ORIGINAL RESEARCH

Effect of *NQO1* C609T polymorphism on prostate cancer risk: a meta-analysis

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Background: Some studies have found that the *NAD(P)H:quinone oxidoreductase 1 (NQO1)* SNP609 is associated with an increased risk for several malignancies. Numerous epidemiological studies have evaluated the association between the *NQO1* C609T polymorphism and the risk of prostate cancer. However, the results of these studies have been conflicting. The aim of this study was to provide a more precise estimation of its relationship with prostate cancer using a meta-analysis.

Methods: Electronic searches of several databases were conducted for all publications on the association between the *NQO1* C609T polymorphism and prostate cancer before May 2013. The odds ratio (OR) and its 95% confidence interval (CI) were used for statistical analysis.

Results: A total of six studies with 717 cases and 1,794 controls were included. No significant association was found between the *NQO1* C609T polymorphism and prostate cancer risk in the total population analysis. In subgroup meta-analysis by ethnicity, a positive association was found in an Asian subgroup (T versus C, OR 1.337, 95% CI 1.014–1.763, *P*=0.040; TT + CT versus CC, OR 1.419, 95% CI 1.053–1.913, *P*=0.021). However, no significant association in any genetic models was observed in Caucasians.

Conclusion: This meta-analysis showed that the *NQO1* SNP609 T allele might be a risk factor for prostate cancer in Asians. However, this result should be verified by additional population-based studies with large sample sizes.

Keywords: *NQO1*, SNP609, polymorphism, prostate cancer

Introduction

Prostate cancer is the most common cancer among men and the second leading cause of cancer death in men.[1] Although a number of risk factors have been identified for prostate cancer, the predominant risk factor is aging. Age-related changes are thought to be caused by oxidative stress, which arises as a result of an imbalance in cellular pro-oxidant-antioxidant status.[2] NAD(P)H:quinone oxidoreductase 1 (NQO1), a part of the antioxidant defense system, is primarily involved in the detoxification of mutagenic and carcinogenic quinones, through their two electron reduction to hydroquinones.[3,4]

Although older age and African American ancestry have long been recognized as important risk factors, there is ample evidence supporting the notion that genetics plays a key role.[5,6] Many gene polymorphisms, such as those of the metabolic pathway, hormone receptors,[7,8] and inflammation,[9,10] have been implicated in prostate cancer. One reason might be that polymorphisms in detoxification genes, which are induced by isothiocyanates, modulate the potential anticarcinogenic effects of these glucosinolate breakdown products. Some polymorphisms in these genes have

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functional consequences, causing the formation of less or no enzymes or enzymes with reduced activity.

The most studied *NQO1* polymorphism is a single nucleotide polymorphism (SNP), a "C" to "T" change at position 609 (C609T) of the *NQO1* cDNA results in a nonsynonymous amino acid change from proline to serine at position 187 (P187S), and this amino acid substitution leads to an extremely unstable NQO1 protein which is rapidly ubiquitinated and degraded by the proteasome.[11] Some studies have found that the C609T SNP is associated with an increased risk for several malignancies, eg, colorectal cancer, breast cancer, lung cancer, and bladder cancer.[12–14] However, in a previous study,[3] a significant inverse association between the *NQO1* polymorphism and lung cancer has been found. Hamajima et al also suggested that the CC genotype of the *NQO1* C609T polymorphism is associated with the risk of lung cancer, and that the TT genotype increases the risk of smoking for cancers of the esophagus and lung but not prostate cancer.[15]

For prostate cancer, only sparse and conflicting data are available. Four studies (three case-control studies in Caucasian cohorts, one case-control study in a Japanese cohort) reported no influence of the *NQO1* C609T SNP on prostate cancer risk.[15–18] In contrast, Steinbrecher et al reported a significantly reduced prostate cancer risk for subjects with the 609CC genotype compared with 609CT and 609TT carriers in a German case-control study.[19] On the whole, studies investigating the association between *NQO1* polymorphism and prostate cancer risk in humans were conflicting and inconclusive. This meta-analysis was undertaken to derive a more precise estimate of the association.

