The Role of Catalase C262T Gene Polymorphism in the Susceptibility and Survival of Cancers

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Catalase (CAT), one antioxidant enzyme, may provide resistance against many diseases. Many previous studies reported predictive and prognostic values of CAT C262T polymorphism in cancers, with divergent results. This study aimed to summarize the overall relationships between CAT C262T polymorphism and cancer risk or survival. A total of 27 eligible publications were included in susceptibility analysis, while 8 publications contained survival outcomes. The results revealed significant relationship between CAT C262T polymorphism and cancer risk (TT + CT vs CC: OR = 1.05, 95%CI = 1.00–1.10, P = 0.036), subgroup analyses indicated the CAT C262T polymorphism was significantly correlated with an increased risk for prostate cancer (TT vs CC + CT: OR = 1.43, 95%CI = 1.20–1.70, P < 0.001) and increased risk among Caucasians (TT vs CC + CT: OR = 1.19, 95%CI = 1.09–1.31, P < 0.001), while no associations between the polymorphism and Asian or mixed population were established. In the survival analysis, no interactions were identified between this polymorphism and cancer survival (TT + CT vs CC: HR = 1.37, 95%CI = 0.70–2.70, P = 0.36). In conclusion, the CAT C262T polymorphism may be a candidate marker for cancer risk with type-specific and population-specific effects but not a fine prognostic factor for cancer survival.

The molecular mechanisms of carcinogenesis have not been well understood, but growing studies have reported that oxidative stress played a significant role in the progression of many diseases, including cancers1. Oxidative stress could contribute to imbalance between the reactive oxygen species (ROS) and antioxidant defense system2. When present at high and/or sustained level, ROS may induce severe DNA damage and chromosomal aberrations3–5, which may be followed by abnormal expression of proto-oncogenes and tumor suppressor genes. However, antioxidant defense system could prevent or combat the negative effects caused by ROS, including myeloperoxidase (MPO), glutathione peroxidase (GPX), catalase (CAT), and mitochondrial manganese superoxide dismutase (MnSOD)6–8.

Catalase is an important endogenous antioxidant enzyme that catalyzes hydrogen peroxide into oxygen and water, thus neutralizing the deleterious effects of ROS9. The CAT gene, which is located on chromosome11p13, consists of 12 introns and 13 exons10. There are several single nucleotide polymorphisms (SNPs) identified in the CAT gene, of which the rs1001179 polymorphism (C262T) was the most extensively studied11,12. The CAT C262T polymorphism is encoded on the promoter region, influencing transcriptional and splicing regulation13. In comparison with the variant C allele, the variant T allele of the CAT C262T polymorphism has been reported to indicate lower enzyme activity, thus raising the levels of ROS and might lead to cancer development or progression14. Recently, a series of studies has demonstrated the associations between the CAT C262T polymorphism and risk for multiple cancers, such as breast cancer15, prostate cancer16, hepatocellular carcinoma17, chronic myeloid leukemia18, etc. So far, some studies have indicated the CAT C262T polymorphism could increase prostate cancer risk16,18. However, the final results were not consistent or conclusive. In terms of survival, no studies confirmed whether the CAT C262T polymorphism could be a prognostic factor of cancer patients. Here, we conducted this updated meta-analysis to comprehensively estimate the relationships between the CAT C262T polymorphism and susceptibility or survival of cancers.

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Results

Eligible studies. The initial search yielded 1676 articles through the databases of Pubmed, Embase and China National Knowledge Infrastructure (CNKI). After screening the titles and abstracts, 82 potentially relevant articles were retrieved for the full-text. 49 articles were excluded: 3 were reviews; 9 were conference abstracts; 4 were related to other SNPs of the CAT gene; 11 did not report extractable data; 22 were irrelevant papers. Finally, a total of 33 articles published from 2005 to 2015 met the inclusion criteria and were included in our meta-analysis. There were 27 publications regarding susceptibility analysis, which involved 35 case-control or cohort studies with 15531 cancer patients and 41816 controls, while 8 publications contained the survival data. The search process was presented in Fig. 1 and the clinical characteristics of the studies or other relevant information were listed in Table 1.

