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*Original Article*

# Association between genetic polymorphisms of antioxidant enzyme genes and susceptibility to hepatocellular carcinoma: a meta-analysis

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**Abstract:** This study was to analysis the correlation between genetic polymorphisms in antioxidant enzyme genes and the susceptibility factors to hepatocellular carcinoma (HCC) using meta analysis. Electronic searches were conducted in Pubmed, Embase and Cochrane library. Retrieval keywords included antioxidant enzyme, superoxide dismutases, catalase, glutathione peroxidase, and hepatocellular carcinoma. Retrieval strategy was: ((antioxidant enzyme) OR (superoxide dismutases) OR catalase OR (glutathione peroxidase)) AND (hepatocellular carcinoma) OR HCC) AND polymorphism (OR gene OR based OR Allele * OR Genotyp * OR susceptibility). Selection criteria, data extraction and quality evaluation, and statistical analysis of articles were performed. For MnSOD, there were 2351 cases, including 1048 patients and 1303 control. For CAT, there were 2166 cases, including 987 patients and 1179 control. For GPX1, there were 1437 cases, including 614 patients and 823 control. The recessive model (Ala/Ala *vs*. Val/Val/Val + Ala) of MnSOD was associated with the risk of HCC (OR = 1.49, [95% CI: 1.04, 2.15]) (P = 0.03). MnSOD (allele model [Ala vs. Val], codominant model [Ala/Ala vs. Val/Val], codominant model [Val/Ala vs. Val/Val], and dominant model [Ala/Ala + Val/Ala vs. Val/Val]), CAT (262 C > T) (allele model [T vs. C], codominant model [TT vs. CC], codominant model [CT vs. CC], dominant model [TT + CT vs. CC], and recessive model [TT vs. CT + CT]), and GPX1 (Pro198Leu) (allele model [Leu vs. Pro], codominant model [Leu/Leu vs. Pro/Pro], codominant model [Leu/Pro vs. Pro/Pro], dominant model [Leu/Leu + Leu/Pro vs. Pro/Pro] and recessive model [Leu/Leu vs. Pro/Pro + Leu/Pro]) were no significant correlation with the incidence of HCC (P > 0.05). The implicit model (Ala/Ala *vs*. Val/Val/Val + Ala) of MnSOD was significantly correlated with the incidence of HCC. However, CAT (262 C > T) and GPX1 (Pro198Leu) were no significant correlation with the incidence of HCC.

**Keywords:** Meta-analysis, genetic polymorphisms, hepatocellular carcinoma

## Introduction

Hepatic carcinoma (HCC) is one of the most common malignant tumor in the world [1]. Hepatocarcinogenesis is a long-term multistage process with the involvement of both environmental factors and susceptibility genes [2]. Genetic polymorphisms of genes may be associated with the development of HCC [3, 4]. Identification of susceptibility genes will help to reveal the pathogenesis of HCC, predict the risk factors of HCC and make basis of the theoretical for individualizing health care.

HCC is a complex tumor with multiple genetic alterations, and hepatitis C virus (HCV) infection is one of the major etiological factors [5]. HCV could induce hepatic oxidative stress, which plays a critical role in the development of HCC [6], with increased oxidative DNA damage, lipid peroxidation, and decreased activity of cellular antioxidant systems [5]. Oxidative stress could cause the imbalance of antioxidant defense system or the production of excessive reactive oxygen species (ROS) [7]. Superoxide dismutases (SOD), catalase (CAT), glutathione peroxidase (GPX) were the main antioxidant enzyme genes, of which the genetic variation could influence and may finally lead to genotype-dependent differences in risk of HCC [8]. So far, there are some research analyzes the relationships between the gene polymorphism

