original Article*

# Lack of association between *HMGB1* polymorphisms and cancer risk: a meta-analysis of case-control studies

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**Abstract:** Previous studies have shown that single-nucleotide polymorphisms in the *HMGB1* gene contribute to development of malignant tumors. The association of polymorphisms in the *HMGB1* gene with cancer susceptibility has, therefore, been extensively studied. However, results have been contradictory. To evaluate the association between this polymorphism and overall cancer risk, the current study conducted a meta-analysis, with 3,062 cases and 4,217 controls, from 8 eligible studies retrieved from PubMed and Embase databases. The strength of the connection, using odds ratios (ORs) and 95% confidence intervals (CIs), was assessed under allele contrast, dominant, recessive, homozygous, and heterozygous models. Pooled risk estimates indicated no significant association for polymorphisms *rs1045411*, *rs2249825*, *rs1412125*, or *rs1360485* and overall cancer susceptibility, according to comparisons using all five genetic models. Results of subgroup analysis indicated that *rs1045411* was significantly associated with cancer susceptibility under all genetic models in ligase detection reaction-polymerase chain reaction (LDR-PCR) studies. In addition, *rs1412125* was significantly associated with cancer risk under allele contrast, dominant, and heterozygous models in hospital-based studies. Despite certain limitations, the current meta-analysis provides solid statistical evidence of the absence of association between *HMGB1* polymorphisms and cancer risk.

**Keywords:** Cancer, genetic susceptibility, *HMGB1*, single nucleotide polymorphism

## Introduction

High mobility group box 1 (HMGB1) protein was first isolated and characterized in 1973. It was named based on its electrophoretic mobility in polyacrylamide gels [1]. The function of HMGB1 depends on its level of expression and subcellular location. In the nucleus, HMGB1 is engaged in many processes involving DNA, such as DNA repair, transcription, telomere maintenance, and genome stability. In the cytoplasm or extracellularly, this protein mediates more complex functions, including regulation of cell proliferation, autophagy, inflammation, and immunity [1-3].

Evidence suggesting that HMGB1 dysfunction is associated with cancer and contributes to cancer development and response to therapy has increased [2-4]. During tumor development and in cancer therapy, HMGB1 has been reported to play paradoxical roles in promoting both cell survival and cell death by regulating multiple signaling pathways. In the nucleus, HMGB1 acts as a tumor suppressor through various mechanisms, sustaining genome stability. In the cytoplasm or at the cell surface, it has been shown to act as either an oncogene or a tumor suppressor [1, 5].

Extracellular HMGB1 exhibits a variety of functions. It has been found to be a prototypic damage-associated molecular pattern molecule (DAMP) interacting with several receptors, including the receptor for advanced glycation end products (RAGE) and toll-like receptors

(TLRs). HMGB1 signaling through RAGE mediates increases in migration, invasion, and proliferation of cancer cells [3, 4, 6]. However, extracellular HMGB1 is also important for the immunogenic cell death of cancer cells. It stimulates antitumor immunity response during chemotherapy or radiotherapy [6]. In addition, HMGB1 is a critical regulator of autophagy [7-9]. The roles of autophagy in cancer are complex, likely dependent on tumor type, stage, genetic context, and tumor microenvironment [10].

Based on these roles in cancer development, molecular mechanisms contributing to the regulation of HMGB1 and/or function have been under intense investigation. Recent studies have examined the association of specific single nucleotide polymorphisms (SNPs) in the *HMGB1* gene with cancer risk. However, the significance of these findings remains unclear. Due to insufficient population sizes, the statistical power of each study, individually, was relatively low. Evidence of the risk associated with each polymorphism was inconclusive. To increase statistical power, the current study conducted a systematic review and meta-analysis of published studies, investigating the association between *HMGB1* polymorphisms and cancer susceptibility. Present analysis, however, failed to identify any significant association between *HMGB1* polymorphisms and cancer types examined.

## Materials and methods

### *Search strategy*

A systematic search was performed in PubMed for studies reporting the association of *HMGB1* polymorphisms with cancer risk in any type of cancer. The search included studies published in English up to May 18, 2018. Gene-specific terms (HMGB1 or high mobility group box 1) were combined with polymorphism-(polymorphism or polymorphisms or variation or variations or variant or variants or mutation or mutations or genotype or genotypes) and disease-specific terms (cancer or cancers or tumor or tumors or neoplasm or neoplasms). The search was performed using the method of free-text words combined with Medical Subject Headings (MeSH). The search included the following search terms: “Neoplasms”, “HMGB1 Protein”, and “Polymorphism, Single Nucleotide”. A thorough review of all reference materials within retrieved studies was also performed, aiming to identify additional potentially eligible studies.

### *Inclusion criteria and exclusion criteria*

Inclusion criteria: (1) Case-control or cohort study design; (2) Sufficient data for evaluation of *HMGB1* SNPs in cancer risk; (3) Articles published in English; (4) Studies performed on humans; and (5) In cases of multiple publications from the same study group, the most complete and most recent results were used.

Exclusion criteria: (1) Abstracts, reviews, and animal studies; (2) Useless reported data, such as genotype number or frequency; and (3) Articles published in languages other than English.

### *Data extraction*

Two researchers, independently, selected studies and extracted the following data from each study: First author’s surname, publication year, ethnicity, cancer types, numbers of cases and controls, and genotype distributions of cases and controls. All authors of this meta-analysis participated in data extraction. A consensus was reached after discussion. Study design was stratified into population-based studies and hospital-based studies.

### *Quality assessment*

The Newcastle-Ottawa Scale and Agency for Healthcare Research and Quality (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, maximum score = 9 points) was used to evaluate methodological quality. This system scored studies according to the selection of patients, comparability of the groups, and quality of the sampling process. Generally, studies scoring > 5 points are considered high-quality studies.

### *Statistical analysis*

The current meta-analysis assessed association between polymorphisms and cancer risks under allele contrast, dominant, recessive, homozygous, and heterozygous models. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate the strength of association. Heterogeneity among included studies was evaluated using Chi square-based Q statis-

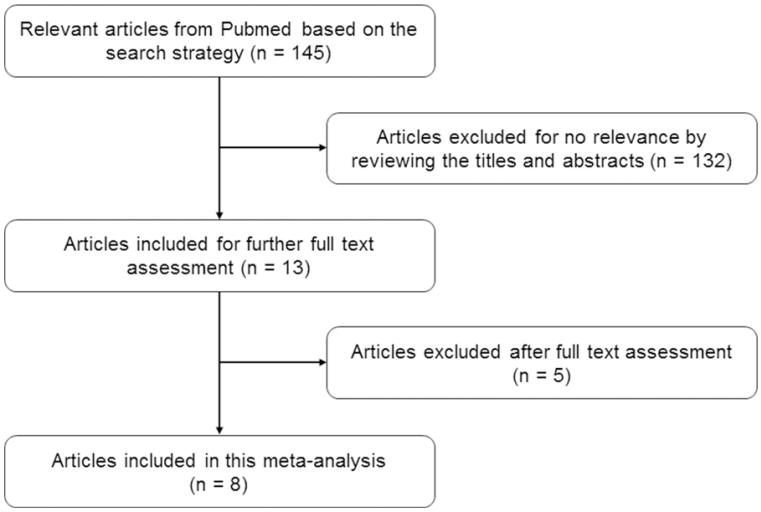



**Figure 1.** Flowchart of selection of studies included in the current meta-analysis for the correlation between *HMGB1* polymorphisms and overall cancer susceptibility.

tic. A fixed-effects (Mantel-Haenszel method) or random-effects model (DerSimonian-Laird method) was used to calculate pooled effect estimates in the presence ($P < 0.05$) or absence ($P > 0.05$) of heterogeneity. Sensitivity analysis was conducted by sequentially excluding one study at a time. Begg's tests and Egger's tests were performed to assess publication bias. If any possible bias was observed, the trim and fill method was used to identify and adjust for those studies. Data analysis was carried out using Stata software, version 11.0 (Stata Corporation; College Station, TX, USA). *P*-values < 0.05 indicate statistical significance.

## Results

### *Study characteristics*

After applying inclusion and exclusion criteria (**Figure 1**), 8 publications were eligible for the meta-analysis. They included a total of 3,062 cancer patients and 4,217 controls, with 6 different cancer types [11-18]. Main characteristics of the eligible studies are listed in **Table 1**. All studies scored a value of 7 or above, as determined in the Newcastle-Ottawa Scale, and individuals therein were of Chinese or Caucasian descent. The following is a breakdown of the number of studies, including cancer types, cases, and controls, meeting eligibility criteria for each polymorphism evaluated: *rs1045411*, 8 case-control studies, including 6 different cancer types, with 2,927 cases and 4,217 controls; *rs2249825*, 8 case-control studies, including 6 different cancer types, with 2,927 cases and 4,217 controls; *rs1412125*, 7 case-control studies, including 6 different cancer types, with 2,834 cases and 4,117 controls; and *rs1360485*, 4 case-control studies, including 4 different cancer types, with 1,530 cases and 2,579 controls (**Table 1**).

### *Quantitative synthesis*

Results of the association of *HMGB1* SNPs with general risks for cancer, including data for all individuals, are shown in **Table 2**. Overall, pooled risk estimates indicated that no significant association existed for polymorphisms *rs1045411*, *rs2249825*, *rs1412125*, or *rs1360485* and overall cancer susceptibility, according to comparisons using all five genetic models (**Figures 2**-**5**).

### *Subgroup analysis*

Stratified analysis based on ethnicity (Chinese or Caucasian), genotyping method (Taqman or LDR-PCR), source of controls (hospital-based or population-based), and Hardy-Weinberg equilibrium, in controls, was only performed on polymorphism *rs1045411* (**Table 3**). In ethnicity subgroup analysis, polymorphism *rs1045411* was not significantly associated with cancer susceptibility for Chinese populations. The magnitude of association in hospital-based studies was not significantly changed. When stratification analysis was conducted based on genotyping method, *rs1045411* was significantly associated with cancer susceptibility under all genetic models in LDR-PCR studies, but not in TaqMan studies. Pooled ORs were not significantly changed under stratification based on Hardy-Weinberg equilibrium (**Figure 2**).

