Association of NAD(P)H Quinine Oxidoreductase 1 rs1800566 Polymorphism with Bladder and Prostate Cancers – a Systematic Review and Meta-Analysis

Asociace polymorfizmu NAD(P)H chininové oxidoreduktázy 1 rs1800566 s karcinomem močového měchýře a prostaty – systematický přehled a metaanalýza

Abedinzadeh M.[1], Moghimi M.[2], Dastgheib S. A.[3], Maleki H. [1], Salehi E.[4], Mohammad Z.[5], Jarahzadeh M. H.[6], Neamatzadeh H.[7,8]

[1] Department of Urology, Shahid Sadoughi University of Medical Sciences, Shahid Rahnamoun Hospital, Yazd, Iran
[2] Department of Pathology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Medical Genetics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Department of Basic Science, Faculty of Veterinary Medicine, Ardakan University, Ardakan, Iran
[5] Department of Surgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[6] Department of Anesthesiology and Critical Care, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[7] Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[8] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Summary

Background: Number of studies has been performed to investigate the association of NAD(P)H quinine oxidoreductase 1 (*NQO1*) rs1800566 polymorphism with risk of bladder and prostate cancers, but presented inconsistent results. Therefore, we performed a meta-analysis to provide a comprehensive data on the association of *NQO1* rs1800566 polymorphism with bladder and prostate cancers. ***Methods:*** All eligible studies were identified in PubMed, Google Scholar, EMBASE, and China National Knowledge Infrastructure databases before June 01, 2019. ***Results:*** A total of 22 case-control studies including 15 studies with 4,413 cases and 4,275 controls on bladder cancer and 7 studies with 762 cases and 1,813 controls on prostate cancer were selected. Overall, pooled data showed that the *NQO1* rs1800566 polymorphism was significantly associated with an increased risk of bladder cancer (T vs. C: OR 1.300; 95% CI 1.112–1.518; P = 0.001; TT vs. CC: OR 1.415; 95% CI 1.084–1.847; P = 0.011; TC vs. CC: OR 1.389; 95% CI 1.111–1.738; P = 0.004; TT + TC vs. CC: OR 1.428; 95% CI 1.145–1.782; P = 0.002) and prostate cancer (TC vs. CC: OR 1.276; 95% CI 1.047–1.555; P = 0.016; TT + TC vs. CC: OR 1.268; 95% CI 1.050–1.532; P = 0.014). The stratified analysis by ethnicity revealed an increased risk of bladder cancer among Caucasians and prostate cancer among Asians. ***Conclusion:*** This meta-analysis suggested that the *NQO1* rs1800566 polymorphism was significantly associated with increased risk of bladder and prostate cancers.

Key words

urinary bladder neoplasms – prostatic neoplasms – *NQO1* gene – polymorphism – meta-analysis

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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Dr. Mansour Moghimi
Department of Pathology
Shahid Sadoughi University
of Medical Sciences
Yazd, Iran
e-mail:
dr_mansour_moghimi@yahoo.com

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Souhrn

Východiska: Bylo provedeno několik studií s cílem zkoumání asociace polymorfizmu NAD(P)H chinin oxidoreduktázy 1 (*NQO1*) rs1800566 s rizikem karcinomu močového měchýře a prostaty, ale byly předloženy nekonzistentní výsledky. Proto jsme provedli metaanalýzu, abychom poskytli komplexní údaje o asociaci polymorfizmu *NQO1* rs1800566 s karcinomem močového měchýře a prostaty. ***Metody:*** Příslušné studie byly identifikovány v databázích PubMed, Google Scholar, EMBASE a China National Knowledge Infrastructure před 1. červnem 2019. ***Výsledky:*** Bylo vybráno celkem 22 případových kontrolních studií zahrnujících 15 studií karcinomu močového měchýře se 4 413 případy a 4 275 kontrolami a 7 studií karcinomu prostaty s 762 případy a 1 813 kontrolami. Souhrnná data ukázala, že polymorfizmus *NQO1* rs1800566 byl významně asociován se zvýšeným rizikem karcinomu močového měchýře (T vs. C: OR 1,300; 95% CI 1,112–1,518; p = 0,001; TT vs. CC: OR 1,415; 95% CI 1,084–1,847; p = 0,011; TC vs. CC: OR 1,389; 95% CI 1,111–1,738; p = 0,004; TT + TC vs. CC: OR 1,428; 95% CI 1,145–1,782; p = 0,002) a karcinomu prostaty (TC vs. CC: OR 1,276; 95% CI 1,047–1,555; p = 0,016; TT + TC vs. CC: OR 1,268; 95% CI 1,050–1,532; p = 0,014). Analýza stratifikovaná podle etnicity odhalila zvýšené riziko karcinomu močového měchýře u Kavkazanů a karcinomu prostaty u Asiatů. ***Závěr:*** Tato metaanalýza naznačuje, že polymorfizmus *NQO1* rs1800566 byl významně spojen se zvýšeným rizikem karcinomu močového měchýře a prostaty.