Materials and methods
Publication search

Electronic databases (PubMed, Embase, and Google Scholar) were searched independently by two authors for all publications regarding the association between the *NQO1* polymorphism and prostate cancer before May 2013. The keywords were as follows: prostate cancer/prostate carcinoma, polymorphism/variant/genotype/SNP, and NAD(P)H dehydrogenase/quinone 1/*NQO1*. The reference lists of the retrieved articles were handsearched for additional studies. We evaluated the associated publications to retrieve the most eligible studies. The results were limited to papers published in the English language.

Inclusion criteria

Studies included in this meta-analysis were required to meet the following criteria: have a case-control design; be about

NQO1 C609T polymorphism and the risk of prostate cancer; include at least two comparison groups (cancer group versus control group); and contain data on genotype frequency.

Data extraction

Two investigators independently extracted the data and reached a consensus on all the items according to the inclusion criteria listed above. For each study, the following characteristics were collected: author's last name, year of publication, country of origin, ethnicity, type of cancer, sources of control and case groups, methods used to genotype *NQO1* C609T polymorphism, total number of cases and controls, as well as number of cases and controls with C/C, C/T, and T/T genotypes.

Statistical analysis

For the control group of each study, the observed genotype frequencies of the *NQO1* C609T polymorphism were assessed for Hardy–Weinberg equilibrium using the Pearson chi-squared test; $P<0.05$ was considered to be statistically significant. Based on both fixed effects and random-effects models, a pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of association between *NQO1* C609T polymorphism and prostate cancer risk, depending on the heterogeneity of the analysis. In the overall meta-analysis, pooled ORs and 95% CIs were calculated. Heterogeneity was evaluated using the Q test and I^2 score. If the result of the heterogeneity test was $P>0.1$, ORs were pooled according to the fixed-effects (Mantel–Haenszel) model. Otherwise, ORs were pooled according to the random-effects (DerSimonian and Laird) model. Sensitivity analysis was performed by omitting one study at a time and recalculating the pooled OR for the remaining studies to assess the stability of the results.

Publication bias was assessed using Egger's test and Begg's test. All statistical tests were performed using STATA version 10.0 software (Stata Corporation, College Station, TX, USA). The results were considered statistically significant if the P-value was <0.05.