Stratified analysis based on ethnicity, genotyping method, source of controls, and Hardy-Weinberg equilibrium, in controls, was only performed on polymorphism *rs2249825* (**Table 4**). In ethnicity subgroup analysis, polymorphism

**Table 1.** Characteristics of studies on association between *HMGB1* single nucleotide polymorphisms and cancers

| Single Nucleotide Polymorphisms | Author | Year | Ethnicity | Cancers | Genotyping Method | Quality Score | Cases | Controls | Source of Controls | *P* for HWE in controls | Cases | | | Controls | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | WW | WM | MM | WW | WM | MM |
| *rs1045411* | Wang | 2017 | Chinese | HCC | LDR-PCR | 7 | 540 | 540 | HB | > 0.05 | 349 | 158 | 33 | 405 | 127 | 8 |
| *rs1045411* | Lin | 2017 | Chinese | OSCC | TaqMan | 8 | 772 | 1200 | PB | > 0.05 | 438 | 274 | 60 | 649 | 457 | 94 |
| *rs1045411* | Hu | 2017 | Chinese | LC | TaqMan | 7 | 372 | 379 | HB | > 0.05 | 130 | 54 | 6 | 109 | 71 | 7 |
| *rs1045411* | Yue | 2016 | Chinese | BC | LDR-PCR | 7 | 524 | 518 | HB | > 0.05 | 373 | 138 | 13 | 389 | 124 | 5 |
| *rs1045411* | Wu | 2016 | Chinese | UCN | TaqMan | 7 | 197 | 305 | HB | > 0.05 | 117 | 69 | 11 | 204 | 91 | 10 |
| *rs1045411* | Wang J | 2016 | Chinese | CRC | PCR-RFLP | 7 | 240 | 480 | HB | < 0.05 | 144 | 82 | 14 | 268 | 194 | 18 |
| *rs1045411* | Wang B | 2016 | Chinese | HCC | TaqMan | 7 | 324 | 695 | HB | > 0.05 | 223 | 89 | 12 | 425 | 239 | 31 |
| *rs1045411* | Supic | 2015 | Caucasian | OSCC | TaqMan | 7 | 93 | 100 | HB | > 0.05 | 48 | 40 | 5 | 64 | 30 | 6 |
| *rs2249825* | Wang | 2017 | Chinese | HCC | LDR-PCR | 7 | 540 | 540 | HB | > 0.05 | 349 | 158 | 33 | 405 | 127 | 8 |
| *rs2249825* | Lin | 2017 | Chinese | OSCC | TaqMan | 8 | 772 | 1200 | PB | > 0.05 | 438 | 274 | 60 | 649 | 457 | 94 |
| *rs2249825* | Hu | 2017 | Chinese | LC | TaqMan | 7 | 372 | 379 | HB | > 0.05 | 130 | 54 | 6 | 109 | 71 | 7 |
| *rs2249825* | Yue | 2016 | Chinese | BC | LDR-PCR | 7 | 524 | 518 | HB | > 0.05 | 373 | 138 | 13 | 389 | 124 | 5 |
| *rs2249825* | Wu | 2016 | Chinese | UCN | TaqMan | 7 | 197 | 305 | HB | > 0.05 | 117 | 69 | 11 | 204 | 91 | 10 |
| *rs2249825* | Wang J | 2016 | Chinese | CRC | PCR-RFLP | 7 | 240 | 480 | HB | < 0.05 | 144 | 82 | 14 | 268 | 194 | 18 |
| *rs2249825* | Wang B | 2016 | Chinese | HCC | TaqMan | 7 | 324 | 695 | HB | > 0.05 | 223 | 89 | 12 | 425 | 239 | 31 |
| *rs2249825* | Supic | 2015 | Caucasian | OSCC | TaqMan | 7 | 93 | 100 | HB | > 0.05 | 48 | 40 | 5 | 64 | 30 | 6 |
| *rs1412125* | Wang | 2017 | Chinese | HCC | LDR-PCR | 7 | 540 | 540 | HB | > 0.05 | 273 | 216 | 51 | 290 | 205 | 45 |
| *rs1412125* | Lin | 2017 | Chinese | OSCC | TaqMan | 8 | 772 | 1200 | PB | > 0.05 | 438 | 274 | 60 | 649 | 457 | 94 |
| *rs1412125* | Hu | 2017 | Chinese | LC | TaqMan | 7 | 372 | 379 | HB | > 0.05 | 109 | 70 | 11 | 107 | 69 | 11 |
| *rs1412125* | Yue | 2016 | Chinese | BC | LDR-PCR | 7 | 524 | 518 | HB | > 0.05 | 281 | 213 | 30 | 300 | 193 | 25 |
| *rs1412125* | Wu | 2016 | Chinese | UCN | TaqMan | 7 | 197 | 305 | HB | > 0.05 | 83 | 97 | 17 | 173 | 114 | 18 |
| *rs1412125* | Wang J | 2016 | Chinese | CRC | PCR-RFLP | 7 | 240 | 480 | HB | < 0.05 | 126 | 103 | 11 | 270 | 195 | 15 |
| *rs1412125* | Wang B | 2016 | Chinese | HCC | TaqMan | 7 | 324 | 695 | HB | > 0.05 | 173 | 130 | 21 | 374 | 275 | 46 |
| *rs1360485* | Lin | 2017 | Chinese | OSCC | TaqMan | 8 | 772 | 1200 | PB | > 0.05 | 452 | 273 | 47 | 682 | 440 | 78 |
| *rs1360485* | Hu | 2017 | Chinese | LC | TaqMan | 7 | 372 | 379 | HB | > 0.05 | 124 | 56 | 10 | 107 | 68 | 12 |
| *rs1360485* | Wu | 2016 | Chinese | UCN | TaqMan | 7 | 197 | 305 | HB | > 0.05 | 111 | 73 | 13 | 183 | 110 | 12 |
| *rs1360485* | Wang B | 2016 | Chinese | HCC | TaqMan | 7 | 324 | 695 | HB | > 0.05 | 192 | 188 | 14 | 399 | 257 | 39 |

HCC: hepatocellular carcinoma. OSCC: oral squamous cell carcinoma. LC: lung cancer. BC: breast cancer. UCN: uterine cervical neoplasia. CRC: colorectal cancer. PB: population-based. HB: hospital-based. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. LDR-PCR: ligase detection reaction-polymerase chain reaction. HWE: Hardy-Weinberg equilibrium.

**Table 2.** ORs and 95% CIs for cancers and *HMGB1* single nucleotide polymorphisms under different genetic models

| Genetic models | N | OR [95% CI] | *P* (OR) | Model (method) | *I*-square (%) | *P* (H) | *P* (Begg) | *P* (Egger) |
|---|---|---|---|---|---|---|---|---|
| *rs1045411* | | | | | | | | |
| Allele contrast | 8 | 1.079 [0.874-1.333] | 0.477 | R (D-L) | 81.4 | < 0.001 | 1.000 | 0.651 |
| Dominant model | 8 | 1.046 [0.826-1.325] | 0.710 | R (D-L) | 79.2 | < 0.001 | 0.902 | 0.676 |
| Recessive model | 8 | 1.429 [0.941-2.171] | 0.094 | R (D-L) | 58.2 | 0.019 | 0.386 | 0.328 |
| Homozygous model | 8 | 1.432 [0.900-2.278] | 0.130 | R (D-L) | 65.4 | 0.005 | 0.386 | 0.305 |
| Heterozygous model | 8 | 1.005 [0.808-1.250] | 0.967 | R (D-L) | 73.3 | < 0.001 | 1.000 | 0.633 |
| *rs2249825* | | | | | | | | |
| Allele contrast | 8 | 1.066 [0.826-1.375] | 0.622 | R (D-L) | 84.0 | < 0.001 | 0.711 | 0.940 |
| Dominant model | 8 | 1.105 [0.824-1.482] | 0.503 | R (D-L) | 84.5 | < 0.001 | 0.902 | 0.673 |
| Recessive model | 8 | 1.070 [0.783-1.460] | 0.672 | F (M-H) | 18.9 | 0.281 | 0.386 | 0.248 |
| Homozygous model | 8 | 1.122 [0.821-1.534] | 0.471 | F (M-H) | 41.2 | 0.104 | 0.711 | 0.318 |
| Heterozygous model | 8 | 1.123 [0.841-1.499] | 0.433 | R (D-L) | 82.9 | < 0.001 | 0.711 | 0.538 |
| *rs1412125* | | | | | | | | |
| Allele contrast | 7 | 1.070 [0.989-1.157] | 0.093 | F (M-H) | 46.2 | 0.084 | 0.368 | 0.167 |
| Dominant model | 7 | 1.118 [0.961-1.301] | 0.148 | R (D-L) | 53.5 | 0.044 | 0.368 | 0.132 |
| Recessive model | 7 | 1.107 [0.911-1.344] | 0.307 | F (M-H) | 0.0 | 0.910 | 0.230 | 0.185 |
| Homozygous model | 7 | 1.137 [0.932-1.387] | 0.206 | F (M-H) | 0.0 | 0.596 | 0.230 | 0.160 |
| Heterozygous model | 7 | 1.074 [0.968-1.190] | 0.177 | F (M-H) | 47.9 | 0.074 | 0.548 | 0.130 |
| *rs1360485* | | | | | | | | |
| Allele contrast | 4 | 1.016 [0.914-1.129] | 0.765 | F (M-H) | 57.3 | 0.071 | 0.734 | 0.996 |
| Dominant model | 4 | 1.042 [0.794-1.368] | 0.765 | R (D-L) | 72.5 | 0.012 | 0.734 | 0.945 |
| Recessive model | 4 | 0.904 [0.684-1.196] | 0.480 | F (M-H) | 24.4 | 0.265 | 1.000 | 0.856 |
| Homozygous model | 4 | 0.922 [0.694-1.226] | 0.577 | F (M-H) | 7.5 | 0.356 | 1.000 | 0.789 |
| Heterozygous model | 4 | 1.049 [0.775-1.420] | 0.758 | R (D-L) | 76.0 | 0.006 | 0.734 | 0.872 |