Klíčová slova

karcinom močového měchýře – karcinom prostaty – gen *NQO1* – polymorfizmus – metaanalýza

Introduction

Bladder cancer is one of the most common malignancies, with approximately 430,000 new cases diagnosed worldwide, with 118,000 new cases and 52,000 deaths recorded in Europe in 2012 [1]. Bladder cancer is a heterogeneous disease appearing in different forms, e. g. non-muscle invasive and muscle invasive. It mainly affects elderly people and the average age at the time of diagnosis is 73 years [2]. The leading risk factor for bladder cancer is tobacco use, with cigarette smokers showing an approximately threefold higher risk compared to non-smokers [1,3]. Moreover, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths among men in the United States [4]. Risk factors for developing localized prostate cancer are not well known. However, a family history of prostate cancer and age has long been identified as an important risk for development of the disease [5,6]. Although several notable advances in our knowledge about risk factors of bladder and prostate cancers were published in recent years, their exact mechanisms remains poorly understood [7]. It is suggested that both bladder and prostate cancers are caused by a combination of genetic and environmental risk factors [5].

The NAD(P)H quinine oxidoreductase 1 (*NQO1*; also known as diphtheria toxin diaphorase), a key phase II enzyme, plays an important role in the metabolism of several carcinogens; it also protects cells against oxidative stress [8,9]. *NQO1* activity prevents the one electron reduction of quinones and thus prevents generation of free radicals by redox cycle. The human *NQO1* gene is located on chromosome 16q22, consists of seven exons (first exon is non-coding) spanning 20 kb of genomic DNA [10]. *NQO1* genetic variations may play important roles in etiology of genitourinary malignancies, especially bladder cancer and prostate cancer. Therefore, *NQO1* is considered as an anticancer enzyme, and its polymorphisms can highly impact bioreductive cancer therapy [11,12].

Several single nucleotide polymorphisms have been identified in the *NQO1* gene; among them, rs1800566 C>T (Pro187Ser) polymorphism at nucleotide 609 of exon 6, codes for a proline (Pro)-to-serine (Ser) amino acid substitution is one of the most studied [13]. Genotype-phenotype correlation studies have showen that the rs1800566 polymorphism is associated with a decreased activity of *NQO1* enzymatic activity and an increased susceptibility to carcinogenesis, xenobiotic induced toxicity and also a phenotypic gene-dose effect [14]. A number of case-control studies showed that the *NQO1* rs1800566 polymorphism might increase susceptibility to bladder and prostate cancers, but the results remain inconclusive and contradictive. In addition, the sample size in each study was relatively small, and the statistical power might be insufficient. Therefore, we performed a comprehensive meta-analysis to derive a more precise estimate for association of the *NQO1* rs1800566 polymorphism with susceptibility to bladder and prostate cancers.

Materials and methods

Publication search

A comprehensive literature search was performed in PubMed, EMBASE, Cochrane Library database, Springer Link, Chinese Biomedical Database, China National Knowledge Infrastructure platforms, WanFang and VIP database to collect all the eligible studies evaluating the association of *NQO1* rs1800566 polymorphism with bladder and prostate cancers up to June 01, 2019. The following terms, keywords and their combinations were used: ("Prostate cancer" or "Bladder cancer") and ("NAD(P)H dehydrogenase (Quinone) 1" or "*NQO1*" or "DT-diaphorase" or "DTD" or "quinone reductase") and ("609C>T" or "rs1800566" or "Pro187Ser") and ("Polymorphism" or "SNPs" or "Mutation" or "Variation" or "Allele"). Additionally, we reviewed the reference list of all relevant articles and reviews to identify potential eligible studies. If there were multiple publications from the same population, only the most recent was included.