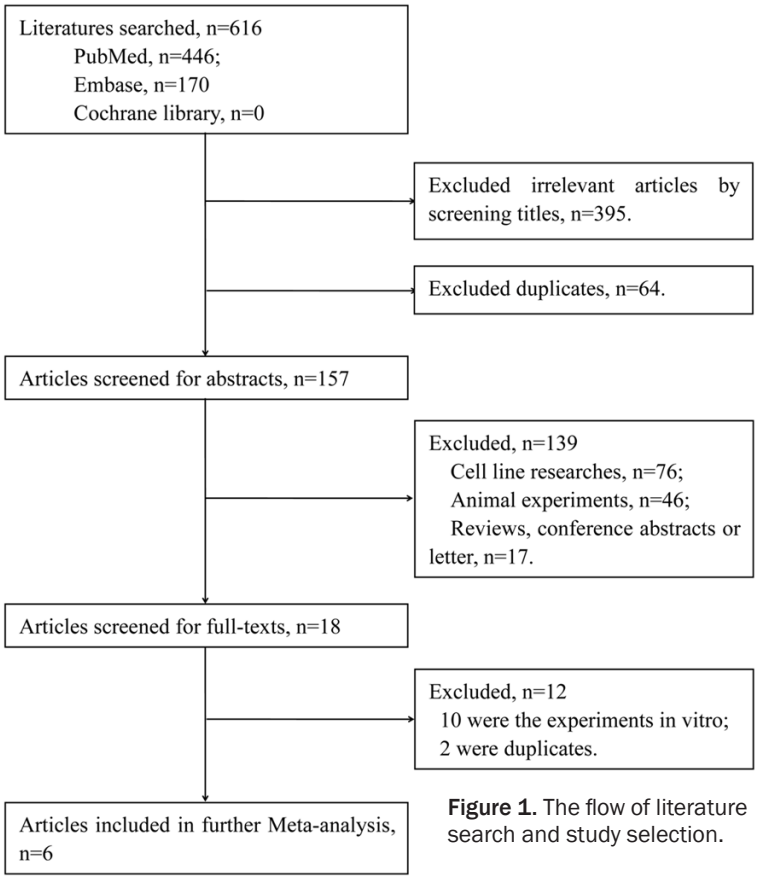


**Figure 1.** The flow of literature search and study selection.

of antioxidant enzymes and the susceptibility of HCC. In this study, a meta-analysis was performed by integration of previous studies to evaluate the association between the gene polymorphism of antioxidant enzyme and HCC occurrence.

## Methods

*Searching strategy*

Searches were conducted in Pubmed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://www.embase.com) and Cochrane library, which were three English electronic literature databases. Meanwhile, related case-control studies were found by the methods of literature back. Retrieval keywords included antioxidant enzyme, superoxide dismutases, catalase, glutathione peroxidase, and hepatocellular carcinoma. Retrieval strategy was: ((antioxidant enzyme) OR (superoxide dismutases) OR catalase OR (glutathione peroxidase)) AND (hepatocellular carcinoma) OR HCC) AND polymorphism (OR gene OR based OR Allele * OR Genotyp * OR susceptibility). The deadline was January 21, 2016.

*Selection criteria*

Literature were selected based on the following criteria: (1) case-control study, in which the case group included patients with HCC and the control group was healthy people or hospital-based breast cancer patients; (2) published English literature associated with the antioxidant enzyme gene (superoxide dismutases, catalase and glutathione peroxidase) gene polymorphisms and hepatocellular carcinoma were included; (3) the studies that provide or calculate genotype and allele number of the case group and the control group were included; (4) reviews, reports, comments, and letters were eliminated.

*Data extraction and quality evaluation*

The data were extracted, including authors, the year of publication, countries, the gene detection method, the genotype distribution in the case group and the control group and the number of the sample. Literature quality was evaluated according to the NOS (Newcastle-Ottawa Scale), which was considered as a evaluation criteria of case-control study and recommended by Agency for Healthcare Research and Quality (AHRQ) [9]. The content of evaluation (a total of 9 points) included the object selection (a total of 4 points), the comparable evaluation (a total of 2 points), and the exposure assessment (a total of 3 points).

*Statistical analysis*

Hardy weinberg equilibrium (HEW) test was performed according to the previous reports [10]. In the progress of sensitivity analysis, literature that were not meet HEW test ($P < 0.05$) were included or excluded. If the OR reversed, the literature were removed [11]. Meta analysis

**Table 1.** Quality assessment of articles

| First author | Representativeness of the cases | case definition adequate | Ascertainment of exposure | Same method of ascertainment for cases and controls | Control for important factor or additional factor | Selection of Controls | Definition of Controls | Non-Response rate | Total quality scores |
|---|---|---|---|---|---|---|---|---|---|
| Ezzikouri 2008 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 8 |
| Ezzikouri 2010 | ☆ | ☆ | ☆ | ☆ | ☆☆ | ☆ | ☆ | ☆ | 9 |
| Lee 2002 | ☆ | ☆ | ? | ☆ | ? | ☆ | ☆ | ? | 5 |
| Liu 2015 | ☆ | ☆ | ? | ☆ | ☆☆ | ☆ | ☆ | ☆ | 8 |
| Nahon 2012 | ☆ | ☆ | ? | ☆ | ☆ | ☆ | ☆ | ? | 6 |
| Su 2015 | ☆ | ☆ | ☆ | ☆ | ☆☆ | ☆ | ☆ | ? | 8 |