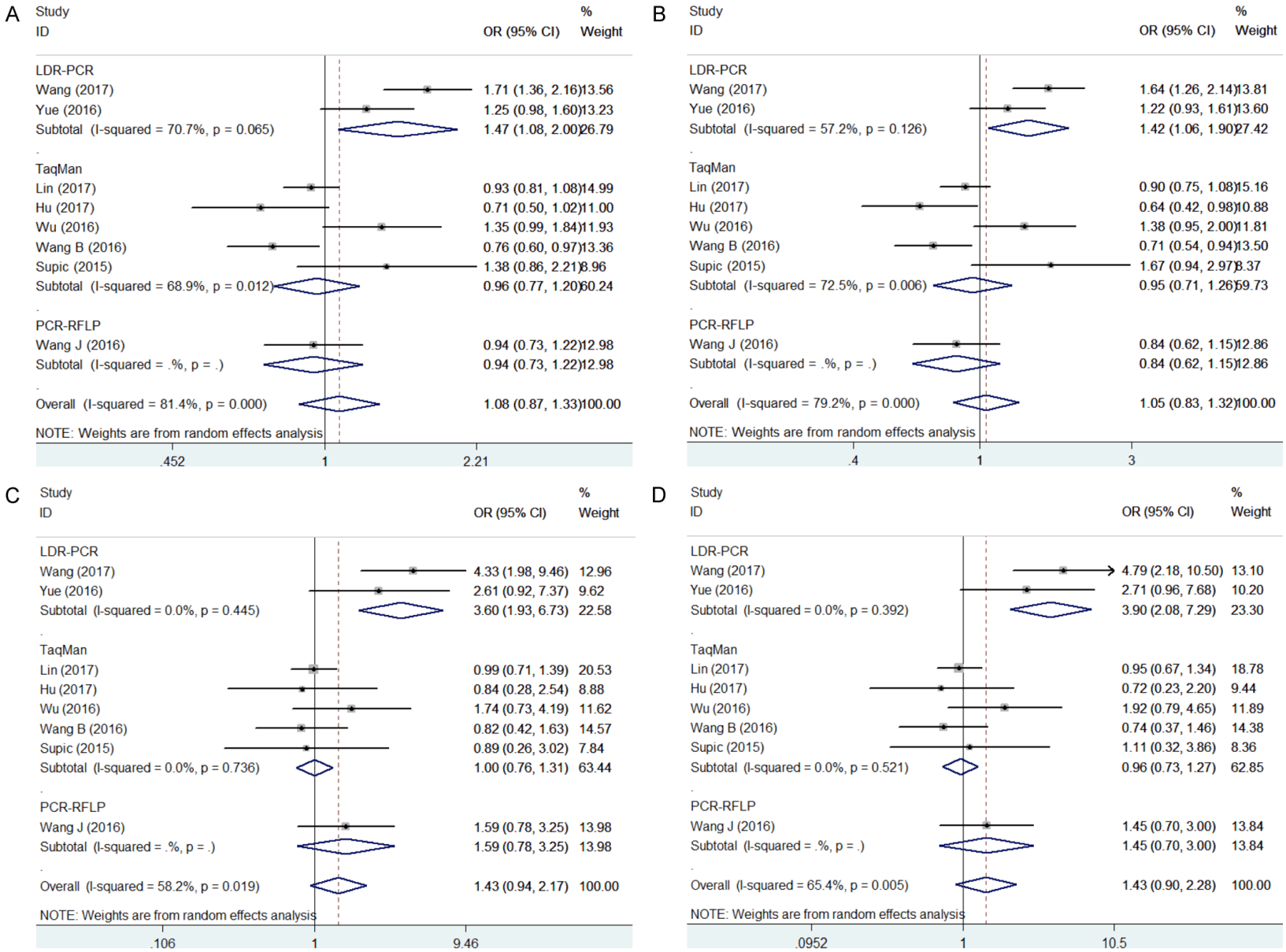
OR: odds ratio. CI: confidence intervals. N: number of included studies. R: random-effects model. D-L: DerSimonian-Laird method. F: fixed-effect model. M-H: Mantel-Haenszel method. *P* (H): *P*-value for heterogeneity.

*rs2249825* was not significantly associated with cancer susceptibility for Chinese populations. The magnitude of association in hospital-based studies was not significantly changed. When stratification analysis was conducted based on genotyping method, no significant correlation between *rs2249825* and cancer susceptibility was found in LDR-PCR studies or in TaqMan studies. Pooled ORs were not significantly changed under stratification using Hardy-Weinberg equilibrium (**Figure 3**).

Stratified analysis based on genotyping method, source of controls, and Hardy-Weinberg equilibrium, in controls, was only performed on polymorphism *rs1412125* (**Table 5**). The magnitude of association in LDR-PCR studies or in TaqMan studies was not significantly changed. When stratification analysis was conducted based on source of controls, *rs1412125* was significantly associated with cancer risk under allele contrast, dominant, and heterozygous models in hospital-based studies. Pooled ORs were not significantly changed under stratification using Hardy-Weinberg equilibrium (**Figure 4**).

*Heterogeneity and sensitivity analysis*

Significant between-study heterogeneity was observed under some models (**Table 1**). Therefore, a random-effects model was adopted to generate wider CIs. Examining the influence of individual data sets on pooled ORs, single studies were sequentially excluded from analysis. Pooled ORs were not significantly altered, indicating that meta-analysis results are stable and reliable.


A
Study
ID
OR (95% CI)
%
Weight
LDR-PCR
Wang (2017) 1.71 (1.36, 2.16) 13.56
Yue (2016) 1.25 (0.98, 1.60) 13.23
Subtotal (I-squared = 70.7%, p = 0.065) 1.47 (1.08, 2.00) 26.79
TaqMan
Lin (2017) 0.93 (0.81, 1.08) 14.99
Hu (2017) 0.71 (0.50, 1.02) 11.00
Wu (2016) 1.35 (0.99, 1.84) 11.93
Wang B (2016) 0.76 (0.60, 0.97) 13.36
Supic (2015) 1.38 (0.86, 2.21) 8.96
Subtotal (I-squared = 68.9%, p = 0.012) 0.96 (0.77, 1.20) 60.24
PCR-RFLP
Wang J (2016) 0.94 (0.73, 1.22) 12.98
Subtotal (I-squared = .%, p = .) 0.94 (0.73, 1.22) 12.98
Overall (I-squared = 81.4%, p = 0.000) 1.08 (0.87, 1.33) 100.00
NOTE: Weights are from random effects analysis
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Study
ID
OR (95% CI)
%
Weight
LDR-PCR
Wang (2017) 1.64 (1.26, 2.14) 13.81
Yue (2016) 1.22 (0.93, 1.61) 13.60
Subtotal (I-squared = 57.2%, p = 0.126) 1.42 (1.06, 1.90) 27.42
TaqMan
Lin (2017) 0.90 (0.75, 1.08) 15.16
Hu (2017) 0.64 (0.42, 0.98) 10.88
Wu (2016) 1.38 (0.95, 2.00) 11.81
Wang B (2016) 0.71 (0.54, 0.94) 13.50
Supic (2015) 1.67 (0.94, 2.97) 8.37
Subtotal (I-squared = 72.5%, p = 0.006) 0.95 (0.71, 1.26) 59.73
PCR-RFLP
Wang J (2016) 0.84 (0.62, 1.15) 12.86
Subtotal (I-squared = .%, p = .) 0.84 (0.62, 1.15) 12.86
Overall (I-squared = 79.2%, p = 0.000) 1.05 (0.83, 1.32) 100.00
NOTE: Weights are from random effects analysis
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Study
ID
OR (95% CI)
%
Weight
LDR-PCR
Wang (2017) 4.33 (1.98, 9.46) 12.96
Yue (2016) 2.61 (0.92, 7.37) 9.62
Subtotal (I-squared = 0.0%, p = 0.445) 3.60 (1.93, 6.73) 22.58
TaqMan
Lin (2017) 0.99 (0.71, 1.39) 20.53
Hu (2017) 0.84 (0.28, 2.54) 8.88
Wu (2016) 1.74 (0.73, 4.19) 11.62
Wang B (2016) 0.82 (0.42, 1.63) 14.57
Supic (2015) 0.89 (0.26, 3.02) 7.84
Subtotal (I-squared = 0.0%, p = 0.736) 1.00 (0.76, 1.31) 63.44
PCR-RFLP
Wang J (2016) 1.59 (0.78, 3.25) 13.98
Subtotal (I-squared = .%, p = .) 1.59 (0.78, 3.25) 13.98
Overall (I-squared = 58.2%, p = 0.019) 1.43 (0.94, 2.17) 100.00
NOTE: Weights are from random effects analysis
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Study
ID
OR (95% CI)
%
Weight
LDR-PCR
Wang (2017) 4.79 (2.18, 10.50) 13.10
Yue (2016) 2.71 (0.96, 7.68) 10.20
Subtotal (I-squared = 0.0%, p = 0.392) 3.90 (2.08, 7.29) 23.30
TaqMan
Lin (2017) 0.95 (0.67, 1.34) 18.78
Hu (2017) 0.72 (0.23, 2.20) 9.44
Wu (2016) 1.92 (0.79, 4.65) 11.89
Wang B (2016) 0.74 (0.37, 1.46) 14.38
Supic (2015) 1.11 (0.32, 3.86) 8.36
Subtotal (I-squared = 0.0%, p = 0.521) 0.96 (0.73, 1.27) 62.85
PCR-RFLP
Wang J (2016) 1.45 (0.70, 3.00) 13.84
Subtotal (I-squared = .%, p = .) 1.45 (0.70, 3.00) 13.84
Overall (I-squared = 65.4%, p = 0.005) 1.43 (0.90, 2.28) 100.00
NOTE: Weights are from random effects analysis
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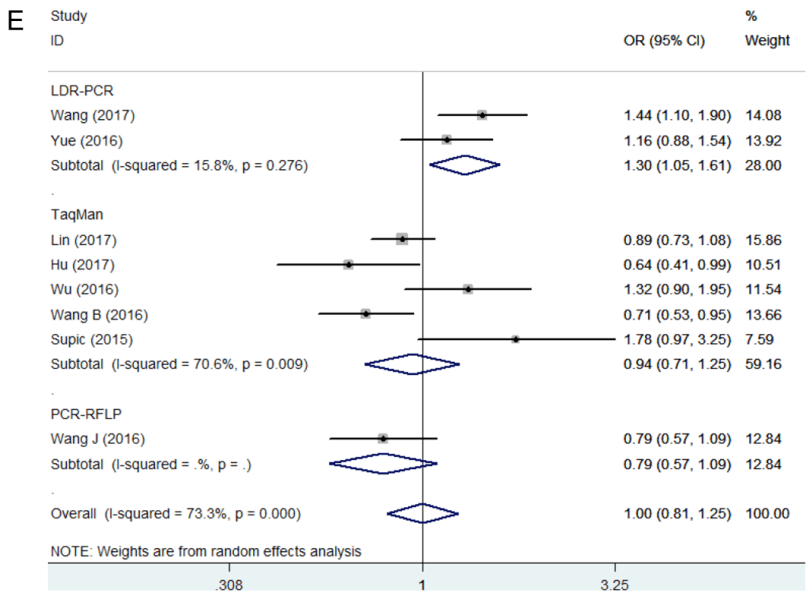
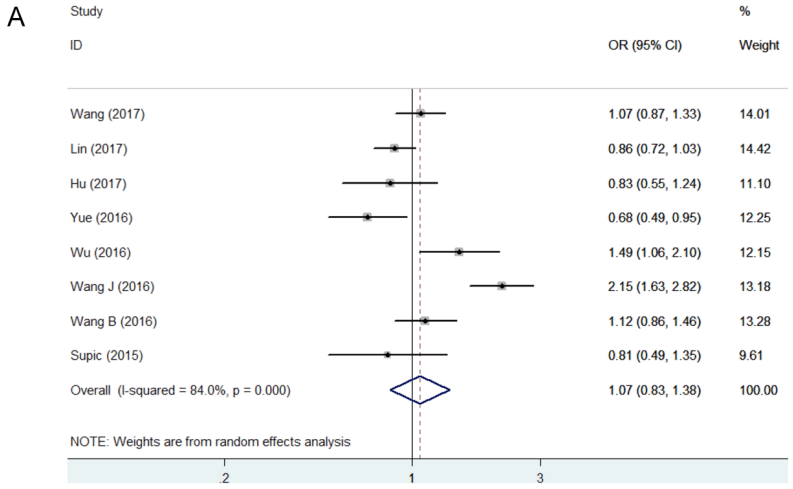
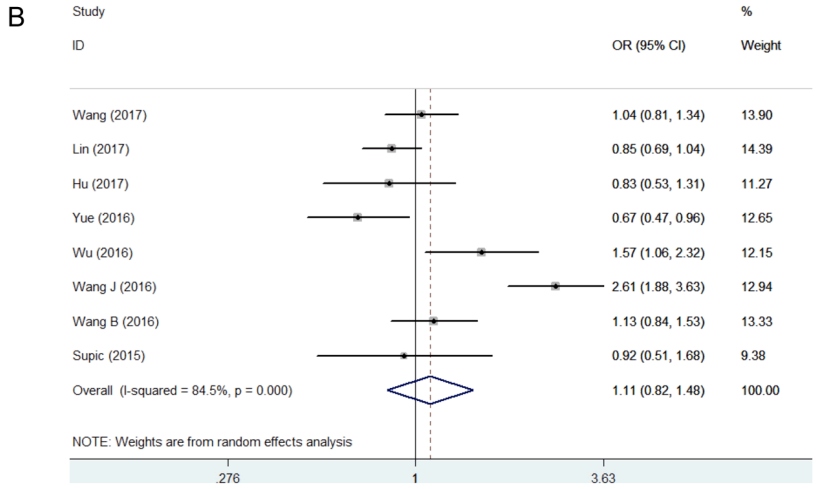