C262T polymorphism and susceptibility to cancer. The meta-analysis of the 27 articles with 35 case-control or cohort studies suggested there was a positive correlation between the CAT C262T polymorphism and cancer risk (TT + CT vs CC: OR = 1.05, 95%CI = 1.00–1.10, P = 0.036; TT vs CC: OR = 1.18, 95%CI = 1.08–1.29, P < 0.001; TT vs CC: OR = 1.22, 95%CI = 1.10–1.35, P < 0.001; T vs C: OR = 1.07, 95%CI = 1.03–1.11, P = 0.001 Fig. 2). In the studies which were not derived from the Hardy-Weinberg equilibrium (HWE), the pooled ORs also showed the significance of CAT C262T polymorphism in susceptibility to cancers (TT vs CT + CC: OR = 1.15, 95%CI = 1.02–1.28, P = 0.019; TT vs CC: OR = 1.14, 95%CI = 1.02–1.28, P = 0.026). Furthermore, a subgroup analysis was also performed stratified by cancer types and ethnicity. There was a significant association between CAT C262T polymorphism and the development of prostate cancer (TT vs CT + CC: OR = 1.43, 95%CI = 1.20–1.70, P < 0.001; TT vs CC: OR = 1.52, 95%CI = 1.27–1.81, P < 0.001; CT vs CC: OR = 1.15, 95%CI = 1.05–1.26, P = 0.002; T vs C: OR = 1.21, 95%CI = 1.05–1.40, P = 0.01). The association between the polymorphism of the CAT C262T gene and increased skin cancer risk was also confirmed (CT + TT vs CC: OR = 1.19, 95%CI = 1.00–1.41, P = 0.04; CT vs CC: OR = 1.21, 95%CI = 1.02–1.44, P = 0.03). Meanwhile, the CAT C262T polymorphism retained its high position for predicting the susceptibility to cervical cancer (TT vs CT + CC: OR = 2.85, 95%CI = 1.44–5.65, P = 0.003; TT vs CC: OR = 2.88, 95%CI = 1.41–5.87, P = 0.004; T vs C: OR = 1.96, 95%CI = 1.31–2.93, P = 0.001). However, no evidence of statistical significance could be detected in other cancer types. In terms of subgroup analysis by ethnicity (Caucasian, Asian and Mixed), the assessment of the results revealed that the CAT C262T polymorphism was associated with cancer risk in Caucasians (TT vs CT + CC: OR = 1.19, 95%CI = 1.09–1.31 P < 0.001; TT vs CC: OR = 1.24, 95%CI = 1.12–1.38, P < 0.001; T vs C: OR = 1.08, 95%CI = 1.01–1.16, P = 0.02). No relationship could be found in Asian or mixed population. The pooled results were shown in Table 2.

C262T polymorphism and cancer survival. The meta-analysis included 8 studies investigating CAT C262T polymorphism and cancer survival. No overall survival (OS) difference was detected between patients with CT/TT genotypes and those with CC genotype (HR = 1.37, 95%CI = 0.70–2.70, P = 0.36), or between patients with TT genotype and allele C carrier (HR = 0.90, 95%CI = 0.44–1.83, P = 0.77). Furthermore, when compared to CC genotype, CT or TT genotype didn’t suggest poorer OS (HR = 1.07, 95%CI = 0.95–1.20, P = 0.29; HR = 1.04, 95%CI = 0.81–1.34, P = 0.74, respectively). In addition, cancer patients
with T allele showed similar survival compared to those with C allele (HR = 1.07, 95% CI = 0.97–1.18, P = 0.21).

The main results were summarized in Table 3.

**Publication bias and sensitivity analysis.** We didn't detect any significant publication bias by Begg's test (Pr > |z| = 0.775 Fig. 3a) or Egger's test (P > |t| = 0.548 Fig. 3b), which indicated the reliability of our meta-analysis. Furthermore, no significant change was detected when we sequentially dropped out each included study and thus the results of our study were stable.