Selection criteria

The eligible studies, included in the current meta-analysis, must have met the following criteria: 1) studies with case-control or cohort design; 2) studies focused on the association of *NQO1* rs1800566 polymorphism with bladder and prostate cancers; 3) providing complete data of cases and controls for calculating an odds ratio (OR) with

95% confidence interval (CI). Studies were excluded for following reasons: 1) abstracts, reviews, case reports, posters, editorials, conference articles; 2) data unavailable for calculating genotype or allele frequencies; 3) studies without reported genotype frequencies; 4) case only studies (without controls); 5) linkage studies, twin and family-based studies; and 6) overlapping data or duplicate of previous publication.

Data extraction

Data were independently extracted by two authors (S. A. Dastgheib and H. Neamatzadeh) using a data-collecting form according to the inclusion criteria. Any disagreement was resolved by discussion with third author (M. Abedinzadeh). The following information was collected from each study: first author's name, year of publication, ethnicity, country of the selected subjects, source of the control groups, definition of metabolic syndrome, frequencies of genotypes in both groups and genotyping methods. Diverse ethnicity descents were categorized as Asian, Caucasian and African. If data were not reported in the primary manuscripts, we contacted the corresponding authors by email to request the missing data.

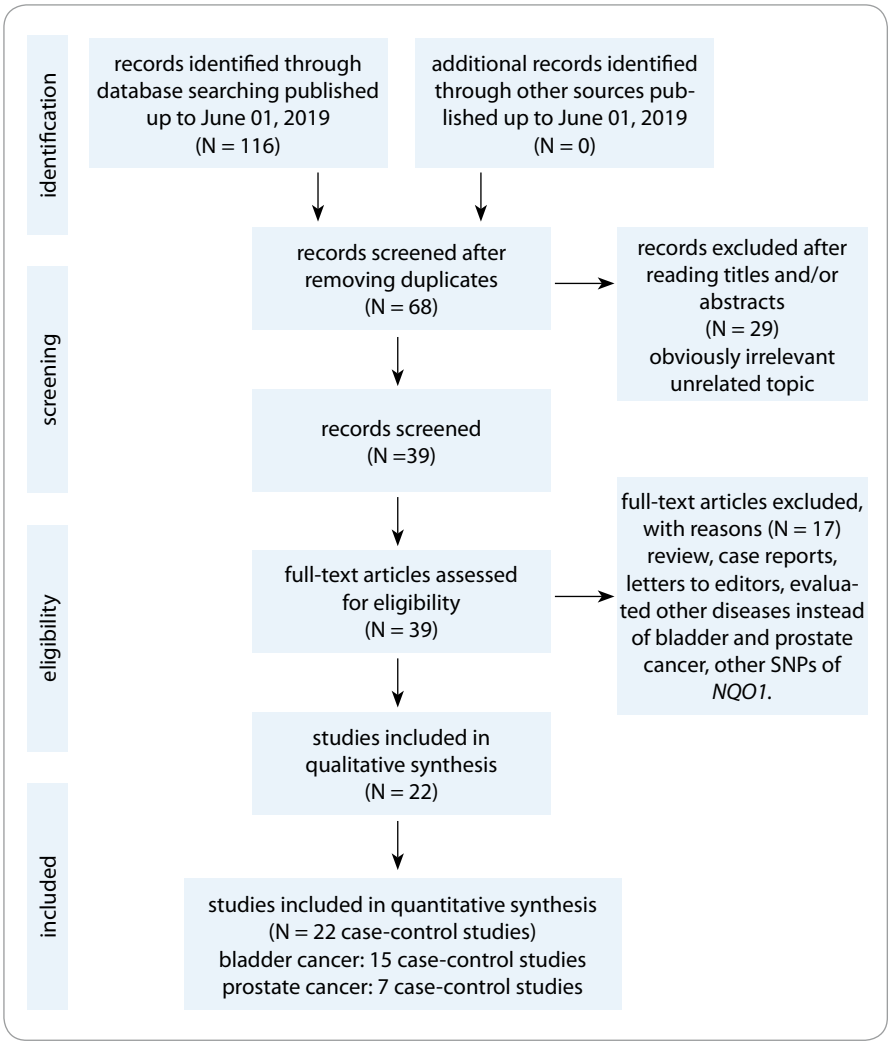

Fig. 1. Flowchart of literature search and selection process [43].