**Figure 2.** Forest plot of cancer risk associated with *HMGB1* polymorphism *rs1045411* using different genotyping methods. Association of the polymorphism with cancer development was analyzed in the following models: (A) Allele contrast; (B) Dominant; (C) Recessive; (D) Homozygous; and (E) Heterozygous. Each square represents a study and the area of each square is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. OR: odds ratio; CI: confidence interval.



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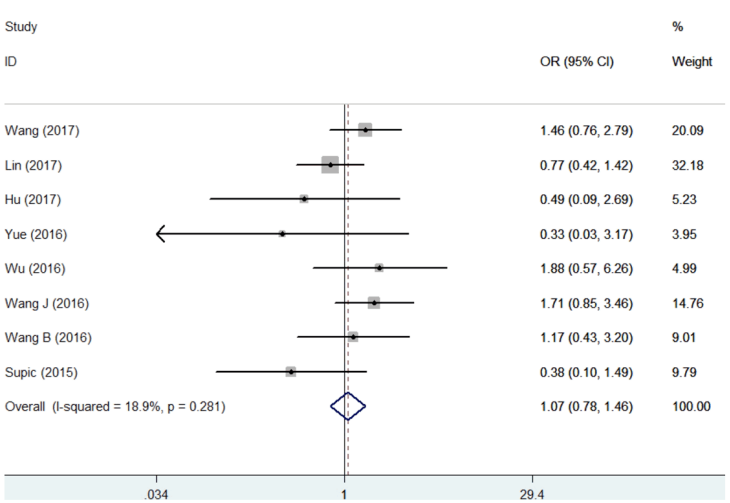


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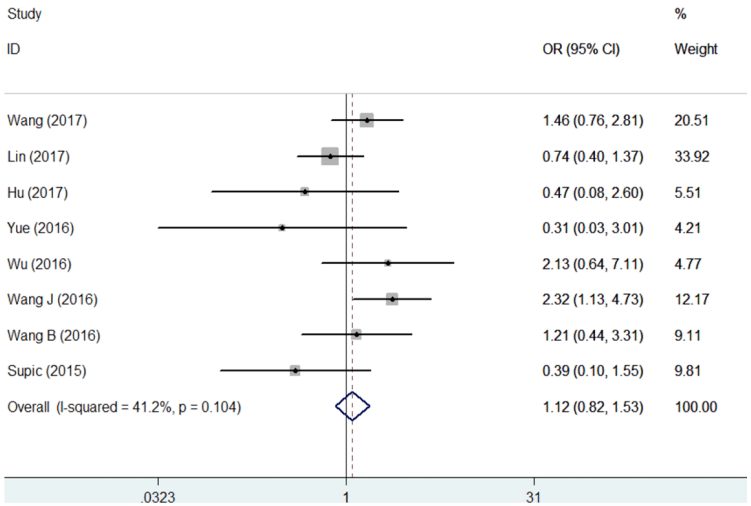



E

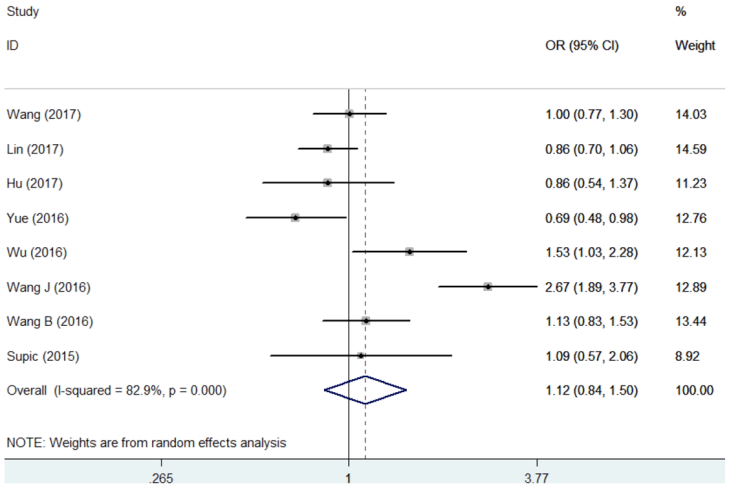
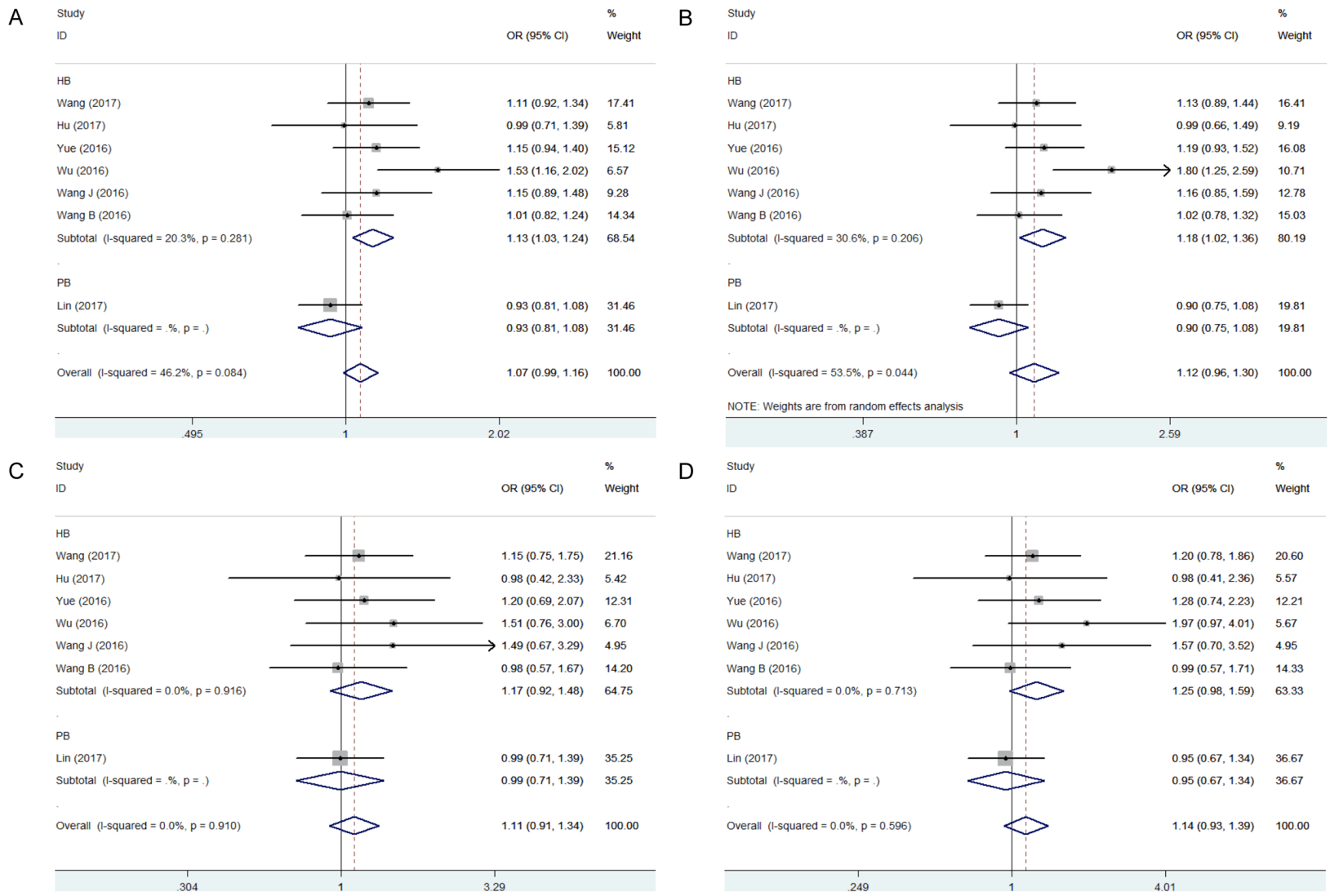



**Figure 3.** Forest plot of cancer risk associated with *HMGB1* polymorphism *rs2249825*. Association of the polymorphism with cancer development was analyzed in the following models: (A) Allele contrast; (B) Dominant; (C) Recessive; (D) Homozygous; and (E) Heterozygous. Each square represents a study and the area of each square is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. OR: odds ratio; CI: confidence interval.


