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# Association between manganese superoxide dismutase (*MnSOD*) Val-9Ala polymorphism and cancer risk – A meta-analysis

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ARTICLE INFO

*Article history:*
Received 30 December 2008
Received in revised form 12 April 2009
Accepted 20 April 2009
Available online 19 May 2009

*Keywords:*
*MnSOD*
Polymorphism
Antioxidant
Susceptibility
Cancer

ABSTRACT

A growing body of evidence suggests that reactive oxygen species (ROS) play an important role in human cancers. Manganese superoxide dismutase (*MnSOD*) is the major antioxidant in the mitochondria, catalysing the dismutation of superoxide radicals to form hydrogen peroxide. Since the identification of a well-characterised functional polymorphism, Val-9Ala of *MnSOD*, a number of molecular epidemiological studies have evaluated the association between Val-9Ala and cancer risk. However, the results remain conflicting rather than conclusive. This meta-analysis on 15,320 cancer cases and 19,534 controls from 34 published case–control studies shows no significant overall main effect of *MnSOD* Val-9Ala on cancer risk. However, we found that the *MnSOD* 9Ala allele was associated with an increased prostate cancer risk (Val/Ala versus Val/Val: odds ratio (OR) = 1.1; 95% confidence intervals (CI): 1.0–1.3; Ala/Ala versus Val/Val: OR = 1.3; 95% CI: 1.0–1.6; Val/Ala + Ala/Ala versus Val/Val: OR = 1.2; 95% CI, 1.0–1.3). In addition, we found that the *MnSOD* Ala-9Ala genotype contributed to an increased breast cancer risk in premenopausal women who had low consumption of antioxidants (Ala/Ala versus Val/Ala + Val/Val: OR = 2.6, 95% CI: 1.0–6.4 with low vitamin C consumption; OR = 2.1, 95%CI: 1.3–3.4 with low vitamin E consumption and OR = 2.9, 95%CI: 1.5–5.7 with low carotenoid consumption). These results suggest that the *MnSOD* Val-9Ala polymorphism may contribute to cancer development through a disturbed antioxidant balance.



## 1. Introduction

A growing body of evidence suggests that reactive oxygen species (ROS) play an important role in the development of human cancers.[1–3] Oxidative stress can result in DNA breakage, lipid peroxidation, protein modification, membrane disruption, as well as mitochondrial damage.[4,5] Oxidative damage to DNA followed by mutations and alterations in gene expression is the principal mechanism by which ROS contributes to carcinogenesis.[1,6] A number of antioxidant enzymes are involved in the scavenging of ROS, including the superoxide dismutase (SOD) family members (e.g. *Mn*, *Cu*

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0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2009.04.024

and ZnSOD). These enzymes catalyse the dismutation of ROS to form hydrogen peroxide (H2O2), which is further detoxified to water, by glutathione peroxidase (Fig. 1, modified from Li et al. [7]).

MnSOD is the only SOD essential for life,[8] and the major antioxidant in the mitochondria involved in the defence against ROS-induced oxidative damage.[9] There is accumulating evidence linking the mitochondria in general, and MnSOD in particular, to the development of different kinds of cancer.[10] The MnSOD precursor protein is synthesised in the cytoplasm with a cleavable, N-terminal mitochondrial targeting sequence (MTS). The 24 amino acid long MnSOD/MTS[11] drives the mitochondrial import of MnSOD precursor through the translocase of the outer and inner membranes.[12] A human genetic polymorphism at codon 16 of *MnSOD/MTS* leads to a substitution from alanine (Ala) to valine (Val) at position-9 of the mature protein (Val-9Ala, rs4880).[13] The *MnSOD* Val-9Ala polymorphism was reported to be functional in affecting the transport of the enzyme into the mitochondria with the Ala variant, accounting for a more efficient importation.[14]

A number of molecular epidemiological studies have been conducted to examine the association between *MnSOD* Val-9Ala and cancer susceptibility,[7,10,15–46] but the results remain inconsistent. To estimate the overall risk of *MnSOD* Val-9Ala association with cancer risk and to quantify the potential between-study heterogeneity, we conducted a meta-analysis on 34 published case–control studies with 15,320 cancer cases and 19,534 controls.