Note: 1 A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. 2 A maximum of 2 stars could be awarded for this item. Studies that controlled for cardiovascular disease received one star, whereas studies that controlled for other important confounders such cancer received an additional star. 3 A cohort study with a follow-up rate > 75% was assigned one star.

was performed using RevMan 5.3 recommended by Cochrane collaboration. The relation of gene polymorphisms of antioxidant enzyme gene (SOD, CAT, and GPx) and the hepatocellular carcinoma susceptibility were analyzed in this study. OR value and 95% CI of the case group (HCC patients) and control group (healthy controls/non HCC patients) were calculated. Heterogeneity inspection was analyzed using chi-square Q and $I^2$ statistic [12]. If the heterogeneity tested showed the statistically significant difference ($P < 0.05$ or $I^2 > 50\%$), a random effect model was choose to calculate the combined effect value. Otherwise, a fixed effect model was selected to merge data [13].

## Results

### *Literature filtering*

The results of literature retrieval and the screening process were shown in **Figure 1**. Based on retrieval strategy, 616 articles in Pubmed, Embase, and Cochrane library database were selected. When 64 duplicate papers and 395 completely unrelated studies were rejected, 157 articles were remained. Subsequently, based on abstract, 76 cell studies *in vitro*, 46 animal testing, and 17 review articles were removed. For 18 remaining articles, the full view were performed, of which 10 studies *in vitro*, and 2 repeated references were excluded. Finally, 6 literature were remained, including Ezzikouri *et al.* [14], Ezzikouri *et al.* [15], Lee *et al.* [16], Liu *et al.* [17], Nahon *et al.* [18], and Su *et al.* [19]. Quality assessment of 6 articles were shown in **Table 1**.

### *General characteristics*

In this analysis, there are 1 references about the MnSOD [15], 2 references about CAT (Lee *et al.* [16] and Liu *et al.* [17]), 3 references reporting MnSOD, CAT and GPX1 (Ezzikouri *et al.* [14], Nahon *et al.* [18], and Su *et al.* [19]). For MnSOD, there were 2351 cases, including 1048 patients and 1303 control. For CAT, there were 2166 cases, including 987 patients and 1179 control. For GPX1, there were 1437 cases, including 614 patients and 823 control. General characteristics of cases were shown in **Table 2**.

The 6 included articles were issued from 2002 to 2016 in Morocco, Chesapeake, China and France. The gene polymorphisms were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and sequencing. According to NOS scale, only the quality of Lee *et al.* [16] was relatively low, the rest were between 6-9 points with the high quality. The genotype distribution of MnSOD, CAT, GPX1 were shown in **Table 3**, and the results showed that all included articles obeyed HWE test.

### *MnSOD (Ala16Val) associated with the risk of HCC*

For mutant Allele model (Ala) and wild type (Val) of MnSOD, three were four genetic models used in meta-analysis, including allele genetic model (Ala vs. Val), codominant genetic model (Ala/Ala *vs*. Val/Val, Val/Ala *vs*. Val/Val), dominant genetic model (Ala/Ala + Val/Ala *vs*. Val/Val), and recessive model (Ala/Ala *vs*. Val/Val/Val + Ala).

For heterogeneity inspection, except the recessive model ($P = 0.20$, $I^2 = 37\%$), the rest of the model merged research had significant heterogeneity ($P < 0.01$ or $I^2 > 50\%$). The research were merged using the random effects model and the fixed effects model, respectively. The