A
Study
ID
OR (95% CI)
%
Weight
HB
Wang (2017) 1.11 (0.92, 1.34) 17.41
Hu (2017) 0.99 (0.71, 1.39) 5.81
Yue (2016) 1.15 (0.94, 1.40) 15.12
Wu (2016) 1.53 (1.16, 2.02) 6.57
Wang J (2016) 1.15 (0.89, 1.48) 9.28
Wang B (2016) 1.01 (0.82, 1.24) 14.34
Subtotal (I-squared = 20.3%, p = 0.281) 1.13 (1.03, 1.24) 68.54
PB
Lin (2017) 0.93 (0.81, 1.08) 31.46
Subtotal (I-squared = .%, p = .) 0.93 (0.81, 1.08) 31.46
Overall (I-squared = 46.2%, p = 0.084) 1.07 (0.99, 1.16) 100.00
.495
1
2.02
B
Study
ID
OR (95% CI)
%
Weight
HB
Wang (2017) 1.13 (0.89, 1.44) 16.41
Hu (2017) 0.99 (0.66, 1.49) 9.19
Yue (2016) 1.19 (0.93, 1.52) 16.08
Wu (2016) 1.80 (1.25, 2.59) 10.71
Wang J (2016) 1.16 (0.85, 1.59) 12.78
Wang B (2016) 1.02 (0.78, 1.32) 15.03
Subtotal (I-squared = 30.6%, p = 0.206) 1.18 (1.02, 1.36) 80.19
PB
Lin (2017) 0.90 (0.75, 1.08) 19.81
Subtotal (I-squared = .%, p = .) 0.90 (0.75, 1.08) 19.81
Overall (I-squared = 53.5%, p = 0.044) 1.12 (0.96, 1.30) 100.00
NOTE: Weights are from random effects analysis
.387
1
2.59
C
Study
ID
OR (95% CI)
%
Weight
HB
Wang (2017) 1.15 (0.75, 1.75) 21.16
Hu (2017) 0.98 (0.42, 2.33) 5.42
Yue (2016) 1.20 (0.69, 2.07) 12.31
Wu (2016) 1.51 (0.76, 3.00) 6.70
Wang J (2016) 1.49 (0.67, 3.29) 4.95
Wang B (2016) 0.98 (0.57, 1.67) 14.20
Subtotal (I-squared = 0.0%, p = 0.916) 1.17 (0.92, 1.48) 64.75
PB
Lin (2017) 0.99 (0.71, 1.39) 35.25
Subtotal (I-squared = .%, p = .) 0.99 (0.71, 1.39) 35.25
Overall (I-squared = 0.0%, p = 0.910) 1.11 (0.91, 1.34) 100.00
.304
1
3.29
D
Study
ID
OR (95% CI)
%
Weight
HB
Wang (2017) 1.20 (0.78, 1.86) 20.60
Hu (2017) 0.98 (0.41, 2.36) 5.57
Yue (2016) 1.28 (0.74, 2.23) 12.21
Wu (2016) 1.97 (0.97, 4.01) 5.67
Wang J (2016) 1.57 (0.70, 3.52) 4.95
Wang B (2016) 0.99 (0.57, 1.71) 14.33
Subtotal (I-squared = 0.0%, p = 0.713) 1.25 (0.98, 1.59) 63.33
PB
Lin (2017) 0.95 (0.67, 1.34) 36.67
Subtotal (I-squared = .%, p = .) 0.95 (0.67, 1.34) 36.67
Overall (I-squared = 0.0%, p = 0.596) 1.14 (0.93, 1.39) 100.00
.249
1
4.01

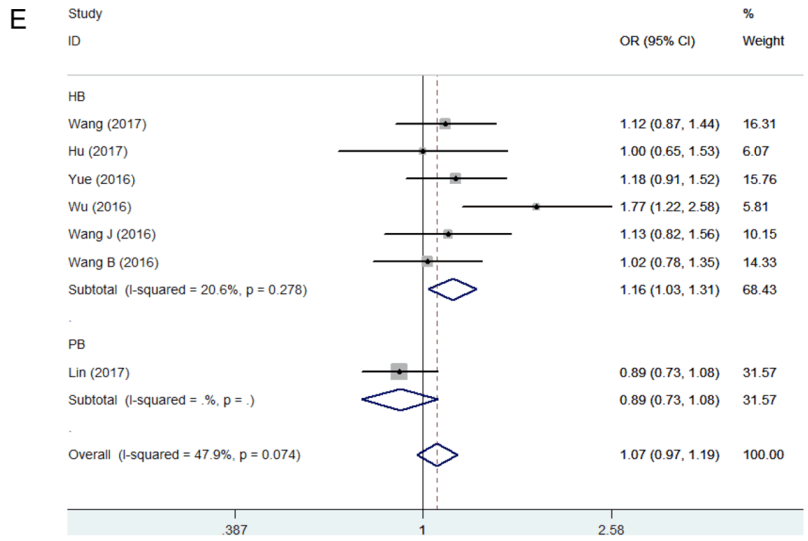
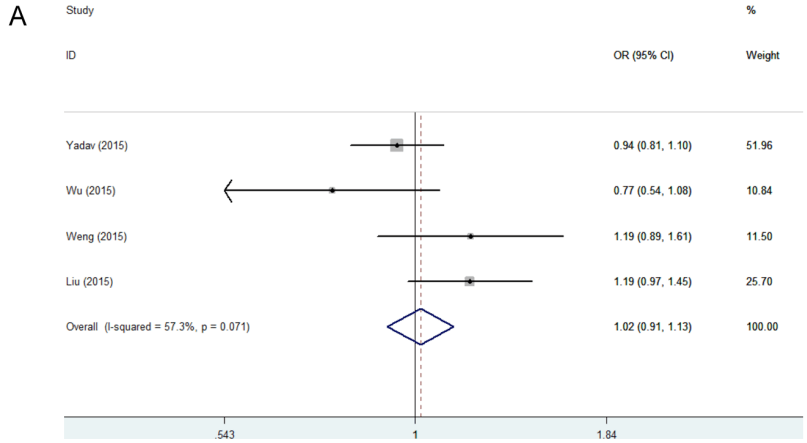
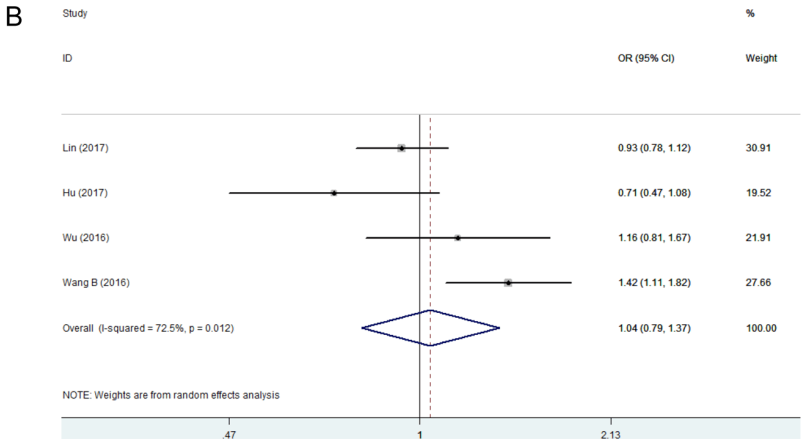



**Figure 4.** Forest plot of cancer risk associated with *HMGB1* polymorphism *rs1412125* using different sources of controls. Association of the polymorphism with cancer development was analyzed in the following models: (A) Allele contrast; (B) Dominant; (C) Recessive; (D) Homozygous; and (E) Heterozygous. Each square represents a study and the area of each square is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. OR: odds ratio; CI: confidence interval.