### Table 1. Baseline characteristics of eligible studies (N = 33).

*Number of data separately reported by articles. HWE: Hardy-Weinberg equilibrium; MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PB: population-based; HB: hospital-based; NA: not available. CML: Chronic myeloid leukemia; NHL: non-Hodgkin lymphoma; BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; AML: Acute myeloid leukemia.*

| First Author | #* | Year | Country | Ethnicity | Source of Controls | Quality Control | Cancer Type | Case/Control | Genotyping Method | HWE |
|--------------|-----|------|---------|-----------|-------------------|----------------|-------------|--------------|------------------|-----|
| Ahn25        | 2005 | USA  | Caucasian | PB  | Yes  | Breast cancer | 1008/1056 | MALDI-TOF | Yes |
| Ambrosone20   | 2005 | USA  | Mixed    | PB  | NA   | Breast cancer | 279/NA  | MALDI-TOF | NA  |
| Aynek21       | 2013 | Turkey | Caucasian | HB  | NA   | Laryngeal cancer | 25/23  | PCR  | Yes |
| Banescu21     | 2014 | USA  | Mixed    | NA  | NA   | Ovarian cancer | NA    | TaqMan | NA  |
| Belote22      | 2015 | USA  | Caucasian | HB  | Yes  | Glioma     | 362/494 | TaqMan | NA  |
| Bharti23      | 1    | 2009 | USA      | Caucasian | HB  | Yes  | Glioblastoma multiforme | 176/494 | TaqMan | NA  |
| Bharti24      | 2    | 2009 | USA      | Caucasian | HB  | Yes  | Meningsoma | 134/494 | TaqMan | NA  |
| Castaldo25     | 2015 | Portugal | Caucasian | HB  | NA   | Cervical cancer | 120/107 | PCR  | No  |
| Cebrian24      | 2006 | UK   | Caucasian | PB  | Yes  | Breast cancer | 2171/2262 | TaqMan | Yes |
| Cheng25        | 2011 | USA  | Mixed    | NA  | NA   | Prostate cancer | 150/761 | PCR  | NA  |
| Choi27        | 2007 | USA  | Mixed    | PB  | Yes  | Prostate cancer | 508/1403 | MALDI-TOF | Yes |
| Ding28        | 2012 | China | Asian    | PB  | NA   | Prostate cancer | 1417/1008 | HapMap | Yes |
| Ezikouri29     | 2010 | France | Caucasian | HB  | Yes  | Hepatocellular carcinoma | 96/222 | PCR-RFLP | Yes |
| Farawela30     | 2012 | Egypt | Caucasian | PB  | Yes  | NHL         | 100/100 | PCR-RFLP | Yes |
| Funker31       | 2009 | Germany | Caucasian | PB  | Yes  | Colorectal Cancer | 632/605 | Pyrosequencing Technology | Yes |
| Geybels32      | 2014 | Netherlands | Caucasian | PB  | Yes  | Prostate cancer | 1527/25184 | PCR  | No  |
| He33          | 1    | 2010 | USA      | Caucasian | PB  | NA   | BCC         | 270/796 | TaqMan | Yes |
| He34          | 2    | 2010 | USA      | Caucasian | PB  | NA   | Melanoma | 211/796 | TaqMan | Yes |
| He35          | 3    | 2010 | USA      | Caucasian | PB  | NA   | SCC         | 266/796 | TaqMan | Yes |
| Ho36          | 2006 | China | Asian    | HB  | NA   | Lung cancer | 230/240 | PCR-RFLP | Yes |
| Kakouros37     | 2015 | Cyprus | Caucasian | PB  | Yes  | Breast cancer | 1057/1114 | TaqMan | Yes |
| Karunasinghe38 | 2012 | New Zealand | Caucasian | HB  | NA   | Prostate cancer | 258/434 | TaqMan | Yes |
| Koskinen39     | 2006 | Finland | Caucasian | NA  | Yes  | AML        | 89/NA  | PCR  | NA  |
| Li40          | 2009 | USA    | Caucasian | PB  | Yes  | Breast cancer | 497/493 | TaqMan | Yes |
| Li41          | 2006 | USA/UK | Caucasian | PB  | NA   | NHL       | 928/1446 | TaqMan | Yes |
| Liu42         | 2015 | China  | Asian    | PB  | Yes  | Hepatocellular carcinoma | 266/248 | PCR-RFLP | Yes |
| Nahon43       | 2009 | France | Caucasian | NA  | NA   | Hepatocellular carcinoma | 190/NA  | PCR  | NA  |
| Quick44        | 1    | 2008 | USA      | Mixed   | PB  | Yes  | Breast cancer | 57/108  | MALDI-TOF | Yes |
| Quick44        | 2    | 2008 | USA      | Caucasian | PB  | Yes  | Breast cancer | 569/974 | MALDI-TOF | Yes |
| Rajaraman45    | 1    | 2008 | USA      | Mixed   | HB  | Yes  | Acoustic neuroma | 69/494  | TaqMan | Yes |
| Rajaraman45    | 2    | 2008 | USA      | Mixed   | HB  | Yes  | Acoustic neuroma | 69/494  | TaqMan | Yes |
| Rajaraman45    | 3    | 2008 | USA      | Mixed   | HB  | Yes  | Meningioma | 134/494 | TaqMan | Yes |
| Saadat46       | 2015 | Iran   | Caucasian | PB  | NA   | Breast cancer | 407/395 | PCR  | Yes |
| Se47          | 2015 | China  | Asian    | HB  | Yes  | Hepatocellular carcinoma | 400/480 | PCR-RFLP | Yes |
| Tang48         | 2010 | USA    | Mixed    | HB  | NA   | Pancreatic cancer | 551/602 | TaqMan | Yes |
| Tek14         | 2013 | Turkey | Caucasian | HB  | NA   | Prostate cancer | 155/195 | PCR  | Yes |
| Tsai49         | 2012 | China  | Asian    | HB  | Yes  | Breast cancer | 260/224 | PCR  | Yes |
| Ulder40        | 2007 | England | Caucasian | PB  | Yes  | Breast cancer | NA    | TaqMan | NA  |
| Van Blarigan41 | 2014 | USA    | Caucasian | PB  | NA   | Prostate cancer | NA    | MALDI-TOF | NA  |
Discussion