## 2. Materials and methods

### 2.1. Identification and eligibility of relevant studies

We attempted to include all the case–control studies published to date on the association between *MnSOD* Val-9Ala and cancer risk. Eligible studies were identified by searching the electronic literature PubMed for relevant reports (last search update September 2008, using the search terms '*MnSOD* and polymorphism and cancer'). Additional studies were identified by hands-on searches from references of original studies or review articles on this topic. If studies had partly overlapped subjects, only the one with a larger and/or the latest sample size was selected for the analysis.

### 2.2. Data extraction

Two investigators independently extracted data and reached a consensus on all of the items. Data extracted from these articles included the first author's name, year of publication, country of origin, type of cancer, number of cases and controls, genotype frequencies for cases and controls, characteristics of cancer cases and controls, ethnicity and antioxidant intake.

### 2.3. Meta-analysis

The risk of cancer associated with *MnSOD* Val-9Ala was estimated for each study by odds ratios (ORs) with 95% confidence intervals (95%CI). For all studies, we evaluated the risk of the variant genotypes Val/Ala and Ala/Ala, compared with the wild-type Val/Val genotype, respectively. We then calculated the ORs of Val/Ala + Val/Ala versus Val/Val, and Ala/Ala versus Val/Ala + Val/Val, using both dominant and recessive genetic models of the variant Ala allele. In addition, we conducted stratification analysis by cancer types. To achieve enough statistical power, we only conducted the meta-analysis on cancer types with more than five studies; otherwise, we merged the studies into the 'other cancer' group. As a result, 13 case–control studies of breast cancer (7943 cases and 9430 controls), nine case–control studies of prostate cancer (3373 cases and 5176 controls), and 13 case–control studies of other cancers (4004 cases and 4928 controls) were available for this meta-analysis. Subgroup analyses were further performed by factors related to antioxidant status (such as vitamin C, vitamin E and carotenoid consumption) whenever possible. The $\chi^2$-based Q statistic test was used for the assessment of heterogeneity, and it was considered significant for $P < 0.05$. We used the fixed-effects model and the random-effects model based on the Mantel–Haenszel method and the DerSimonian and Laird method, respectively, to combine values from each of the studies. When the effects were assumed to be homogenous, the fixed-effects model was then used; otherwise, the random-effects model was more appropriate. The Egger's test and inverted funnel plots were utilised to provide diagnosis of publication bias (linear regression analysis [47]). All analysis was done by using the Statistical Analysis System software (v.9.1.3, SAS Institute, Cary, NC) and Review Manage (v.4.2). All the *P* values were two-sided.

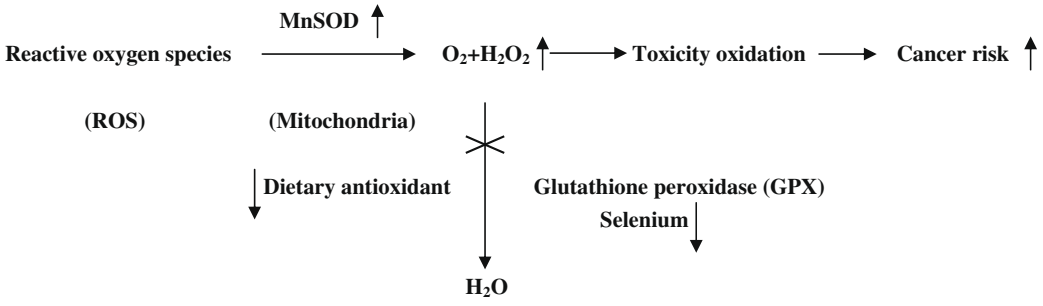


**Fig. 1 – Potential mechanism for the interaction between *MnSOD* and antioxidant status in cancer development (modified from Li et al. [7]). In mitochondria, the ROS is dismutated by *MnSOD* into oxygen and hydrogen peroxide ($H_2O_2$), which is further detoxified to water ($H_2O$) by mitochondrial glutathione peroxidase (an enzyme requiring selenium). High levels of *MnSOD* expression may lead to increased $O_2$ and $H_2O_2$, and induce toxicity if glutathione peroxidase activity is low due to inadequate selenium or dietary antioxidant intake.**