Results
Study selection

The electronic search strategy identified 38 potentially relevant articles, which were evaluated further in detail, including their titles, abstracts, full text, or a combination of these. Thirty-two articles were excluded (Figure 1). Eight studies were not focused on prostate cancer and eleven were not focused on the *NQO1* C609T polymorphism. Twelve studies
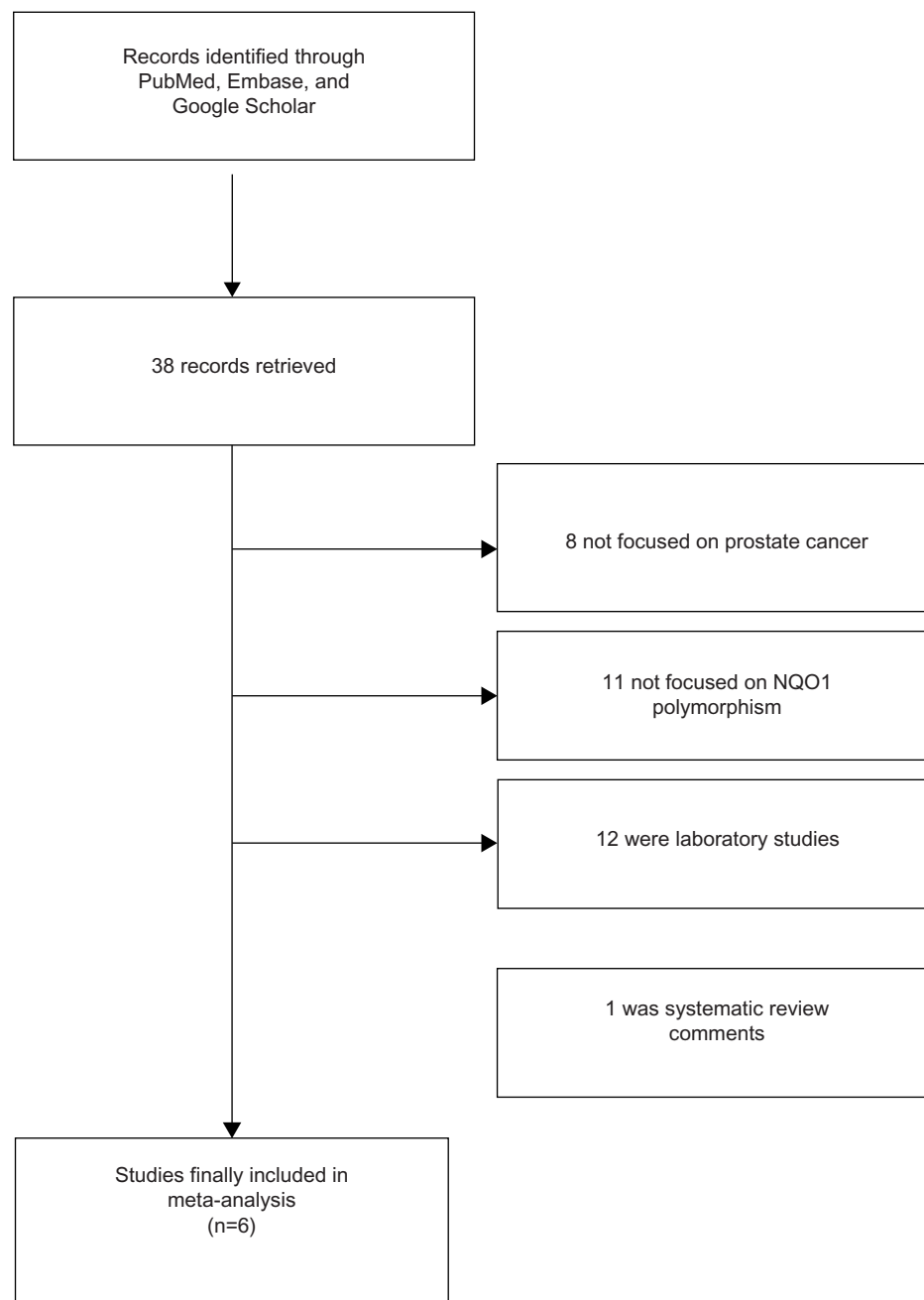
Figure 1 Flow chart of study selection based on inclusion and exclusion criteria.

were laboratory studies, and one study was a systematic review. Finally, six studies[15,17–21] on *NQO1* C609T genotypes and prostate cancer risk including a total of 717 prostate cancer cases and 1,794 controls were identified.

Study characteristics

Table 1 showed the characteristics of the studies included in this meta-analysis. All are case-control studies. One used polymerase chain reaction with confronting two-pair primers, four used polymerase chain reaction-restriction fragment length polymorphism analysis, and one used pyrosequencing. The studies were carried out in Germany, Japan, Turkey, and India. Three studies were in Asians and three were in Caucasians. The distribution of genotypes among the controls was consistent with the Hardy–Weinberg equilibrium ($P > 0.05$) in all studies except for one study by Ergen et al ($P = 0.041$).[17]

Quantitative data synthesis

The results for associations between *NQO1* C609T polymorphism and prostate cancer risk and for heterogeneity

Table 1 *NQO1* C609T genotype distribution in prostate cancer patients and controls