ROS are naturally generated from aerobic metabolism. The human body develops a sophisticated set of antioxidant molecules to prevent the toxic accumulation of these species. CAT belongs to the antioxidant molecules and is present in all aerobic cells while the highest levels of the enzyme are found in the liver, kidney, and erythrocytes. CAT is a heme enzyme that plays a very important role in avoiding hydrogen peroxide concentration by converting H$_2$O$_2$ into H$_2$O and O$_2$, and protects cells from detrimental effects of oxidative stress. Allelic variants of CAT gene may contribute to lower CAT enzymatic activity and higher sensitivity to ROS, and alter ROS detoxification and increase oxidative stress, thereby implicating oxidative DNA damage and modulating disease risk. 245 CAT SNPs have been identified, with most studies investigating the relationships between multiple diseases and rs1001179, a C > T substitution at position −262 from the transcription start site. Previous studies indicated that CAT C262T gene polymorphism had an influence on transcription factors binding thus altering the basal transcription and consequent expression of this enzyme and hence influenced the oxidative status of cells and its microenvironment. Consequently, this polymorphism was believed to play a key role in the pathogenesis of cancer. The growing studies investigated the relation of CAT C262T gene polymorphism to breast cancer, lung cancer, diabetic neuropathy, non-Hodgkin lymphoma, liver cancer and colorectal cancer, however, these results did not reach an agreement. A meta-analysis is a useful strategy because it potentially investigates a large number of individuals and could evaluate the effect of a genetic factor on cancer risk. We performed the current meta-analysis to combine the eligible studies and data to precisely estimate the role of CAT C262T polymorphism in the susceptibility and survival of cancers.

The present meta-analysis, including 15531 cancer patients and 41816 controls from 35 case–control or cohort studies, investigated the association between the CAT C262T polymorphism and cancer risk. Based on current accessible evidences, the individuals who carry the TT homozygote have 17% increased risk of cancer compared with the C allele carriers, revealing that the CAT C262T gene polymorphism may be a risk factor for cancer. For tumor origin could influence the results from meta analysis, we performed subgroup analyses by cancer type. However, we did not find any positive relationship in the studies of breast cancer, head and neck cancer, hematological malignancies, digestive system cancer or brain cancer. Interestingly, the significant association between the CAT C262T gene and prostate cancer was the opposite in most genetic models. The relationships between the CAT C262T gene and skin cancer or cervical cancer were opposite in part genetic models. Meanwhile, in the stratified analysis by ethnicity, significantly elevated cancer risks were indicated in...
Table 2. The results of evidence synthesis of susceptibility analysis. P: P-value of Z-test to evaluate the significance of the ORs; NA: not available.