**Table 2.** Characteristics of the included articles

| Study | Country | Study period | Disease | Antioxidant enzyme | Detection method | Control source | Group | No. (M/F) | Age, y | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| Ezzikouri 2008 | Moroccan | 2003.01-2006.08 | HCC | MnSOD | PCR-RFLP | People were not previously diagnosed for any type of cancer | HCC | 96 (56/40) | 59.3±14.1 | 8 |
| | | | | | | | Healthy | 222 (126/96) | 56.4±10.1 | |
| Ezzikouri 2010 | Moroccan | 2003.01-2006.08 | HCC | MnSOD, CAT, GPX1 | PCR-RFLP and sequencing | Healthy people | HCC | 96 (56/40) | 59.3±14.1 | 9 |
| | | | | | | | Healthy | 222 (126/96) | 56.4±10.1 | |
| Lee 2002 | Koreans | - | HCC | CAT | PCR-RFLP | Healthy Koreans | Case | 107 | 56 (32-79) | 5 |
| | | | | | | | Control | 108 | 35 (19-56) | |
| Liu 2015 | China | 2014.04-2014.10 | HCC | CAT | PCR-RFLP | Healthy volunteers visiting the same hospital | HCC | 266 (236/30) | 49.38±11.14 | 8 |
| | | | | | | | Control | 248 (135/113) | 46.50±6.94 | |
| Nahon 2012 | France | 1995.01-2004.12 | HCC | SOD, CAT, GPX1 | PCR-RFLP | Non-HCC patients | Case | 205 (108/97) | 58.3±0.9 | 6 |
| | | | | | | | Control | | | |
| Su 2015 | China | - | HCC | MnSOD, CAT, GPX1 | PCR-RFLP | Healthy people | Case | 434 | - | 7 |
| | | | | | | | Control | 480 | - | |

Abbreviations: HCC: hepatocellular carcinoma; MnSOD: manganese superoxide dismutase; CAT: catalase; GPX1: glutathione peroxidase; PCR-RFLP: polymerase chain reaction-restriction fragment-length polymorphism; M: male; F: female; y: year; HWE: The Hardy-Weinberg equilibrium.

**Table 3.** Genotype distributions

| MnSOD (Ala-16Val) | Group | Total | Val | Ala | Val/Val | Val/Ala | Ala/Ala | HWE in control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $\chi^2$ | *P* |
| Ezzikouri 2008 | Case | 96 | 87 | 105 | 21 | 45 | 30 | 0.746 | 0.388 |
| | Control | 222 | 263 | 181 | 81 | 101 | 40 | | |
| Nahon 2012 | Case | 84 | 82 | 86 | 26 | 30 | 28 | 0.668 | 0.414 |
| | Control | 121 | 122 | 120 | 33 | 56 | 32 | | |
| Su 2015 | Case | 434 | 746 | 98 | 334 | 78 | 10 | 2.073 | 0.150 |
| | Control | 479 | 825 | 133 | 359 | 107 | 13 | | |
| Catalase (262 C > T) | | | C | T | CC | CT | TT | | |
| Ezzikouri 2010 | Case | 96 | 166 | 26 | 76 | 14 | 6 | 0.285 | 0.593 |
| | Control | 222 | 391 | 53 | 173 | 45 | 4 | | |
| Lee 2002 | Case | 107 | 144 | 68 | 51 | 42 | 13 | 0.530 | 0.467 |
| | Control | 108 | 146 | 70 | 51 | 44 | 13 | | |
| Liu 2015 | Case | 266 | 505 | 27 | 239 | 27 | 0 | 0.760 | 0.383 |
| | Control | 248 | 470 | 26 | 223 | 24 | 1 | | |
| Nahon 2012 | Case | 84 | 145 | 23 | 62 | 21 | 1 | 0.790 | 0.374 |
| | Control | 121 | 191 | 51 | 77 | 37 | 7 | | |
| Su 2015 | Case | 434 | 764 | 36 | 365 | 34 | 1 | 0.056 | 0.813 |
| | Control | 480 | 911 | 49 | 432 | 47 | 1 | | |
| Glutathione peroxidase (Pro198Leu) | | | Pro | Leu | Pro/Pro | Pro/Leu | Leu/Leu | | |
| Ezzikouri 2010 | Case | 96 | 132 | 60 | 50 | 32 | 14 | 1.491 | 0.222 |
| | Control | 222 | 304 | 140 | 108 | 88 | 26 | | |
| Nahon 2012 | Case | 84 | 44 | 124 | 5 | 34 | 45 | 0.056 | 0.812 |
| | Control | 121 | 78 | 164 | 12 | 54 | 55 | | |
| Su 2015 | Case | 434 | 761 | 19 | 371 | 19 | 0 | 0.401 | 0.527 |
| | Control | 481 | 935 | 27 | 454 | 27 | 0 | | |

results implied that allele model (Ala *vs*. Val) (OR = 1.24, [95% CI: 0.90, 1.71]), codominance model (Ala/Ala *vs*. Val/Val) (OR = 1.42, [95% CI: 0.67, 3.04]), codominance model (Val/Ala *vs*. Val/Val) (OR = 0.96, [95% CI: 0.57, 1.61]) and dominant model (Ala/Ala + Val/Ala *vs*. Val/Val) (OR = 1.24, [95% CI: 0.81, 1.91]) were not associated with a risk of HCC (P > 0.05, **Figure 2A**, **2D**). However, the recessive model (Ala/Ala *vs*. Val/Val/Val + Ala) was associated with the risk of HCC (OR = 1.49, [95% CI: 1.04, 2.15]) (P = 0.03), suggesting that the mutant Ala/Ala may be a risk factor for HCC (**Figure 2E**).