Reference	Country	Genotype						HWE for controls
		Case			Control			
		CC	CT	TT	CC	CT	TT	
Steinbrecher et al[19]	Germany	163	80	5	333	163	26	0.301
Stoehr et al[21]	Germany	76	37	6	166	60	6	0.835
Ergen et al[17]	Turkey	23	17	5	23	26	1	0.041
Mandal et al[20]	India	105	67	23	164	72	14	0.113
Hamajima et al[15]	Japan	17	30	9	240	286	114	0.076
Steiner et al[18]	Germany	37	15	2	67	31	2	0.461

Abbreviation: HWE, Hardy–Weinberg equilibrium.

testing are shown in Table 2. The combined results of all studies showed that there was no statistically significant difference in prostate cancer risk for the different genetic models (OR 1.457, 95% CI 0.722–2.941 for TT versus CC, P=0.585; OR 1.154, 95% CI 0.947–1.407 for CT versus CC, P=0.156; OR 1.178, 95% CI 0.975–1.423 for the dominant model CT + TT versus CC, P=0.089; OR 1.341, 95% CI 0.673–2.674 for the recessive model TT versus CC + CT, P=0.404, Figure 2). Further, we did not detect an association between the *NQO1* C609T polymorphism and prostate cancer when examining the comparison of T versus C (OR 1.171, 95% CI 0.921–1.448 for T versus C, P=0.198).

Subgroup analysis by ethnicity showed a significant difference in prostate cancer risk when examining the comparison of T versus C in the Asian group (OR 1.337, 95% CI 1.014–1.763, P=0.040, Figure 3). Additionally, a significant association was found in the dominant model comparison in the Asian group (OR 1.419, 95% CI 1.053–1.913, P=0.021). However, no significant difference was found in the other genotype distributions (TT versus CC, OR 1.933, 95% CI 0.955–3.912,

P=0.067; CT versus CC, OR 1.301, 95% CI 0.948–1.785, P=0.103; recessive model TT versus CT + CC, OR 1.718, 95% CI 0.711–4.151, P=0.229).

In contrast, no significant association was found for any genetic models in Caucasians (T versus C, OR 1.047, 95% CI 0.748–1.465, P=0.788; TT versus CC, OR 1.045, 95% CI 0.296–3.684, P=0.946; CT versus CC, OR 1.067, 95% CI 0.827–1.377, P=0.618; dominant model CT + TT versus CC, OR 1.036, 95% CI 0.810–1.325, P=0.776; recessive model TT versus CC + CT, OR 1.015, 95% CI 0.301–3.421, P=0.981).

Tests of heterogeneity

Statistically significant heterogeneity was found between the trials using the Q statistic and I^2 score (T versus C, P=0.059, I^2=53.0%; TT versus CC, P=0.042, I^2=56.7%; recessive model TT versus CC + CT, P=0.035, I^2=58.2%); the random-effects model was employed in these studies. There was no significant heterogeneity between the following comparisons: CT versus CC (P=0.392, I^2=3.9%) and dominant model

**Table 2** Meta-analysis of the association between *NQO1* SNP609 polymorphism and prostate cancer risk

Comparisons	Odds ratio	95% CI	*P*-value	Heterogeneity		Effects model
				I^2	*P*-value	
T versus C	1.171	0.921–1.488	0.198	53.0%	0.059	Random
Caucasians	1.047	0.748–1.465	0.788	51.1%	0.129	
Asians	1.337	1.014–1.763	0.040	26.7%	0.255	
TT versus CC	1.457	0.722–2.941	0.585	56.7%	0.042	Random
Caucasians	1.045	0.296–3.684	0.946	64.0%	0.062	
Asians	1.933	0.955–3.912	0.067	32.9%	0.226	
CT versus CC	1.154	0.947–1.407	0.156	3.9%	0.392	Fixed
Caucasians	1.067	0.827–1.377	0.618	0.0%	0.528	
Asians	1.301	0.948–1.785	0.103	33.6%	0.222	
TT + CT versus CC	1.178	0.975–1.423	0.089	31.1%	0.202	Fixed
Caucasians	1.036	0.810–1.325	0.776	16.1%	0.304	
Asians	1.419	1.053–1.913	0.021	14.8%	0.309	
TT versus CT + CC	1.341	0.673–2.674	0.404	58.2%	0.035	Random
Caucasians	1.015	0.301–3.421	0.981	62.0%	0.072	
Asians	1.718	0.711–4.151	0.229	58.2%	0.088	