| Variables                      | Allelic model       | N | HR(95%CI) | P | OR(95%CI) | P | OR(95%CI) | P | OR(95%CI) | P | OR(95%CI) | P | OR(95%CI) | P |
|--------------------------------|---------------------|---|-----------|---|-----------|---|-----------|---|-----------|---|-----------|---|-----------|---|
| Dominant model (TT vs CT)      | CC                  | 3 | Reference |   | 1.06 (0.98–1.15) | 0.13 | 50.20 | 1.19 (1.09–1.31) | <0.001 | 14.10 | 1.24 (1.12–1.38) | <0.001 | 31.00 | 1.04 (0.98–1.09) | 0.18 | 39.80 | 1.08 (1.01–1.16) | 0.02 | 58.00 |
|                                | CT/TT               |   | Reference |   | 1.00 (0.96–1.04) | 0.35 | 17.1% | 0.99 (0.93–1.06) | 0.27 | 49.10 | 0.97 (0.92–1.03) | 0.18 | 54.7 | 0.94 (0.89–1.00) | 0.27 | 49.10 |
|                                | CT                 | 2 | Reference |   | 1.04 (0.99–1.09) | 0.03 | 62.30 | 1.02 (0.96–1.09) | 0.20 | 52.2 | 0.98 (0.92–1.04) | 0.17 | 51.0 | 0.98 (0.92–1.04) | 0.17 | 51.0 |
|                                | TT                 | 2 | Reference |   | 0.99 (0.94–1.05) | 0.53 | 66.4 | 0.99 (0.94–1.05) | 0.53 | 66.4 | 0.99 (0.94–1.05) | 0.53 | 66.4 | 0.99 (0.94–1.05) | 0.53 | 66.4 |
| Recessive model (CT vs TT)     | CC                  | 3 | Reference |   | 1.57 (0.70–2.70) | 0.35 | 66.7 | 1.57 (0.70–2.70) | 0.35 | 66.7 | 1.57 (0.70–2.70) | 0.35 | 66.7 | 1.57 (0.70–2.70) | 0.35 | 66.7 |
|                                | CT                 | 2 | Reference |   | 1.04 (0.81–1.34) | 0.77 | 0% | 1.04 (0.81–1.34) | 0.77 | 0% | 1.04 (0.81–1.34) | 0.77 | 0% | 1.04 (0.81–1.34) | 0.77 | 0% |
|                                | TT                 | 2 | Reference |   | 1.00 (0.95–1.05) | 0.35 | 66.7 | 1.00 (0.95–1.05) | 0.35 | 66.7 | 1.00 (0.95–1.05) | 0.35 | 66.7 | 1.00 (0.95–1.05) | 0.35 | 66.7 |
| Homozygote model (CC vs TT)    | CC                  | 6 | Reference |   | 0.744 | 0.21 | 9.6% | 0.744 | 0.21 | 9.6% | 0.744 | 0.21 | 9.6% | 0.744 | 0.21 | 9.6% |
|                                | CT                 | 6 | Reference |   | 0.77 | 0% | 0% | 0.77 | 0% | 0% | 0.77 | 0% | 0% | 0.77 | 0% | 0% |
|                                | TT                 | 6 | Reference |   | 1.07 (0.95–1.20) | 0.29 | 0% | 1.07 (0.95–1.20) | 0.29 | 0% | 1.07 (0.95–1.20) | 0.29 | 0% | 1.07 (0.95–1.20) | 0.29 | 0% |
| Allelic model (C vs T)         | C                  | 4 | Reference |   | 1.07 (0.97–1.18) | 0.21 | 9.6% | 1.07 (0.97–1.18) | 0.21 | 9.6% | 1.07 (0.97–1.18) | 0.21 | 9.6% | 1.07 (0.97–1.18) | 0.21 | 9.6% |
|                                | T                  |   | Reference |   | 1.07 (0.97–1.18) | 0.21 | 9.6% | 1.07 (0.97–1.18) | 0.21 | 9.6% | 1.07 (0.97–1.18) | 0.21 | 9.6% | 1.07 (0.97–1.18) | 0.21 | 9.6% |

Table 3. The results of evidence synthesis of overall survival analysis. *Number of studies in analysis.