**Table 1 – Characteristics of published studies included in the meta-analysis.**

| Author (ref) | Year | Origin | Type of cancer | Sample size (case/control) | HWE | MAF in controls | Power (%)[b] | | Data available[d] | Genotypic ORs[e] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Homozygotes | Heterozygotes |
| Ambrosone CB[10] | 1999 | United States | Breast | 266/295 | 0.012 | 0.50 | 18.9 | 66.2 | Yes | 2.3 | 1.3 |
| Mitrunen K[15] | 2001 | Finland | Breast | 479/482 | 0.527 | 0.44 | 29.1 | 88.1 | No | 1.3 | 1.2 |
| Green H[16] | 2002 | UK | Breast | 39/36 | 0.175 | 0.47 | 6.8 | 14.0 | No | 0.92 | 0.48 |
| Egan KM[17] | 2003 | United States | Breast | 470/497 | 0.446 | 0.50 | 29.3 | 88.0 | No | 1.2 | 1.3 |
| Millikan RC[18] | 2004 | United States | Breast | 2025/1812 | 0.075 | 0.48 | 80.3 | 100.0 | No | 0.94 | 0.97 |
| Cai Q[19] | 2004 | Shanghai | Breast | 1125/1197 | 0.890 | 0.14 | 34.9 | 95.2 | Yes | 1.3 | 0.98 |
| Tamimi RM[20] | 2004 | United States | Breast | 968/1205 | 0.584 | 0.50 | 55.8 | 99.7 | Yes | 0.96 | 0.89 |
| Bergman M[21] | 2005 | Sweden | Breast | 118/174 | 0.879 | 0.50 | 11.8 | 38.9 | No | 0.36 | 1.1 |
| Gaudet MM[22] | 2005 | USA and Japan | Breast | 1034/1084 | 0.862 | 0.51 | 55.2 | 99.6 | No | 1.0 | 0.99 |
| Cheng TC[23] | 2005 | Taiwan | Breast | 469/739 | 0.322 | 0.14 | 20.3 | 73.0 | No | 1.6 | 1.0 |
| Silva SN[24] | 2006 | Portugal | Breast | 241/457 | 0.000 | 0.48 | 20.8 | 71.7 | No | 0.74 | 0.89 |
| Slanger TE[25] | 2006 | German | Breast | 614/1080 | 0.477 | 0.51 | 43.5 | 97.8 | No | 0.96 | 1.1 |
| Bica CG[a26] | 2008 | Brazil | Breast | 95/372 | 0.000 | 0.41 | 12.5 | 42.3 | No | 1.3 | 0.72 |
| Woodson K[27] | 2003 | Finland | Prostate | 199/191 | 0.330 | 0.48 | 14.6 | 51.2 | Yes | 1.7 | 1.1 |
| Li H[7] | 2005 | United States | Prostate | 567/764 | 0.829 | 0.50 | 37.5 | 95.3 | No | 1.1 | 1.1 |
| Kang D[28] | 2007 | United States | Prostate | 1253/1797 | 0.428 | 0.48 | 69.6 | 99.9 | Yes | 1.3 | 1.2 |