Abbreviation: CI, confidence interval.
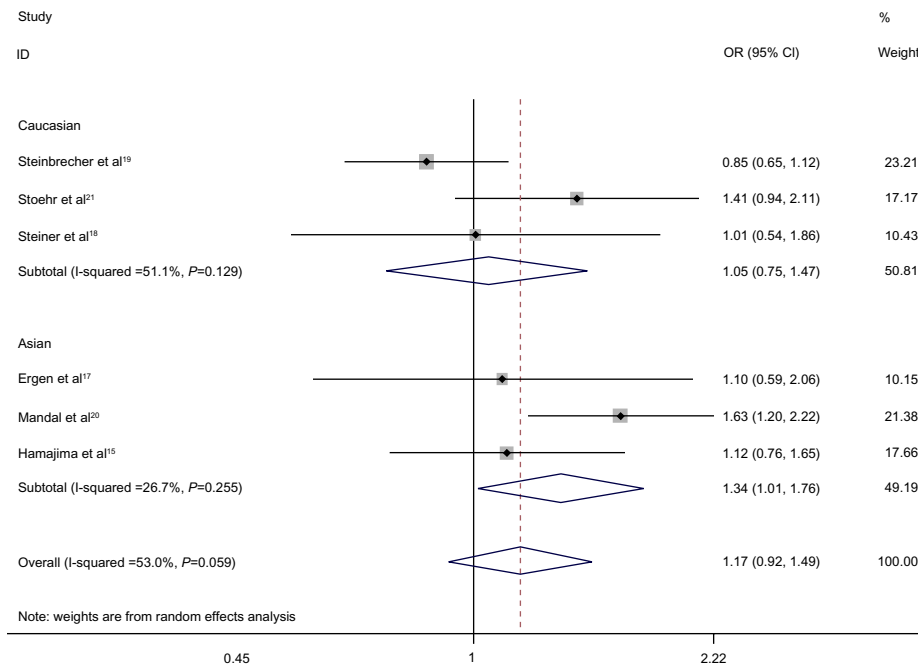
Figure 2 Forest plot showing the association of the *NQO1* SNP609 T allele with risk of prostate cancer compared with the C allele.
Notes: The squares and horizontal lines correspond to the study-specific OR and 95% CI. The diamond represents the summary OR and 95% CI.
Abbreviations: CI, confidence interval; OR, odds ratio.