- Caucasian group but not in Asian population. The underlying genetic backgrounds and/or environmental and social factors may account for the ethnic discrepancy.
- It is worth mentioning that the current study was the first meta-analysis to investigate the survival outcomes. While the TT genotype was associated with increased cancer risk especially in prostate cancer and Caucasian population, however, neither of TT or CT genotype contributed to poorer survival of cancer patients. These results indicated that CAT C262T polymorphism might only influence susceptibility to cancer instead of cancer prognosis. In addition, the association between C262T polymorphism and treatment efficiency such as chemotherapy and radiotherapy remained unclear and those data were insufficient to reach a pooled result. Further studies could focus on the role of CAT C262T polymorphism on treatment strategy. The exact mechanisms of the C262T polymorphism on cancer development and progression were warranted to investigate in future.
- In interpreting the current results, several limitations of the meta-analysis should be addressed. Only if literatures that were indexed by the selected databases were included for the current study, and some relevant published studies or unpublished studies with null results were missed or ongoing studies were not sought, which might have influenced our results. Secondly, the numbers of published studies were not large to identify possible associations, especially in survival analysis. Thirdly, part studies investigated several cases with the same control, which might reduce the statistical power to identify possible associations. Fourthly, lacking the original data of...
the reviewed studies limited our further evaluation of the potential interaction. However, our current study also had some merits. On one hand, over 30 case-control or cohort studies from different publications significantly increased statistical power of the analyses. On the other hand, on the basis of our studies, we find a novel mechanism to predict cancer risk. In addition, the current study is the first to investigate the survival outcomes.

To sum up, the results from the current study suggest that the CAT C262T polymorphism may contribute to genetic susceptibility to cancer, supporting the hypothesis that the polymorphism serves as a potential susceptibility tumor marker. However the CAT C262T polymorphism may not be a fine prognostic factor for cancer survival. Further well-designed, multicenter epidemiological studies including a wider spectrum of subjects should be performed to investigate the role of this functional polymorphism in other populations and biological mechanism of CAT C262T polymorphism, which should lead to better, comprehensive interpretation of the association between the CAT C262T polymorphism and cancer risk.

Methods
Identification and Eligibility of Relevant Studies. Two investigators performed a comprehensive and systematic search through the databases of Pubmed, EMBASE and CNKI for relevant studies with the following terms: “catalase” or “CAT”, “polymorphism” or “variant” or “mutation”, and “cancer” or “carcinoma” or “malignancy” (Last search update December 2015). The publication language and publication date were not restricted in our search. Some potential publications were obtained from a manual search of the references of retrieved articles.

The inclusion criteria were: (1) case-control studies or cohort studies; (2) evaluating the associations between the CAT C262T polymorphism and cancer risk or survival outcomes; (3) detailed data on genotype frequency of the CAT C262T for calculating the odds ratios (ORs), available hazards ratios (HRs) and 95% confidence intervals (95%CIs). The exclusion criteria were: (1) reviews, conference abstracts, case reports, animal studies or editorials; (2) without available genotype frequency of the CAT C262T; (3) when the same or overlapped population and duplicated studies were met, only the most recent studies with sufficient information were included.

Data extraction. Two investigators extracted data independently and consensus on all the items was reached after discussion. The main information included the first author, publication year, country, ethnicity, source of controls, sample, quality control, quality health, cancer type, number of cases and controls, genotype distributions of cases and controls, genotyping method, HWE of the control groups, and HR with 95%CI of this polymorphism in survival analysis.
Statistical Analysis. All statistical analyses were conducted with STATA 12.0 (Stata Corp, College Station, TX, USA). The statistical heterogeneity among the studies was calculated by the $\Gamma^2$ statistics. If $\Gamma^2 > 50\%$, the random-effects model was applied to analysis; otherwise, the fixed-effects model was adopted. ORs with 95% CIs were used to stabilize risk estimates, while HRs with 95% CIs were required to predict whether the CAT C262T gene polymorphism had influence on OS of cancer patients. The following genetic models were used to evaluate the susceptibility: dominant model (TT + CT vs CC), recessive model (TT vs CT + CC), homozygote model (TT vs CC), heterozygote model (CT vs CC), and allelic contrast model (T vs C). We also performed the subgroup analyses based on cancer type and ethnicity. The significance of the pooled OR was assessed by Z test and the statistically significant outcome was defined as $P < 0.05$. HWE was evaluated by the chi-square test in control groups for each study, where $P > 0.05$ was considered significant. Both Egger’s and Begg’s tests were used to evaluate the publication bias. Sensitivity analysis, which aimed to identify whether the heterogeneity across these studies was from one individual study, was also performed to ensure the reliability of the results.

References

1. Dalle-Donne, I., Giustarini, D., Colombo, R., Rossi, R. & Milzani, A. Protein carbonylation in human diseases. 
*Trends Mol Med* 9, 169–176 (2003).