*CAT (262 C > T) associated with the risk of HCC*

For heterogeneity test, there were no significant difference among all studies (P > 0.05 and $I^2$ < 50%). The merge results showed that the CAT had no significant correlation with the incidence of HCC, including allele model (T *vs*. C) (OR = 0.90, [95% CI: 0.73, 1.12]), codominant model (TT *vs*. CC) (OR = 1.00, [95% CI: 0.54, 1.82]), codominant model (CT *vs*. CC) (OR = 0.86, [95% CI: 0.66, 1.10]), dominant model (TT + CT *vs*. CC) (OR = 0.85, [95% CI: 0.66, 1.08]), and recessive model (TT *vs*. CT + CT) (OR = 1.03, [95% CI: 0.57, 1.85]) (P > 0.05, **Figure 3**).

*GPX1 (Pro198Leu) associated with the risk of HCC*

For heterogeneity test, there were no significant difference among all studies (P > 0.05 and $I^2$ < 50%). GPX1 (Pro198Leu) had no significant correlation with the incidence of HCC, including allele model (Leu *vs*. Pro) (OR = 1.07, [95% CI: 0.83, 1.37]), codominant model (Leu/Leu *vs*. Pro/Pro) (OR = 1.37, [95% CI: 0.75, 2.51]), codominant model (Leu/Pro *vs*. Pro/Pro) (OR = 0.88, [95% CI: 0.61, 1.27]), dominant model (Leu/Leu + Leu/Pro *vs*. Pro/Pro) (OR = 0.90, [95% CI: 0.64, 1.28]), and recessive model