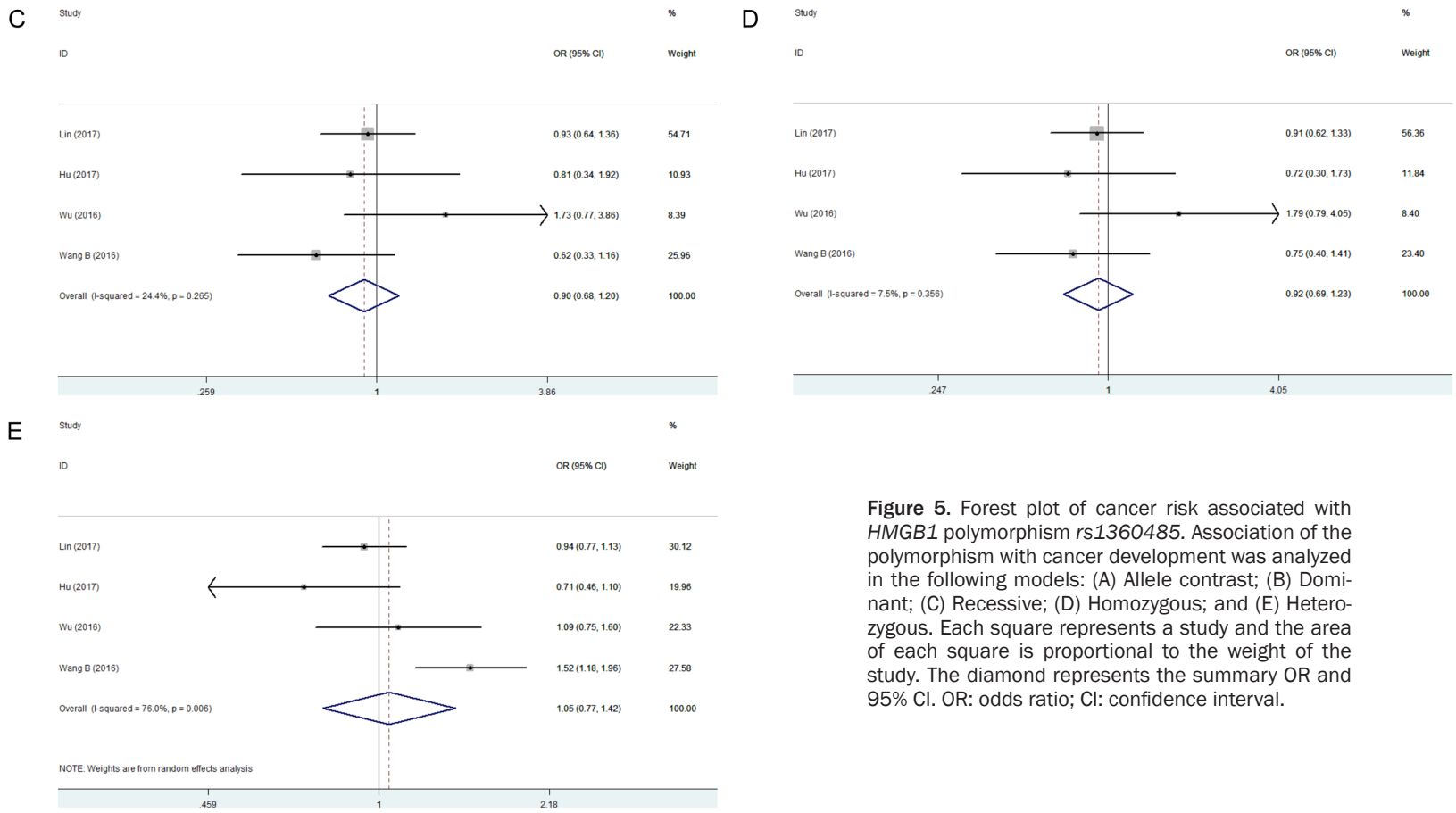



**Figure 5.** Forest plot of cancer risk associated with *HMGB1* polymorphism *rs1360485*. Association of the polymorphism with cancer development was analyzed in the following models: (A) Allele contrast; (B) Dominant; (C) Recessive; (D) Homozygous; and (E) Heterozygous. Each square represents a study and the area of each square is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. OR: odds ratio; CI: confidence interval.

**Table 3.** Subgroup analyses for *HMGB1* rs1045411 and cancers under different genetic models

| Genetic models | N | OR [95% CI] | *P* (OR) | Model (method) | *I*-square (%) | *P* (H) | *P* (Begg) | *P* (Egger) |
|---|---|---|---|---|---|---|---|---|
| Allele contrast | | | | | | | | |
| Overall | 8 | 1.079 [0.874-1.333] | 0.477 | R (D-L) | 81.4 | < 0.001 | 1.000 | 0.651 |
| Chinese | 7 | 1.053 [0.842-1.318] | 0.650 | R (D-L) | 83.5 | < 0.001 | - | - |
| LDR-PCR | 2 | 1.468 [1.076-2.003] | 0.015 | R (D-L) | 70.7 | 0.065 | - | - |
| TaqMan | 5 | 0.962 [0.770-1.202] | 0.735 | R (D-L) | 68.9 | 0.012 | - | - |
| HB | 7 | 1.108 [0.858-1.430] | 0.434 | R (D-L) | 82.2 | < 0.001 | - | - |
| HWE > 0.05 | 7 | 1.102 [0.866-1.402] | 0.431 | R (D-L) | 83.7 | < 0.001 | - | - |
| Dominant model | | | | | | | | |
| Overall | 8 | 1.046 [0.826-1.325] | 0.710 | R (D-L) | 79.2 | < 0.001 | 0.902 | 0.676 |
| Chinese | 7 | 1.002 [0.785-1.280] | 0.985 | R (D-L) | 80.5 | < 0.001 | - | - |
| LDR-PCR | 2 | 1.420 [1.062-1.898] | 0.018 | R (D-L) | 57.2 | 0.126 | - | - |
| TaqMan | 5 | 0.948 [0.715-1.259] | 0.714 | R (D-L) | 72.5 | 0.006 | - | - |
| HB | 7 | 1.076 [0.807-1.435] | 0.618 | R (D-L) | 80.6 | < 0.001 | - | - |
| HWE > 0.05 | 7 | 1.081 [0.828-1.410] | 0.567 | R (D-L) | 81.3 | < 0.001 | - | - |
| Recessive model | | | | | | | | |
| Overall | 8 | 1.429 [0.941-2.171] | 0.094 | R (D-L) | 58.2 | 0.019 | 0.386 | 0.328 |
| Chinese | 7 | 1.494 [0.949-2.352] | 0.083 | R (D-L) | 63.5 | 0.012 | - | - |
| LDR-PCR | 2 | 3.605 [1.930-6.732] | < 0.001 | R (D-L) | 0.0 | 0.445 | - | - |
| TaqMan | 5 | 1.001 [0.764-1.311] | 0.996 | R (D-L) | 0.0 | 0.736 | - | - |
| HB | 7 | 1.568 [0.958-2.566] | 0.073 | R (D-L) | 53.9 | 0.043 | - | - |
| HWE > 0.05 | 7 | 1.413 [0.869-2.296] | 0.163 | R (D-L) | 63.2 | 0.012 | - | - |
| Homozygous model | | | | | | | | |
| Overall | 8 | 1.432 [0.900-2.278] | 0.130 | R (D-L) | 65.4 | 0.005 | 0.386 | 0.305 |
| Chinese | 7 | 1.471 [0.886-2.443] | 0.136 | R (D-L) | 70.3 | 0.003 | - | - |
| LDR-PCR | 2 | 3.895 [2.081-7.292] | < 0.001 | R (D-L) | 0.0 | 0.392 | - | - |
| TaqMan | 5 | 0.964 [0.732-1.270] | 0.796 | R (D-L) | 0.0 | 0.521 | - | - |
| HB | 7 | 1.574 [0.908-2.729] | 0.106 | R (D-L) | 62.4 | 0.014 | - | - |
| HWE > 0.05 | 7 | 1.111 [0.320-3.857] | 0.190 | R (D-L) | 70.1 | 0.003 | - | - |
| Heterozygous model | | | | | | | | |
| Overall | 8 | 1.005 [0.808-1.250] | 0.967 | R (D-L) | 73.3 | < 0.001 | 1.000 | 0.633 |
| Chinese | 7 | 0.959 [0.772-1.192] | 0.707 | R (D-L) | 73.2 | 0.001 | - | - |
| LDR-PCR | 2 | 1.298 [1.048-1.607] | 0.017 | R (D-L) | 15.8 | 0.276 | - | - |
| TaqMan | 5 | 0.940 [0.706-1.251] | 0.672 | R (D-L) | 70.6 | 0.009 | - | - |
| HB | 7 | 1.031 [0.789-1.347] | 0.825 | R (D-L) | 75.8 | < 0.001 | - | - |
| HWE > 0.05 | 7 | 1.043 [0.819-1.328] | 0.735 | R (D-L) | 75.3 | < 0.001 | - | - |

OR: odds ratio. CI: confidence intervals. N: number of included studies. R: random-effects model. D-L: DerSimonian-Laird method. *P* (H): *P*-value for heterogeneity. HB: hospital-based. LDR-PCR: ligase detection reaction-polymerase chain reaction. HWE: Hardy-Weinberg equilibrium.

*Publication bias*

Begg's and Egger's tests were performed to quantitatively evaluate publication bias of included studies (**Figure 6**). No asymmetry was found in the funnel plots for any of the polymorphisms. In addition, results of Egger's tests did not suggest any evidence of publications bias. *P*-values from the two tests are listed in **Table 2**.

## Discussion

In the present meta-analysis, involving 3,062 cases and 4,217 controls, the association between four *HMGB1* polymorphisms and cancer risks was evaluated. Pooled risk estimates indicated that no significant association was identified for polymorphisms *rs1045411*, *rs2249825*, *rs1412125*, or *rs1360485* and overall cancer susceptibility, according to com-