2. Klaunig, J. E. & Kamendulis, L. M. The role of oxidative stress in carcinogenesis. 
*Annu Rev Pharmacol Toxicol* 44, 239–267 (2004).

3. Ziech, D. *et al.* The role of reactiveoxygen species and oxidative stress in environmental carcinogenesisis and biomarker development. 
*Chem Biol Interact* 188, 334–339 (2010).

4. Kang, D. H. Oxidative stress, DNA damage, and breast cancer. 
*AACN Clin Issues* 13, 540–549 (2002).

5. Bensaad, K. & Vousden, K. H. Savoir and Slayer: the two faces of p53. 
*Annu Rev Pharmacol Toxicol* 55, 334–339 (2010).

6. Farawela, H. *et al.* Manganese superoxide dismutase polymorphism and outcome of chemotherapy in acute myeloid leukemia. 
*Haematologica* 91, 829–832 (2006).

7. Li, Y. *et al.* Oxidative stress-related gene polymorphisms, fruit and vegetable consumption and breast cancer risk. 
*Cardiovasc Genet* 30, 777–784 (2009).

8. Rajaraman, P. *et al.* Associations between catalase phenotype and genotype: modification by epidemiologic factors. 
*Cancer Epidemiol Biomarkers Prev* 15, 1217–1222 (2006).

9. Laurent, A. *et al.* Controlling tumor growth by modulating endogenous production of reactive oxygen species. 
*Cancer Res* 65, 948–956 (2005).

10. Jiang, Z. *et al.* A polymorphism in the promoter region of catalase is associated with blood pressure levels. 
*Hum Genet* 109, 95–98 (2001).

11. Su, S. *et al.* Genetic polymorphisms in antioxidant enzyme genes and susceptibility to hepatocellular carcinoma in Chinese population: a case-control study. 
*Tumour Biol* 36, 4627–4632 (2015).

12. Castaldo, S. A. *et al.* The role of CYBA (p22phox) and catalase genetic polymorphisms and their possible epistatic interaction in cervical cancer. 
*Tumour Biol* 36, 909–914 (2015).

13. Forsberg, L., Lyrens, L., de Faire, U. & Svanberg, N. A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. 
*Free Radic Biol Med* 30, 500–505 (2001).

14. Ahn, J. *et al.* Polymorphic variants of MnSOD Val16Ala, CAT-262 C and myeloperoxidase G-463A gene polymorphisms in chronic myeloid leukemia: a case-control study. 
*Oxidative Medicine and Cellular Longevity* 2014, 875861 (2014).

15. Белов, Е. *et al.* Single Nucleotide Polymorphism in Catalase Is Strongly Associated with Ovarian Cancer Survival. 
*PloS one* 10, e0135739 (2015).

16. Bhatti, P. *et al.* Lead exposure, polymorphisms in genes related to oxidative stress, and risk of adult brain tumors. 
*Cancer Epidemiol Biomarkers Prev* 18, 1841–1848 (2009).

17. Cebrian, A. *et al.* Genomic background of the human body determines gene expression. 
*AACN Clin Issues* 16, 2336–2338 (2009).

18. Cebrian, A. *et al.* Tagging single-nucleotide polymorphisms in antioxidant defense enzymes and susceptibility to cancer. 
*Cancer Res* 66, 1225–1233 (2006).

19. Cheng, T. Y. *et al.* Oxidative response gene polymorphisms and risk of adult brain tumors. 
*Neuro Oncol* 10, 709–715 (2008).

20. Laurent, A. *et al.* Controlling tumor growth by modulating endogenous production of reactive oxygen species. 
*Cancer Res* 65, 948–956 (2005).

21. Lauritsen, K. A. & Milzani, A. Protein carbonylation in human diseases. 
*Trends Mol Med* 9, 169–176 (2003).

22. Klaunig, J. E. & Kamendulis, L. M. The role of oxidative stress in carcinogenesis. 
*Annu Rev Pharmacol Toxicol* 44, 239–267 (2004).

23. Ziech, D. *et al.* The role of reactive oxygen species and oxidative stress in environmental carcinogenesis and biomarker development. 
*Chem Biol Interact* 188, 334–339 (2010).