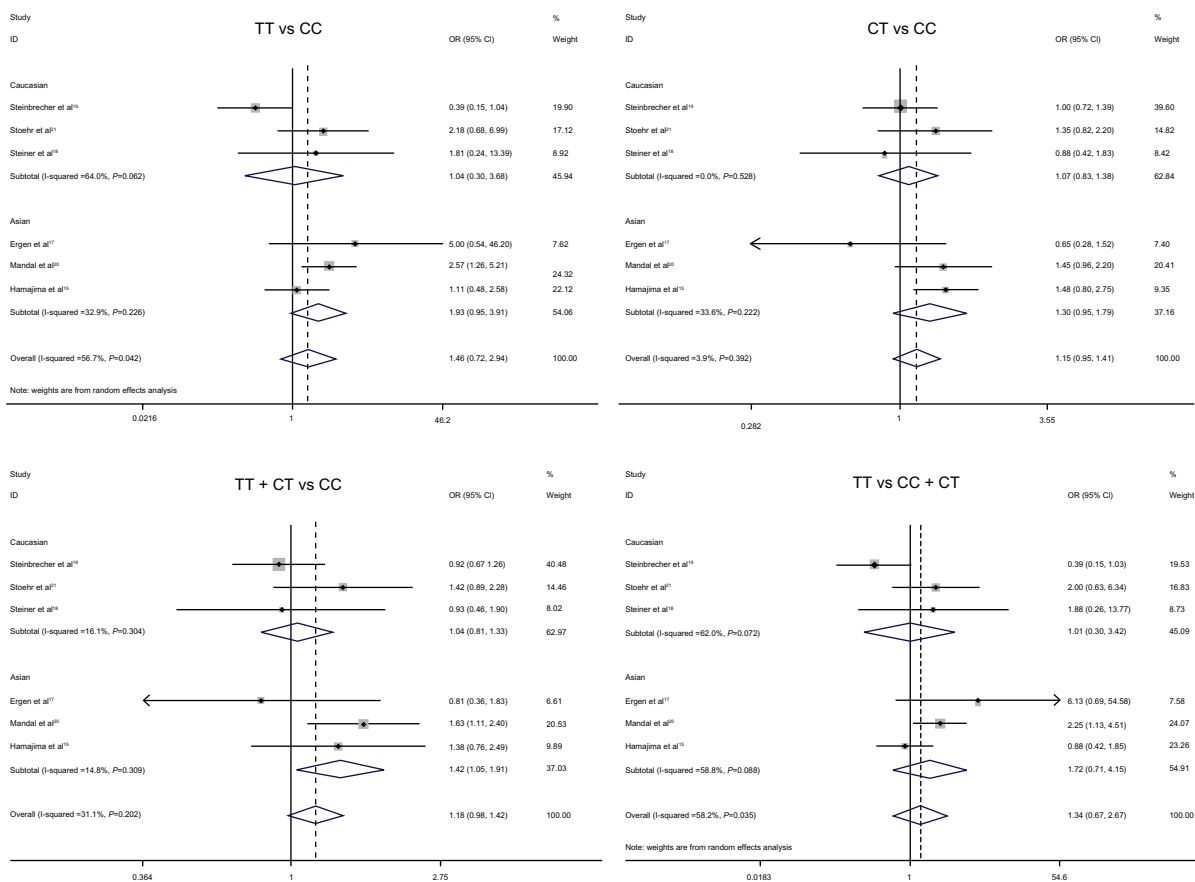
Figure 3 Forest plot describing the association of the *NQO1* SNP609 genetic models (TT versus CC, CT versus CC, TT + CT versus CC, TT versus CC + CT) with the risk of prostate cancer.
Notes: The squares and horizontal lines correspond to the study-specific OR and 95% CI. The diamond represents the summary OR and 95% CI.
Abbreviations: CI, confidence interval; OR, odds ratio.