| Ergen HA[29] | 2007 | Turkey | Prostate | 50/50 | 0.121 | 0.18 | 6.5 | 13.0 | No | 21.7 | 2.3 |
| Mikhak B[30] | 2008 | United States | Prostate | 642/652 | 0.695 | 0.50 | 37.4 | 95.2 | No | 1.1 | 1.0 |
| Bica CG[a26] | 2008 | Brazil | Prostate | 51/155 | 0.000 | 0.39 | 8.8 | 24.2 | No | 4.7 | 1.3 |
| Choi JY[31] | 2008 | United States | Prostate | 469/1279 | 0.803 | 0.50 | 39.1 | 96.2 | No | 0.91 | 1.1 |
| Iguchi T[32] | 2008 | United States | Prostate | 57/137 | 0.106 | 0.51 | 8.8 | 24.2 | No | 2.4 | 1.7 |
| Arsova-Sarafinovska Z[33] | 2008 | Macedonia | Prostate | 85/151 | 0.690 | 0.49 | 10.3 | 31.5 | No | 1.2 | 1.4 |
| Hirvonen A[34] | 2002 | Finland | Lung | 20/63 | 0.248 | 0.52 | 6.3 | 11.6 | No | 1.6 | 1.2 |
| Lin P[35] | 2003 | Taiwan | Lung | 198/332 | NA[c] | NA[c] | NA[c] | NA[c] | No | NA[c] | NA[c] |
| Wang LI[36] | 2004 | United States | Lung | 708/861 | 0.912 | 0.52 | 43.2 | 97.7 | No | 0.60 | 0.83 |
| Ho JC[37] | 2006 | Hong Kong | Lung | 234/239 | 0.184 | 0.14 | 10.8 | 36.6 | No | 0.07 | 1.1 |
| Hung RJ[38] | 2004 | Italy | Bladder | 201/214 | 0.262 | 0.52 | 15.1 | 52.9 | No | 0.54 | 0.51 |
| Ichimura Y[39] | 2004 | Japan | Bladder | 213/209 | 0.882 | 0.13 | 9.9 | 32.2 | No | 0.70 | 0.79 |
| di Martino E[40] | 2007 | UK | Oesophageal | 340/93 | 0.171 | 0.42 | 11.8 | 40.1 | No | 1.6 | 1.7 |
| Murphy SJ[41] | 2007 | Ireland | Oesophageal | 396/221 | 0.703 | 0.47 | 19.2 | 67.4 | No | 1.4 | 1.1 |
| Li D[42] | 2002 | United States | Pancreatic | 24/23 | 0.580 | 0.43 | 6.1 | 10.5 | No | 0.48 | 0.88 |
| Martin RC[43] | 2004 | Poland | Gastric | 274/361 | 0.000 | 0.44 | 20.1 | 71.4 | No | 1.3 | 1.0 |
| Johnatty SE[44] | 2007 | Australia | Ovarian | 543/1130 | 0.269 | 0.51 | 41.2 | 97.1 | Yes | 1.1 | 1.1 |
| Landi S[45] | 2007 | Italy | MPM[c] | 80/349 | 0.661 | 0.48 | 11.4 | 36.7 | No | 2.8 | 0.97 |
| Han J[46] | 2007 | United States | Skin | 773/833 | 0.549 | 0.51 | 44.5 | 98.1 | Yes | 0.94 | 1.0 |