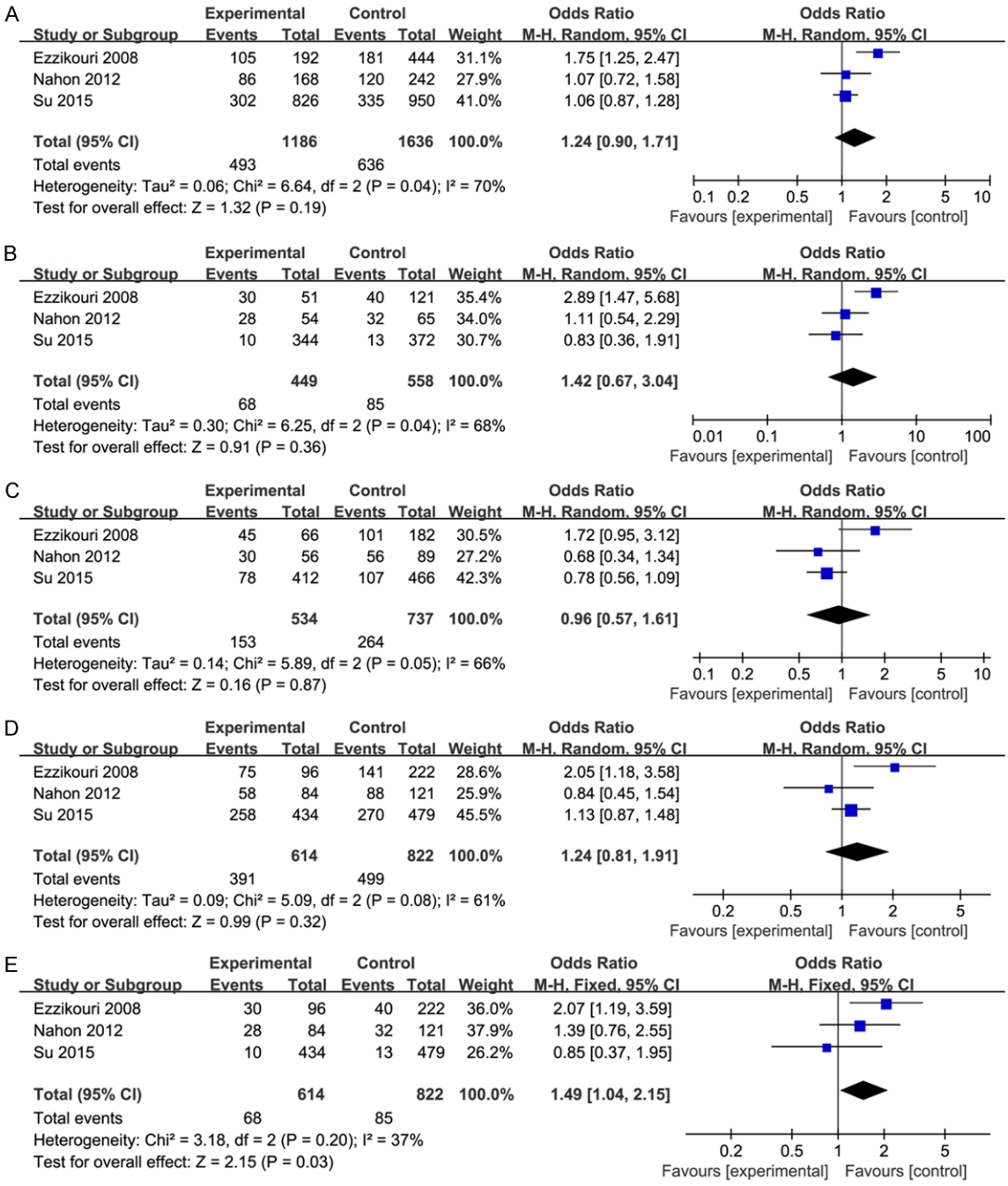


**Figure 2.** The forest plot of MnSOD. A: Allele model: Ala *vs*. Val; B: Codominant model: Ala/Ala *vs*. Val/Val; C: Codominant model: Val/Ala *vs*. Val/Val; D: Dominant model: Ala/Ala + Val/Ala *vs*. Val/Val; E: Recessive model: Ala/Ala *vs*. Val/Val + Val/Ala.3.4 262 C > T.

(Leu/Leu *vs*. Pro/Pro + Leu/Pro) (OR = 1.35, [95% CI: 0.87, 2.08]) (P > 0.05, **Figure 4**).

*Sensitivity analysis*

In the progress of sensitivity analysis, when the research that were not conformed to HWE were eliminated one by one, the combined results were agreed with the original results, demonstrating that the merged result was stable.

## Discussion

HCC was a complex tumor with multiple genetic alterations, and HCV infection was one of the major etiological factors [5]. HCV could induce