**Table 4.** Subgroup analyses for *HMGB1 rs2249825* and cancers under different genetic models

| Genetic models | N | OR [95% CI] | *P* (OR) | Model (method) | *I*-square (%) | *P* (H) | *P* (Begg) | *P* (Egger) |
|---|---|---|---|---|---|---|---|---|
| Allele contrast | | | | | | | | |
| Overall | 8 | 1.066 [0.826-1.375] | 0.622 | R (D-L) | 84.0 | < 0.001 | 0.711 | 0.940 |
| Chinese | 7 | 1.097 [0.835-1.442] | 0.505 | R (D-L) | 86.0 | < 0.001 | - | - |
| LDR-PCR | 2 | 0.871 [0.558-1.361] | 0.545 | R (D-L) | 80.3 | 0.024 | - | - |
| TaqMan | 5 | 1.003 [0.804-1.253] | 0.976 | R (D-L) | 59.9 | 0.041 | - | - |
| HB | 7 | 1.103 [0.824-1.478] | 0.511 | R (D-L) | 83.5 | < 0.001 | - | - |
| HWE > 0.05 | 7 | 0.965 [0.809-1.151] | 0.692 | R (D-L) | 60.4 | 0.019 | - | - |
| Dominant model | | | | | | | | |
| Overall | 8 | 1.105 [0.824-1.482] | 0.503 | R (D-L) | 84.5 | < 0.001 | 0.902 | 0.673 |
| Chinese | 7 | 1.126 [0.820-1.546] | 0.463 | R (D-L) | 86.6 | < 0.001 | - | - |
| LDR-PCR | 2 | 0.853 [0.558-1.305] | 0.465 | R (D-L) | 74.4 | 0.048 | - | - |
| TaqMan | 5 | 1.029 [0.812-1.304] | 0.813 | R (D-L) | 55.1 | 0.064 | - | - |
| HB | 7 | 1.153 [0.821-1.621] | 0.411 | R (D-L) | 84.2 | < 0.001 | - | - |
| HWE > 0.05 | 7 | 0.971 [0.806-1.171] | 0.759 | R (D-L) | 55.0 | 0.038 | - | - |
| Recessive model | | | | | | | | |
| Overall | 8 | 1.070 [0.783-1.460] | 0.672 | F (M-H) | 18.9 | 0.281 | 0.386 | 0.248 |
| Chinese | 7 | 1.144 [0.829-1.578] | 0.412 | F (M-H) | 3.1 | 0.402 | - | - |
| LDR-PCR | 2 | 1.272 [0.690-2.344] | 0.441 | F (M-H) | 35.1 | 0.215 | - | - |
| TaqMan | 5 | 0.835 [0.544-1.283] | 0.411 | F (M-H) | 0.0 | 0.418 | - | - |
| HB | 7 | 1.211 [0.840-1.745] | 0.306 | F (M-H) | 12.9 | 0.331 | - | - |
| HWE > 0.05 | 7 | 0.958 [0.677-1.357] | 0.811 | F (M-H) | 10.0 | 0.353 | - | - |
| Homozygous model | | | | | | | | |
| Overall | 8 | 1.122 [0.821-1.534] | 0.471 | F (M-H) | 41.2 | 0.104 | 0.711 | 0.318 |
| Chinese | 7 | 1.201 [0.870-1.660] | 0.266 | F (M-H) | 35.8 | 0.155 | - | - |
| LDR-PCR | 2 | 1.263 [0.682-2.338] | 0.457 | F (M-H) | 39.3 | 0.199 | - | - |
| TaqMan | 5 | 0.837 [0.544-1.287] | 0.417 | F (M-H) | 12.4 | 0.335 | - | - |
| HB | 7 | 1.316 [0.911-1.903] | 0.144 | F (M-H) | 33.9 | 0.170 | - | - |
| HWE > 0.05 | 7 | 0.957 [0.674-1.357] | 0.804 | F (M-H) | 18.6 | 0.288 | - | - |
| Heterozygous model | | | | | | | | |
| Overall | 8 | 1.123 [0.841-1.499] | 0.433 | R (D-L) | 82.9 | < 0.001 | 0.711 | 0.538 |
| Chinese | 7 | 1.127 [0.824-1.540] | 0.455 | R (D-L) | 85.4 | < 0.001 | - | - |
| LDR-PCR | 2 | 0.847 [0.586-1.224] | 0.376 | R (D-L) | 64.6 | 0.093 | - | - |
| TaqMan | 5 | 1.045 [0.838-1.303] | 0.693 | R (D-L) | 45.5 | 0.119 | - | - |
| HB | 7 | 1.174 [0.837-1.647] | 0.352 | R (D-L) | 82.9 | < 0.001 | - | - |
| HWE > 0.05 | 7 | 0.977 [0.820-1.164] | 0.793 | R (D-L) | 46.3 | 0.083 | - | - |

OR: odds ratio. CI: confidence intervals. N: number of included studies. R: random-effects model. D-L: DerSimonian-Laird method. *P* (H): *P*-value for heterogeneity. HB: hospital-based. LDR-PCR: ligase detection reaction-polymerase chain reaction. HWE: Hardy-Weinberg equilibrium.

parisons using all five genetic models. Results of subgroup analysis indicated that *rs1045411* was significantly associated with cancer susceptibility under all genetic models in LDR-PCR studies. In addition, *rs1412125* was significantly associated with cancer risk under allele contrast, dominant, and heterozygous models in hospital-based studies. These findings are consistent with most included studies summarized in the present analysis.

*HMGB1* polymorphisms have been the subject of intense investigations in many cancer susceptibility studies. Polymorphism *rs1045411* is located in the 3'-untranslated region (3'-UTR) of *HMGB1*, consistent with a function in mRNA

**Table 5.** Subgroup analyses for *HMGB1 rs1412125* and cancers under different genetic models

| Genetic models | N | OR [95% CI] | *P* (OR) | Model (method) | *I*-square (%) | *P* (H) | *P* (Begg) | *P* (Egger) |
|---|---|---|---|---|---|---|---|---|
| Allele contrast | | | | | | | | |
| Overall | 7 | 1.070 [0.989-1.157] | 0.093 | F (M-H) | 46.2 | 0.084 | 0.368 | 0.167 |
| LDR-PCR | 2 | 1.129 [0.985-1.294] | 0.082 | F (M-H) | 0.0 | 0.804 | - | - |
| TaqMan | 4 | 1.024 [0.923-1.137] | 0.655 | F (M-H) | 68.5 | 0.023 | - | - |
| HB | 6 | 1.133 [1.032-1.244] | 0.009 | F (M-H) | 20.3 | 0.281 | - | - |
| HWE > 0.05 | 6 | 1.062 [0.977-1.153] | 0.157 | F (M-H) | 53.8 | 0.055 | - | - |
| Dominant model | | | | | | | | |
| Overall | 7 | 1.118 [0.961-1.301] | 0.148 | R (D-L) | 53.5 | 0.044 | 0.368 | 0.132 |
| LDR-PCR | 2 | 1.161 [0.979-1.378] | 0.087 | R (D-L) | 0.0 | 0.784 | - | - |
| TaqMan | 4 | 1.106 [0.835-1.465] | 0.481 | R (D-L) | 73.5 | 0.010 | - | - |
| HB | 6 | 1.176 [1.019-1.358] | 0.027 | R (D-L) | 30.6 | 0.206 | - | - |
| HWE > 0.05 | 6 | 1.116 [0.937-1.328] | 0.218 | R (D-L) | 60.6 | 0.027 | - | - |
| Recessive model | | | | | | | | |
| Overall | 7 | 1.107 [0.911-1.344] | 0.307 | F (M-H) | 0.0 | 0.910 | 0.230 | 0.185 |
| LDR-PCR | 2 | 1.166 [0.836-1.626] | 0.366 | F (M-H) | 0.0 | 0.903 | - | - |
| TaqMan | 4 | 1.044 [0.812-1.342] | 0.739 | F (M-H) | 0.0 | 0.740 | - | - |
| HB | 6 | 1.169 [0.922-1.483] | 0.198 | F (M-H) | 0.0 | 0.916 | - | - |
| HWE > 0.05 | 6 | 1.087 [0.889-1.327] | 0.416 | F (M-H) | 0.0 | 0.909 | - | - |
| Homozygous model | | | | | | | | |
| Overall | 7 | 1.137 [0.932-1.387] | 0.206 | F (M-H) | 0.0 | 0.596 | 0.230 | 0.160 |
| LDR-PCR | 2 | 1.233 [0.876-1.735] | 0.230 | F (M-H) | 0.0 | 0.863 | - | - |
| TaqMan | 4 | 1.052 [0.813-1.360] | 0.701 | F (M-H) | 12.0 | 0.333 | - | - |
| HB | 6 | 1.247 [0.977-1.592] | 0.076 | F (M-H) | 0.0 | 0.713 | - | - |
| HWE > 0.05 | 6 | 1.114 [0.908-1.368] | 0.302 | F (M-H) | 0.0 | 0.557 | - | - |
| Heterozygous model | | | | | | | | |
| Overall | 7 | 1.074 [0.968-1.190] | 0.177 | F (M-H) | 47.9 | 0.074 | 0.548 | 0.130 |
| LDR-PCR | 2 | 1.148 [0.960-1.373] | 0.130 | F (M-H) | 0.0 | 0.779 | - | - |
| TaqMan | 4 | 1.022 [0.891-1.172] | 0.758 | F (M-H) | 70.8 | 0.016 | - | - |
| HB | 6 | 1.159 [1.026-1.310] | 0.018 | F (M-H) | 20.6 | 0.278 | - | - |
| HWE > 0.05 | 6 | 1.067 [0.957-1.190] | 0.244 | F (M-H) | 56.1 | 0.044 | - | - |

OR: odds ratio. CI: confidence intervals. N: number of included studies. R: random-effects model. D-L: DerSimonian-Laird method. *P* (H): *P*-value for heterogeneity. HB: hospital-based. LDR-PCR: ligase detection reaction-polymerase chain reaction. HWE: Hardy-Weinberg equilibrium.

stability and regulation of gene expression at the posttranscriptional level [19]. Moreover, *rs1045411* has been identified as an miRNA-505 binding site [12]. Previous studies have demonstrated that miRNA-505 acts as tumor suppressor in cancers, [20, 21] and that it suppresses proliferation and invasion in hepatoma cells by directly targeting HMGB1 [22]. Wu et al. conducted *in silico* analysis, confirming that the minor allele of polymorphism *rs2249825* creates a putative binding site for v-Myb [17]. This potential v-Myb binding site might function as a powerful enhancer, causing increased expression of *HMGB1* [23]. Polymorphism *rs1412125* is located-1615 base pairs upstream of the *HMGB1* transcription start site. It may also have a role in promoting *HMGB1* expression through interference with the binding of the human Cut homeodomain repressor protein [24]. Mutant allele C may impair binding and repression induced by the Cut protein, thereby contributing to overexpression of *HMGB1*. Overexpression of *HMGB1* has been observed in various human carcinomas [25-27]. However, pooled risk estimates indicated no significant association for the above polymorphisms and overall cancer susceptibility in the present study.