24. Kang, D. H. Oxidative stress, DNA damage, and breast cancer. 
*AACN Clin Issues* 13, 540–549 (2002).

25. Bensaad, K. & Vousden, K. H. Savoir and Slayer: the two faces of p53. 
*Annu Rev Pharmacol Toxicol* 55, 334–339 (2010).

26. Farawela, H. *et al.* Manganese superoxide dismutase polymorphism and outcome of chemotherapy in acute myeloid leukemia. 
*Haematologica* 91, 829–832 (2006).

27. Li, Y. *et al.* Oxidative stress-related gene polymorphisms, fruit and vegetable consumption and breast cancer risk. 
*Cardiovasc Genet* 30, 777–784 (2009).
34. Lightfoot, T. J. et al. Polymorphisms in the oxidative stress genes, superoxide dismutase, glutathione peroxidase and catalase and risk of non-Hodgkin's lymphoma. *Haematologica* **91**, 1222–1227 (2006).
35. Liu, Y. et al. Association between catalase gene polymorphisms and risk of chronic hepatitis B, hepatitis B virus-related liver cirrhosis and hepatocellular carcinoma in Guangxi population. *Medicine* **94**, e702 (2015).
36. Nahon, P. et al. Myeloperoxidase and superoxide dismutase 2 polymorphisms comodulate the risk of hepatocellular carcinoma and death in alcoholic cirrhosis. *Hepatology* **50**, 1494–1493 (2009).
37. Quick, S. K. et al. Effect modification by catalase genotype suggests a role for oxidative stress in the association of hormone replacement therapy with postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* **17**, 1082–1087 (2008).
38. Saadat, M. & Saadat, S. Genetic Polymorphism of CAT C-262 T and Susceptibility to Breast Cancer, a Case-Control Study and Meta-Analysis of the Literatures. *Pathol Oncol Res* **21**, 433–437 (2015).
39. Tang, H., Dong, X., Dayi, R. S., Hassan, M. M. & Li, D. Antioxidant genes, diabetes and dietary antioxidants in association with risk of pancreatic cancer. *Carcinogenesis* **31**, 607–613 (2010).
40. Tsai, S. M. et al. Oxidative stress-related enzyme gene polymorphisms and susceptibility to breast cancer in non-smoking, non-alcohol-consuming Taiwanese women: a case-control study. *Ann Clin Biochem* **49**, 152–158 (2012).
41. Udler, M. et al. Common germline genetic variation in antioxidant defense genes and survival after diagnosis of breast cancer. *J Clin Oncol* **25**, 3015–3023 (2007).
42. Van Blarigan, E. L. et al. Plasma antioxidants, genetic variation in SOD2, CAT, GPX1, GPX4, and prostate cancer survival. *Cancer Epidemiol Biomarkers Prevention* **23**, 1037–1046 (2014).
43. Finkel T. Oxidant signals and oxidative stress. *Cur Opin Cell Biol* **15**, 247–254 (2003).
44. Crawford, A. et al. Relationships between single nucleotide polymorphisms of antioxidant enzymes and disease. *Gene* **501**, 89–103 (2012).
45. Bauer, G. Tumor cell-protective catalase as a novel target for rational therapeutic approaches based on specific intercellular ROS signaling. *Anticancer Res* **32**, 2599–2624 (2012).
46. Forsberg, L., de Faire, U. & Morgenstern, R. Oxidative stress, human genetic variation, and disease. *Arch Biochem Biophys* **389**, 84–93 (2001).
47. Shen, Y. et al. The catalase C-262T gene polymorphism and cancer risk: a systematic review and meta-analysis. *Medicine* **94**, e679 (2015).
48. DerSimonian, R. & Kacker, R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* **28**, 105–114 (2007).
49. Mantel, N. & Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* **22**, 719–748 (1959).
50. Thakkinstian, A., McElduff, P., D’Este, C., Duffy, D. & Attia, J. A method for meta-analysis of molecular association studies. *Stat Med* **24**, 1291–1306 (2005).
51. Egger, M., Davey Smith, G., Schneider, M. & Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634 (1997).

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**Author Contributions**

C.D. and Y.L. proposed the project. Y.S. and C.D. searched the databases and obtained the data. N.C. and C.D. performed the statistical analysis and assessed the results. Y.S. And N.C. wrote the manuscript draft. L.H. and J.W. did the data analysis. C.D., Y.L., L.H., J.W., M.Z. and T.W. commented on the manuscript. All authors revised and approved of the final manuscript.

**Additional Information**

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