a There were different diseases in one study.

b Power was calculated by the PS software with MAF in controls as the frequency of risk factor and OR was selected with 1.2 and 1.5 as the relative risk.

c NA: Not available, MPM: malignant pleural mesothelioma.

d The available antioxidant consumption data.

e Genotypic odds ratios for homozygotes (Ala/Ala vs Val/Val) and heterozygotes (Val/Ala vs Val/Val).

**Table 2 – Summary ORs for associations between the MnSOD Val-9Ala polymorphism and cancer risk.**

| Comparisons | No. of cases | No. of controls | OR | 95% CI | P[a] |
|---|---|---|---|---|---|
| *Total cancer* | | | | | |
| Val/Ala vs Val/Val | 11942 | 15177 | 1.0 | 0.97–1.1 | 0.25 |
| Ala/Ala vs Val/Val | 7953 | 10056 | 1.1 | 0.97–1.3 | 0.00[b] |
| Ala/Ala vs Val/Val + Val/Ala | 15122 | 19202 | 1.1 | 0.97–1.2 | 0.00[b] |
| Val/Ala + Ala/Ala vs Val/Val | 15320 | 19534 | 1.0 | 0.96–1.1 | 0.03[b] |
| *Prostate cancer* | | | | | |
| Val/Ala vs Val/Val | 2526 | 3960 | 1.1 | 1.0–1.3 | 0.72 |
| Ala/Ala vs Val/Val | 1660 | 2594 | 1.3 | 1.0–1.6 | 0.04[b] |
| Ala/Ala vs Val/Val + Val/Ala | 3373 | 5176 | 1.1 | 0.95–1.4 | 0.03[b] |
| Val/Ala + Ala/Ala vs Val/Val | 3373 | 5176 | 1.2 | 1.0–1.3 | 0.29 |
| *Breast cancer* | | | | | |
| Val/Ala vs Val/Val | 6422 | 7678 | 1.0 | 0.94–1.1 | 0.27 |
| Ala/Ala vs Val/Val | 4278 | 5057 | 1.1 | 0.90–1.2 | 0.03[b] |
| Ala/Ala vs Val/Val + Val/Ala | 7943 | 9430 | 1.0 | 0.90–1.2 | 0.01[b] |
| Val/Ala + Ala/Ala vs Val/Val | 7943 | 9430 | 1.0 | 0.94–1.1 | 0.22 |
| *Other cancer* | | | | | |
| Val/Ala vs Val/Val | 2994 | 3553 | 0.97 | 0.87–1.1 | 0.14 |
| Ala/Ala vs Val/Val | 2015 | 2405 | 1.0 | 0.76–1.4 | 0.00[b] |
| Ala/Ala vs Val/Val + Val/Ala | 3086 | 4596 | 1.1 | 0.83–1.4 | 0.00[b] |
| Val/Ala + Ala/Ala vs Val/Val | 4004 | 4928 | 0.98 | 0.84–1.2 | 0.02[b] |

a Test for heterogeneity.
b Random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effects model was used.

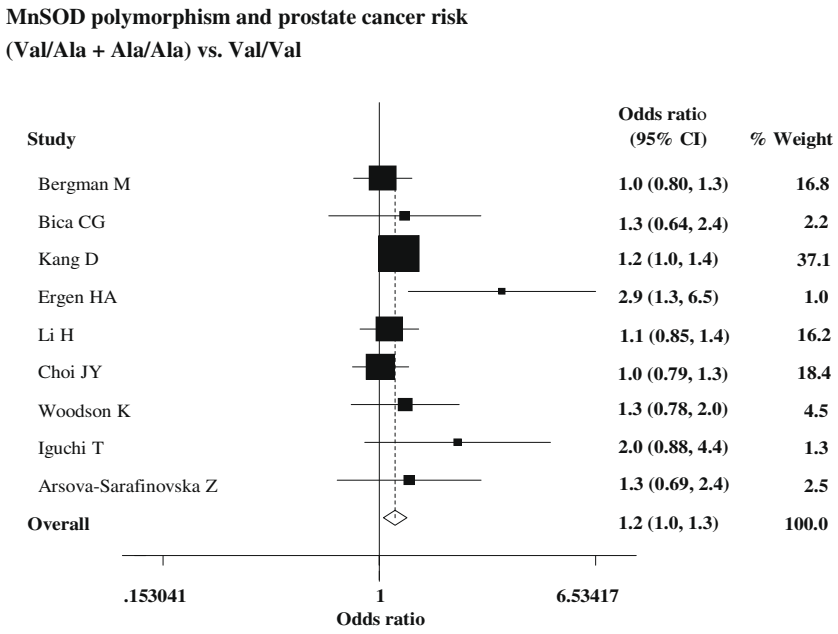


**Fig. 2 – ORs (log scale) of prostate cancer associated with *MnSOD* Val-9Ala for the Val/Ala + Ala/Ala genotypes, compared with the Val/Val genotype.**

## 3. Results

The selected study characteristics are listed in Table 1. All studies indicated that the distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium except for four studies.[10,23,25,43] However, only one study had a statistical power over 80% when we assumed an allelic OR of 1.2.[48] The minor Ala allele frequency (MAF) was lower than 0.2 for Asian studies, while around 0.5 for Caucasus populations (Table 1).