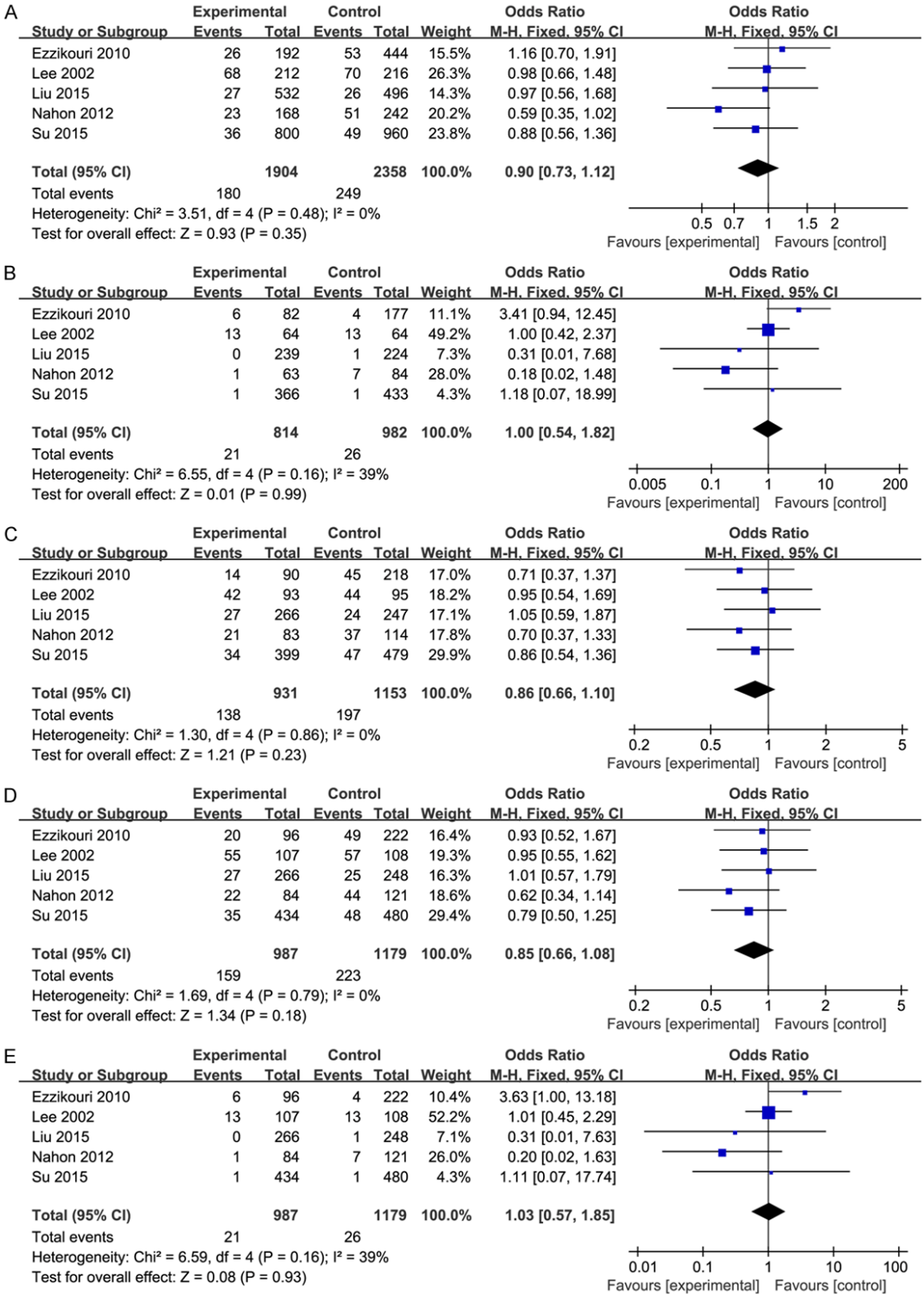


**Figure 3.** The forest plot of CAT. A: Allele model: T *vs*. C; B: Codominant model: TT *vs*. CC; C: Codominant model: CT *vs*. CC; D: Dominant model: TT + CT *vs*. CC; E: Recessive model: TT *vs*. CT + CT.