TT + CT versus CC (*P*=0.202, *I*²=31.1%, Table 2), and the fixed-effects model was employed in these studies.

Sensitivity analysis

To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary OR. The significance of the pooled ORs was not influenced by any single study (Figure 4), indicating that our results were statistically robust.

Publication bias

Begg's test and Egger's test were used to assess for publication bias. Egger's weighted regression did not indicate publication bias (T versus C, *P*=0.886; TT versus CC, *P*=0.829; CT versus CC, *P*=0.655; dominant model TT + CT versus CC, *P*=0.914; recessive model TT versus CC + CT, *P*=0.645). This was confirmed by Begg's rank correlation (T versus C, *P*=1.000; TT versus CC, *P*=1.000; CT versus CC, *P*=0.452; dominant model TT + CT versus CC, *P*=0.452; recessive model TT versus CC + CT, *P*=1.000, Table 3).

Discussion

Many studies have attempted to reveal the genetic basis of prostate cancer. Despite suggestive evidence of gene association, reports have been difficult to replicate, indicating that prostate cancer is more genetically heterogeneous than initially believed. It is known that oxidative damage is one of the main reasons for development of cancer.[22] The evidence indicates that oxidative damage, probably due to prostatic inflammation, is an important contributor to prostate cancer.[23]

NQO1, a part of the antioxidant defense system, is a cytosolic enzyme catalyzing the reduction of quinones. A C609T base change leads to a mutant enzyme with <4% of the activity of the wild-type protein and is unstable in vivo.[24] Since the identification of the *NQO1* C609T polymorphism, a number of studies have investigated the genetic effect of this polymorphism on susceptibility to prostate cancer, but the results are inconclusive. Therefore, it is important to determine the relationship between the *NQO1* gene and prostate cancer. Meta-analysis is a powerful statistical method that can provide a quantitative approach for pooling the results of different studies on the same topic, and can estimate and explain their diversity.[14,25]
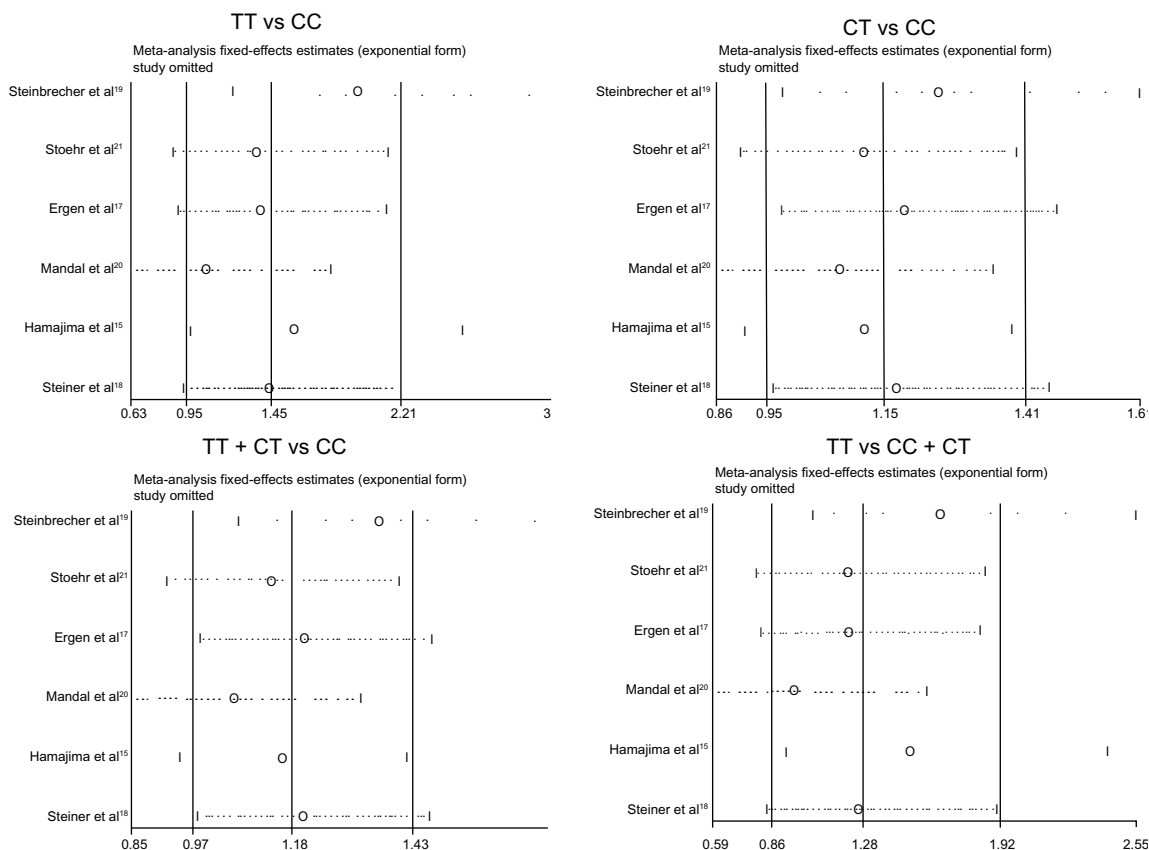
Figure 4 Sensitivity analysis of *NQO1* SNP609 genetic models (TT versus CC, CT versus CC, TT + CT versus CC, TT versus CC + CT).
Notes: The horizontal axis shows the omitted study. Every circle indicates the pooled odds ratio when the left study is removed from the meta-analysis. The horizontal axis represents the odds ratio. The two ends of each broken line represent the lower and upper 95% confidence interval.