The evaluations of the association of *MnSOD* Val-9Ala with cancer risk are presented in Table 2. We failed to find any significant main effects for *MnSOD* Val-9Ala on cancer risk in different genetic models tested. However, variant genotypes of *MnSOD* Val-9Ala were associated with a significantly increased risk of prostate cancer. As shown in Table 2, both variant homozygotes (Ala/Ala) and heterozygotes (Val/Ala) had significantly increased risks of prostate cancer compared with the wild-type Val/Val homozygotes (Val/Ala versus Val/Val: OR = 1.1, 95%CI: 1.0–1.3, *P* = 0.72 for heterogeneity test; Ala/

**Table 3 – Associations between breast cancer risk and the MnSOD polymorphism, stratified by nutrient intake rich in antioxidants.**

| Stratified variable | | Premenopausal women | | | | | Postmenopausal women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | No. of controls | OR[b] | 95% CI | P[c] | No. of cases | No. of controls | OR[b] | 95% CI | P[c] |
| Vitamin C | Low consumption[a] | 546 | 550 | 2.6 | 1.0–6.4 | 0.03[d] | 1142 | 1445 | 0.95 | 0.78–1.2 | 0.98 |
| | High consumption[a] | 497 | 517 | 1.4 | 0.85–2.2 | 0.90 | 1236 | 1456 | 1.2 | 0.92–1.5 | 0.09 |
| Vitamin E | Low consumption[a] | 520 | 510 | 2.1 | 1.3–3.4 | 0.51 | 869 | 1064 | 1.0 | 0.81–1.3 | 0.66 |
| | High consumption | 347 | 364 | 1.6 | 0.9–2.9 | 0.55 | 364 | 487 | 0.99 | 0.66–1.5 | 0.64 |
| Carotenoids | Low consumption[a] | 444 | 446 | 2.9 | 1.5–5.7 | 0.78 | 260 | 310 | 1.3 | 0.69–2.4 | 0.23 |
| | High consumption[a] | 437 | 437 | 1.8 | 0.95–3.4 | 0.41 | 293 | 349 | 1.3 | 0.75–2.4 | 0.49 |

a Low consumption was defined as no supplement and ⩽ median intake in studies; otherwise, high consumption was defined.
b The OR was obtained in the regressive model (Ala/Ala vs Val/Val + Val/Ala).
c Test for heterogeneity.
d Random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effects model was used.

Ala versus Val/Val: OR = 1.3, 95%CI: 1.0–1.6, *P* = 0.04 for heterogeneity test, respectively). Significant main effects were also observed in the dominant genetic model (Val/Ala + Ala/Ala versus Val/Val: OR = 1.2, 95%CI: 1.0–1.3, *P* = 0.29 for heterogeneity test; Table 2 and Fig. 2). Because only five studies[19,23,35,37,39] were of Asian origin, excluding and including these studies did not change the results substantially on cancer risk (OR = 1.1, 95% CI: 0.97–1.2, *P* = 0.01 for heterogeneity test in a dominant model).

Although we did not find any significant main effects for *MnSOD* Val-9Ala polymorphism on the risk of breast cancer (Table 2), we further performed stratified analysis according to antioxidant intake. We were only able to extract data from three studies[10,19,20] in a recessive genetic model, and we found that *MnSOD* Val-9Ala was associated with an increased risk of breast cancer among premenopausal women who had low consumption of antioxidants (OR = 2.6, 95% CI: 1.0–6.4 with low vitamin C consumption; OR = 2.1, 95% CI: 1.3–3.4 with low intake of vitamin E and OR = 2.9, 95% CI: 1.5–5.7 with low consumption of carotenoids) (Table 3 and Fig. 3).