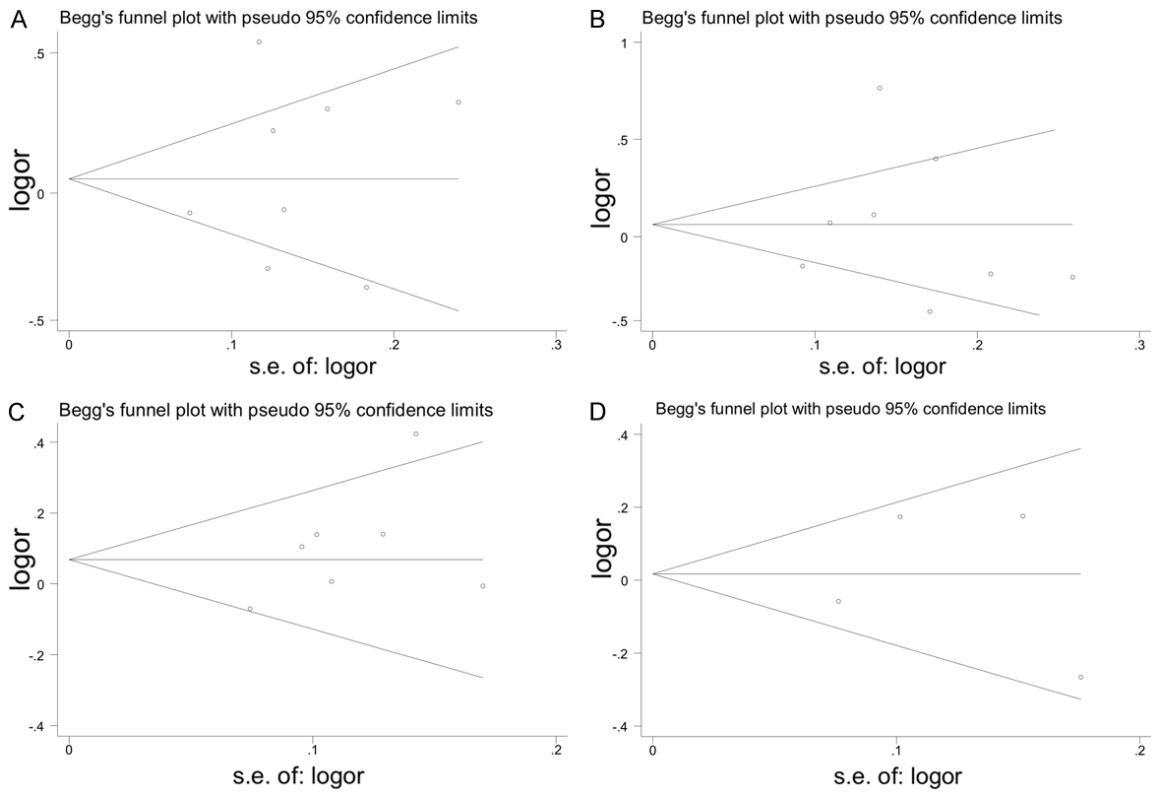



**Figure 6.** Begg's funnel plots to assess publication bias in eligible studies under the allele contrast model. Begg's funnel plots representing publication bias analysis of polymorphisms (A) rs1045411, (B) rs2249825, (C) rs1412125, and (D) rs1360485. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR): log-transformed OR; OR: odds ratio.

The current meta-analysis had several advantages. First, this study pooled the available data from eligible studies, significantly increasing the statistical power, compared to any single study. Second, all eligible studies included in this meta-analysis were high-quality studies and met inclusion criterion. Third, no publication bias was detected. Sensitivity analysis indicated that current results are statistically stable and robust. However, there were several limitations to the current study. First, statistically significant heterogeneity was confirmed within all genotype models. Stratified analysis was, therefore, performed to explore the source of heterogeneity. Between-study heterogeneity was not dramatically reduced after subgroup analysis was performed based on ethnicity, genotyping method, source of controls, and Hardy-Weinberg equilibrium in controls. Therefore, between-study heterogeneity might be mainly attributed to various cancer types. Second, current analysis was limited to Chinese or Caucasian ethnicities. Therefore, it is uncertain whether present results can be generalized to other populations.

In summary, polymorphisms *rs1045411*, *rs2249825*, *rs1412125*, and *rs1360485* are not associated with overall cancer susceptibility, according to comparisons using all five genetic models. Moreover, larger population-based case-control studies, as well as well-designed mechanistic studies, are warranted to validate current findings.

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## Disclosure of conflict of interest

None.

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## References


[1] Kang R, Zhang Q, Zeh HJ 3rd, Lotze MT and Tang D. HMGB1 in cancer: good, bad, or both? Clin Cancer Res 2013; 19: 4046-57.

[2] Martinotti S, Patrone M and Ranzato E. Emerging roles for HMGB1 protein in immunity, inflammation, and cancer. Immunotargets Ther 2015; 4: 101-9.

[3] Sims GP, Rowe DC, Rietdijk ST, Herbst R and Coyle AJ. HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol 2010; 28: 367-388.

[4] Wang X, Xiang L, Li H, Chen P, Feng Y, Zhang J, Yang N, Li F, Wang Y, Zhang Q, Li F and Cao F. The role of HMGB1 signaling pathway in the development and progression of hepatocellular carcinoma: a review. Int J Mol Sci 2015; 16: 22527-40.

[5] Tang D, Kang R, Zeh HJ 3rd, Lotze MT. High-mobility group box 1 and cancer. Biochim Biophys Acta 2010; 1799: 131-40.

[6] Chen RC, Yi PP, Zhou RR, Xiao MF, Huang ZB, Tang DL, Huang Y and Fan XG. The role of HMGB1-RAGE axis in migration and invasion of hepatocellular carcinoma cell lines. Mol Cell Biochem 2014; 390: 271-80.

[7] Liu K, Huang J, Xie M, Yu Y, Zhu S, Kang R, Cao L, Tang D and Duan X. MIR34A regulates autophagy and apoptosis by targeting HMGB1 in the retinoblastoma cell. Autophagy 2014; 10: 442-52.

[8] Zhan Z, Li Q, Wu P, Ye Y, Tseng HY, Zhang L and Zhang XD. Autophagy-mediated HMGB1 release antagonizes apoptosis of gastric cancer cells induced by vincristine via transcriptional regulation of Mcl-1. Autophagy 2012; 8: 109-21.

[9] Tang D, Kang R, Livesey KM, Cheh CW, Farkas A, Loughran P, Hoppe G, Bianchi ME, Tracey KJ, Zeh HJ 3rd and Lotze MT. Endogenous HMGB1 regulates autophagy. J Cell Biol 2010; 190: 881-92.

[10] Sun X and Tang D. HMGB1-dependent and-independent autophagy. Autophagy 2014; 10: 1873-6.

[11] Hu W, Liu PY, Yang YC, Chen PC, Su CM, Chao CC and Tang CH. Association of HMGB1 gene polymorphisms with lung cancer susceptibility and clinical aspects. Int J Med Sci 2017; 14: 1197-1202.

[12] Lin CW, Chou YE, Yeh CM, Yang SF, Chuang CY and Liu YF. A functional variant at the miRNA binding site in HMGB1 gene is associated with risk of oral squamous cell carcinoma. Oncotarget 2017; 8: 34630-34642.

[13] Supic G, Kozomara R, Zeljic K, Stanimirovic D, Magic M, Surbatovic M, Jovic N and Magic Z. HMGB1 genetic polymorphisms in oral squamous cell carcinoma and oral lichen planus patients. Oral Dis 2015; 21: 536-543.

[14] Wang B, Yeh CB, Lein MY, Su CM, Yang SF, Liu YF and Tang CH. Effects of HMGB1 polymorphisms on the susceptibility and progression of hepatocellular carcinoma. Int J Med Sci 2016; 13: 304-309.

[15] Wang D, Qi X, Liu F, Yang C, Jiang W, Wei X, Li X, Mi J and Tian G. A multicenter matched case-control analysis on seven polymorphisms from HMGB1 and RAGE genes in predicting hepatocellular carcinoma risk. Oncotarget 2017; 8: 50109-50116.

[16] Wang JX, Yu HL, Bei SS, Cui ZH, Li ZW, Liu ZJ and Lv YF. Association of HMGB1 gene polymorphisms with risk of colorectal cancer in a Chinese population. Med Sci Monit 2016; 22: 3419-3425.

[17] Wu HH, Liu YF, Yang SF, Lin WL, Chen SC, Han CP, Wang HL, Lin LY and Wang PH. Association of single-nucleotide polymorphisms of high-mobility group box 1 with susceptibility and clinicopathological characteristics of uterine cervical neoplasia in Taiwanese women. Tumour Biol 2016; [Epub ahead of print].

[18] Yue L, Zhang Q, He L, Zhang M, Dong J, Zhao D, Ma H, Pan H and Zheng L. Genetic predisposition of six well-defined polymorphisms in HMGB1/RAGE pathway to breast cancer in a large Han Chinese population. J Cell Mol Med 2016; 20: 1966-1973.

[19] Lee K, Chang Y, Song K, Park YY, Huh JW, Hong SB, Lim CM and Koh Y. Associations between single nucleotide polymorphisms of high mobility group box 1 protein and clinical outcomes in korean sepsis patients. Yonsei Med J 2016; 57: 111-117.

[20] Chen Y, Bian L and Zhang Y. MiR-505 mediates methotrexate resistance in colorectal cancer by targeting RASSF8. J Pharm Pharmacol 2018; 70: 937-951.

[21] Ma C, Xu B, Husaiyin S, Wang L, Wusainahong K, Ma J, Zhu K and Niyazi M. MicroRNA-505 predicts prognosis and acts as tumor inhibitor in cervical carcinoma with inverse association with FZD4. Biomed Pharmacother 2017; 92: 586-594.

[22] Lu L, Qiu C, Li D, Bai G, Liang J and Yang Q. MicroRNA-505 suppresses proliferation and invasion in hepatoma cells by directly targeting high-mobility group box 1. Life Sci 2016; 157: 12-18.

[23] Chayka O, Kintscher J, Braas D and Klempnauer KH. v-Myb mediates cooperation of a cell-specific enhancer with the mim-1 promoter. Mol Cell Biol 2005; 25: 499-511.

[24] Mailly F, Berube G, Harada R, Mao PL, Phillips S and Nepveu A. The human cut homeodomain protein can repress gene expression by two distinct mechanisms: active repression and competition for binding site occupancy. Mol Cell Biol 1996; 16: 5346-5357.

[25] Liu Y, Xie C, Zhang X, Huang D, Zhou X, Tan P, Qi L, Hu G, Tian Y and Qiu Y. Elevated expression of HMGB1 in squamous-cell carcinoma of the head and neck and its clinical significance. Eur J Cancer 2010; 46: 3007-3015.

[26] Ueda M, Takahashi Y, Shinden Y, Sakimura S, Hirata H, Uchi R, Takano Y, Kurashige J, Iguchi T, Eguchi H, Sugimachi K, Yamamoto H, Doki Y, Mori M and Mimori K. Prognostic significance of high mobility group box 1 (HMGB1) expression in patients with colorectal cancer. Anticancer Res 2014; 34: 5357-5362.

[27] Yang GL, Zhang LH, Bo JJ, Huo XJ, Chen HG, Cao M, Liu DM and Huang YR. Increased expression of HMGB1 is associated with poor prognosis in human bladder cancer. J Surg Oncol 2012; 106: 57-61.