Table 3 Publication bias test for *NQO1* SNP609 polymorphism

Comparisons	Egger's test			Begg's test *P*-value
	Coefficient	*P*-value	95% CI	
T versus C	0.352	0.886	−6.047, 6.751	1.000
TT versus CC	0.441	0.829	−4.876, 5.758	1.000
CT versus CC	−0.692	0.655	−4.681, 3.297	0.452
CT + TT versus CC	−0.201	0.914	−5.054, 4.652	0.452
TT versus CC + CT	0.913	0.645	−4.182, 6.008	1.000

Abbreviation: CI, confidence interval.

The present meta-analysis, which included 717 cancer cases and 1,794 controls, explored the relationship between the *NQO1* C609T polymorphism and overall prostate cancer risk. We found no evidence of any association between the *NQO1* C609T polymorphism and prostate cancer susceptibility in the overall population.

The results of several studies have suggested that SNPs may determine the differences in the risk of prostate cancer between ethnic groups.[26,27] In our present study, we performed a subanalysis according to ethnicity, and found that the *NQO1* C609T polymorphism was significantly associated with cancer risk in the Asian population, which is consistent with a report by Fan et al in hepatocellular carcinoma.[28] The frequency of the T allele in patients with prostate cancer was significantly greater than in controls, and the frequency of TT + CT in patients with prostate cancer was also significantly greater than in controls. These findings suggest that the T allele may be a risk factor for prostate cancer in Asians. But in other genetic models of Asian groups, no significant differences were found, suggesting the influence of the genetic variant may be masked by the presence of other as yet unidentified genes involved in carcinogenesis. However, we did not find that *NQO1* C609T polymorphism was significantly associated with cancer risk in a Caucasian population. This indicates a possible role for ethnic differences in genetic background and the environment the subjects lived in.

This meta-analysis has some limitations, so its findings should be interpreted with caution. First, the influence of the genetic variant may be masked by the presence of other as yet unidentified genes involved in carcinogenesis, which restricted our evaluation of potential gene–gene interactions. Second, the number of cases and controls in the studies we included was relatively small. Third, our results were based on unadjusted evaluation, so a more precise analysis should be conducted with adjustment for other variables, eg, environmental factors. Larger and better designed studies are needed to evaluate further the association between the *NQO1* polymorphism and prostate cancer risk, including considering the possibility of gene–gene or SNP–SNP interactions and the possibility of linkage disequilibrium between polymorphisms.

In conclusion, it is worthwhile searching for polymorphic variants influencing the risk of prostate cancer. This meta-analysis provides evidence of an association between *NQO1* 609 polymorphism and prostate cancer risk, supporting the hypothesis that the *NQO1* SNP609 T allele may act as a risk factor for prostate cancer in Asians but not in Caucasians. However, our results should be interpreted with caution because of some limitations. Given that the results of this meta-analysis are preliminary and may be biased by the relatively small number of subjects, additional population-based studies including large sample sizes should be conducted to verify the association of NQO1 polymorphism in prostate cancer.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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