Heterogeneity between studies was observed in overall comparisons as well as subgroup analyses. We also evaluated the source of heterogeneity in both dominant and recessive

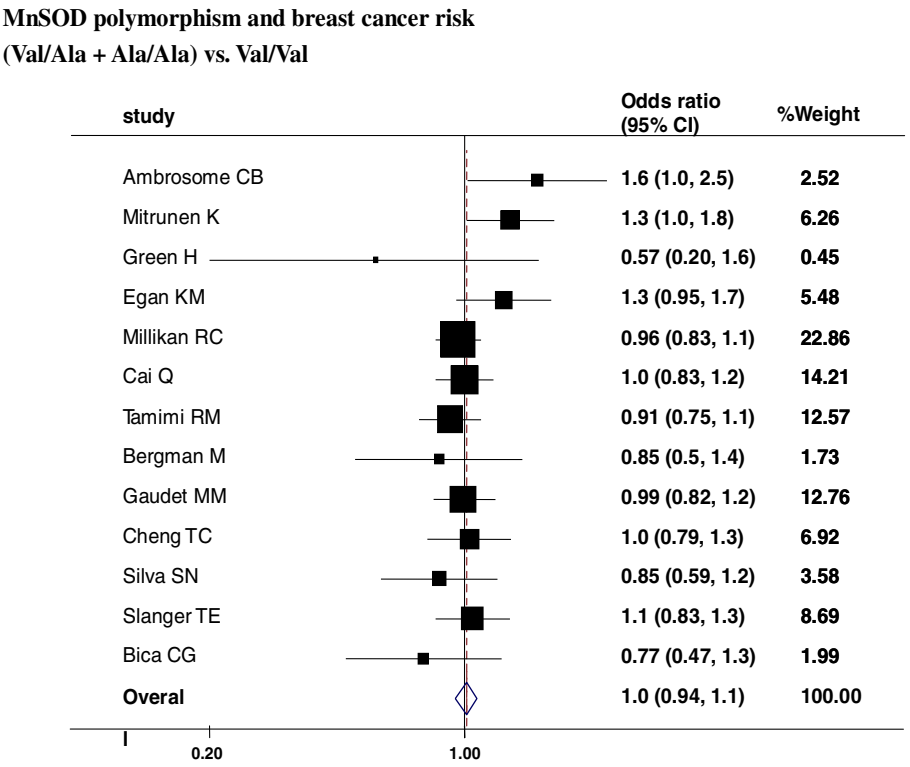


**Fig. 3 – ORs (log scale) of breast cancer associated with *MnSOD* Val-9Ala for the Val/Ala + Ala/Ala genotypes, compared with the Val/Val genotype.**

genetic models of the variant Ala allele by tumour type (prostate cancer, breast cancer and other cancer), ethnicity (Asian, European and mixed ethnicity) and study sample size (subjects more than 300 in both cases and controls or less); however, none of these contributed substantially to the heterogeneity: tumour type (in the dominant model: $\chi^2 = 3.53$, df = 2, $P = 0.171$; in the recessive model: $\chi^2 = 0.84$, df = 2, $P = 0.656$), ethnicity (in the dominant model: $\chi^2 = 1.03$, df = 2, $P = 0.596$; in the recessive model: $\chi^2 = 1.46$, df = 2, $P = 0.482$) and sample size (in the dominant model: $\chi^2 = 0.60$, df = 1, $P = 0.437$; in the recessive model: $\chi^2 = 2.57$, df = 1, $P = 0.109$). Further meta-regression analyses also revealed that none of these three factors could explain significant between-study heterogeneity in different comparisons: tumour type (in the dominant model: $P = 0.758$; in the recessive model: $P = 0.845$), ethnicity (in the dominant model: $P = 0.513$; in the recessive model: $P = 0.400$) and sample size (in the dominant model: $P = 0.928$; in the recessive model: $P = 0.172$).

We used the Egger's test to access the publication bias of literatures on prostate cancer and breast cancer. Publication bias was observed slightly for prostate cancer ($P = 0.04$ in the dominant model and $P = 0.03$ in the recessive model) but this disappeared ($P = 0.27$ in the dominant model and $P = 0.34$ in the recessive model) when we excluded one study[26] with a departure from the Hardy–Weinberg equilibrium and one small study[29] which only had 50 cases and controls. No publication bias was observed for breast cancer ($P = 0.92$ in the dominant model and $P = 0.61$ in the recessive model).