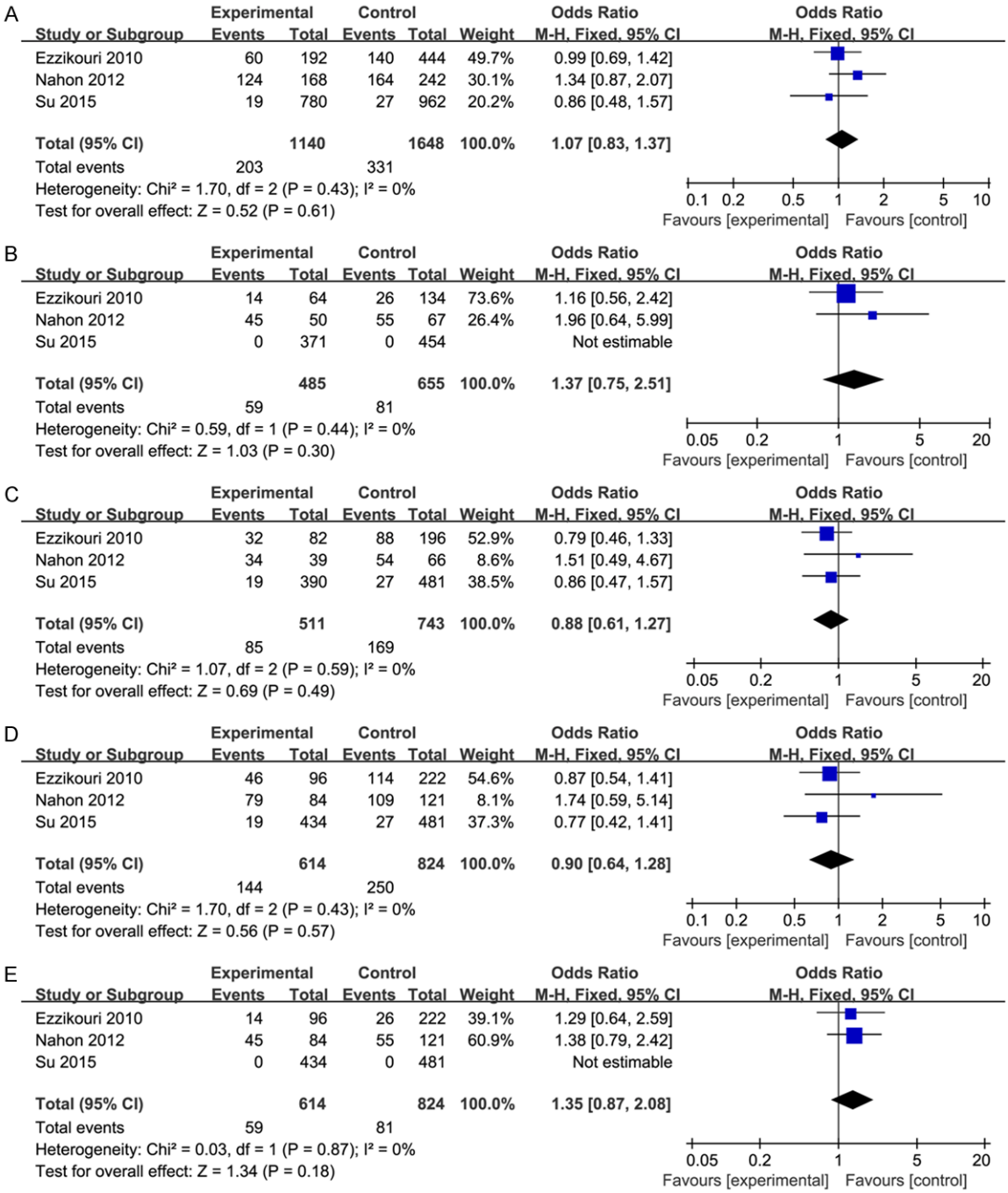


**Figure 4.** The forest plot of GPX1. A: Allele model: Leu *vs*. Pro; B: Codominant model: Leu/Leu *vs*. Pro/Pro; C: Codominant model: Leu/Pro *vs*. Pro/Pro; D: Dominant model: Leu/Leu + Leu/Pro *vs*. Pro/Pro; E: Recessive model: Leu/Leu *vs*. + Pro/Pro Leu/Pro.

hepatic oxidative stress, which plays a critical role in the development of HCC [6]. Oxidative stress could cause the imbalance of antioxidant defense system or the production of excessive ROS [7]. SOD, CAT, GPX were the main antioxidant enzyme genes, of which the genetic variation could influence and may finally lead to genotype-dependent differences in risk of HCC [8]. SOD activity was associated with the progression of HCC carcinogenesis [20]. SOD was considered as a novel tumor suppression gene for HCC [21], and SOD involved in the development of HCC by the Wnt/β-catenin and hypoxia signaling pathway [22].

CAT and GPX also involved in the development of HCC [23]. In this study, the association between antioxidant enzyme gene and HCC was analyzed by meta analysis. Three antioxidant enzyme genes (MnSOD, CAT, and GPX1) and its specific loci were identified through the review of previous works and reviews. Based on the strict selection criteria, 6 high quality case-control study were finally included in this analysis. The results revealed that MnSOD (Ala/Ala vs. Val/Val/Val + Ala) (OR = 1.49, [95% CI: 1.04, 2.15]) (P = 0.03) was significantly associated with the risk of HCC, however, CAT (262 C > T) and GPX1 (Pro198Leu) were no associated with the risk of HCC. Our results were consisted with the previous reports. ROS detoxification may be affected by the structural and/or functional single nucleotide polymorphisms within MnSOD encoding gene, and specifically, MnSOD Ala16Val SNP could alter the enzyme localization and mitochondrial transportation and finally may be correlated to the development of cancer [24]. Mikhak *et al.* Revealed that MnSOD Ala/Ala genotype may be associated with the aggressive prostate cancer risk [25]. Taken together, MnSOD (Ala16Val) may be associated with the HCC risk.

However, there were some limitations in this analysis. The articles included were relative less, so the heterogeneity was little high. The following factors may contribute to the relative high heterogeneity, including national or regional differences, ethnic differences, living habits differences, living environment differences, gender, age, or other factors, etc. Furthermore, the subgroup analysis was not performed due to the relative less studies. Thus, the more case-control studies were needed to support the update of data and to make the higher evidence quality.

## Conclusion

In a word, based on the comprehensive evaluation of meta analysis, the results implied that the implicit model (Ala/Ala *vs*. Val/Val/Val + Ala) of MnSOD was significantly correlated with the incidence of HCC. However, CAT (262 C > T) and GPX1 (Pro198Leu) were no significant correlation with the incidence of HCC.

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## Disclosure of conflict of interest

None.

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