## 4. Discussion

MnSOD plays a critical role in the detoxification of mitochondrial ROS, as inactivation of the *MnSOD* gene is lethal in mice.[49–51] The region of chromosome 6q25.3, where *MnSOD* is located, is deleted in many tumours, implicating *MnSOD* as a candidate tumour suppressor gene.[52–55] Bioinformatic analyses of the Val-9Ala polymorphism showed that the Val allele-containing precursor protein would exhibit impaired transportation (a beta-sheet conformation), while the alpha-helical structure of the Ala-containing precursor would show normal transportation.[56] Recent experiments confirmed this prediction that the Val-*MnSOD* precursor generated 30–40% less efficient transportation activity than the Ala-*MnSOD* precursor.[57] Thus, it is reasonable to hypothesise that the variant (Ala) with higher activity may suppress carcinogenesis.

However, from the present meta-analysis of 34 case–control studies, we failed to find any significant main effects for *MnSOD* Val-9Ala polymorphism on cancer risk. Unexpectedly, the variant Ala allele contributed to a significantly increased risk of prostate cancer. The variant Ala allele was also associated with increased risk of breast cancer among premenopausal women with lower antioxidant consumption. Although there is no sufficient evidence to prove the role of antioxidants in the carcinogenesis associated with the Val-9Ala polymorphism, Li et al. provided a good illustration of the higher activity variant (Ala) that contributes to an increased, rather than decreased, risk of developing prostate cancer, especially when exposed to higher ROS stress and lower antioxidant intake.[7] As shown in Fig. 1, higher ROS stress and *MnSOD* activity resulted in higher $H_2O_2$ concentration, and $H_2O_2$ toxicity would be more severe (as the form $^{\cdot}OH$) with lower dietary antioxidant and glutathione peroxidase (GPX) activity.[18,58] Our meta-analysis also supports and expands the notion to premenopausal breast cancer, but the general applicability to other cancers needs further evaluation.

It is worth emphasising that prostate cells might be more sensitive to ROS stress. *MnSOD* has been known as a tumour suppressor in prostate cancer cells,[54,59–61] and increased levels of hydrogen peroxide ($H_2O_2$) have been found in prostate cancer cells[62] and have been linked to overexpression of *MnSOD*.[63] $H_2O_2$ is a major intracellular oxidant involved in $H_2O_2$-induced DNA damage in prostate cancer[62] and in induction of genes involved in prostate carcinogenesis.[64,65] Studies have also reported that the low soil selenium content (related to GPX activity) and probably low tomato (lycopene) consumption are inversely associated with prostate cancer risk.[26,30] The androgen receptor (AR) is expressed in almost all prostate cancers, and the growth and proliferation of prostate cancer cells is initialled in an androgen-dependent manner.[66] El-Bayoumy et al.[67] reported that AR status may influence the effect of selenium on gene expression profile in prostate cancer, while it may induce the expressions of SOD, but they did not assure whether the oestrogen receptor had such an effect on breast cancer. Chowdhury et al.[68] reported that the level of catalase and *MnSOD* were up-regulated in prostate cancer cell lines. Klapcinska et al.[69] pointed out that castration significantly and negatively affected the antioxidant status, as evidenced by a significant decline in activities of all antioxidant enzymes, which may indirectly support the tissue specific activities of MnSOD and the Val-9Ala polymorphism.

Although there was a publication bias for Val-9Ala-associated prostate cancer risk, the bias disappeared when we rejected one study[26] that departed from the Hardy–Weinberg equilibrium and one small study[29] which only had 50 cases and controls. The remaining significant association (OR = 1.1, 95%CI: 1.0–1.3) suggested that publication bias may not influence our result substantially, if at all. Furthermore, small numbers of individuals and inconsistent stratification standards in antioxidant intake and genotypes by the published studies limited our statistical power to fully investigate the gene-nutrition interaction. Therefore, further well-designed large studies, particularly referring to gene–gene and gene–antioxidant interactions are warranted to confirm the real contribution of *MnSOD* Val-9Ala to cancer susceptibility.

## Conflict of interest statement

None declared.

## Acknowledgement

Grant support: Program for Changjiang Scholars and Innovative Research Team in University (IRT0631).

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