Statistical analysis

The strength of association between *NQO1* polymorphism and bladder and prostate cancers was assessed by ORs with 95% CIs. The significance of the pooled effect size was determined by Z-test, in which $P < 0.05$ was considered statistically significant. The association was evaluated under all five genetic models, i.e., allele (T vs. C), homozygote (TT vs. CC), heterozygote (TC vs. CC), dominant (TT + TC vs. CC), and the recessive (TT vs. TC + CC). Between-study heterogeneity was evaluated by the Cochran Q-test, in which $P \leq 0.10$ indicated significant heterogeneity was found. In addition, the I^2 statistic we applied to qualify between-study heterogeneity (range of 0–100%: I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; I^2 = 75–100%, extreme heterogeneity). The random effects model shows more flexibility with respect to variable effect size in different studies and study populations. Thus, we have applied a random-effects model, using the DerSimonian and Laird method to calculate the pooled OR when heterogeneity was found; otherwise, affixed effect model was applied to use the Mantel-Haenszel method in absence of heterogeneity. A Hardy-Weinberg equilibrium (HWE) test of the *NQO1* rs1800566 polymorphism in controls was tested using chi-square test (P-values < 0.05). Subgroup analyses were conducted by stratification of ethnicity to identifying potential source of heterogeneity. Sensitivity analyses were performed to assess influence of each single study on pooled ORs and the stability of the meta-analysis results by sequential removal of individual studies. In addition, sensitivity analysis was performed to examine the stability of the results by excluding those studies that did not show HWE. Funnel plots and Egger's linear regression test were used to estimate evidence for potential publication bias. All of the statistical calculations were performed using Comprehensive Meta-Analysis software version 2.0 (Biostat, USA). Two-sided P-values < 0.05 were considered statistically significant.

Results

Study characteristics

Fig. 1 shows the flowchart of literature search and selection process. The initial literature searches retrieved 116 potentially relevant studies. After reading the titles and abstracts, 48 studies were

Tab. 1. Characteristics of studies included in the meta-analysis.

First Author	Country (Ethnicity)	Geno-typing Method	SOC	Case/ Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
					CC	CT	TT	C	T	CC	CT	TT	C	T		
Bladder Cancer																
Schulz 1996 [15]	Germany (Caucasian)	PCR-RFLP	PB	99/260	68	26	5	162	36	195	61	4	451	69	0.13	0.755
Park 2003 [21]	USA (Caucasian)	PCR-RFLP	HB	232/239	142	82	8	366	96	163	66	10	392	86	0.18	0.321
Choi 2003 [22]	Korea (Asian)	PCR-RFLP	HB	177/170	81	68	28	230	124	94	60	16	248	92	0.27	0.167
Sanyal 2004 [23]	Sweden (Caucasian)	PCR-RFLP	PB	299/124	206	85	8	497	101	83	34	7	200	48	0.19	0.175
Hung 2004 [24]	Italy (Caucasian)	PCR-RFLP	HB	201/214	113	75	13	301	101	135	66	13	336	92	0.21	0.207
Moore 2004 [25]	Argentina (Caucasian)	PCR-RFLP	PB	106/108	62	35	9	157	53	61	40	7	162	54	0.25	0.897
Terry 2005 [26]	USA (Caucasian)	MS	HB	235/214	156	70	9	382	88	150	58	6	358	70	0.16	0.891
Broberg 2005 [27]	Sweden (Caucasian)	MS	PB	179/156	43	131	5	217	141	107	46	3	260	52	0.17	0.442
Wang 2007 [19]	Taiwan (Asian)	PCR-RFLP	HB	300/300	70	148	82	288	312	94	136	70	324	276	0.46	0.129
Figueroa 2008 [28]	Spain (Caucasian)	TaqMan	HB	1128/1123	685	392	51	1 762	494	661	400	62	1 722	524	0.23	0.884
Pandith 2011 [16]	India (Asian)	PCR-RFLP	HB	104/120	44	53	7	141	67	70	44	6	184	56	0.23	0.785
Fu 2003 [20]	China (Asian)	PCR-RFLP	HB	99/100	30	38	31	68	100	38	46	16	122	78	0.39	0.739
Huang 2014 [8]	Taiwan (Asian)	PCR-RFLP	HB	159/150	36	83	40	155	163	51	67	32	169	131	0.44	0.259
Goerlitz 2014 [17]	Egypt (African)	TaqMan	PB	895/797	519	323	53	1361	429	470	276	51	1 216	378	0.24	0.226
Mandal 2012 [18]	India (Asian)	PCR-RFLP	HB	200/200	105	72	23	282	118	128	61	11	317	83	0.21	0.304
Prostate Cancer																
Steiner 1999 [29]	Germany (Caucasian)	PCR-RFLP	PB	54/100	37	15	2	89	19	67	31	2	165	35	0.18	0.461
Hamajima 2002 [30]	Japan (Asian)	PCR-RFLP	HB	56/640	17	30	9	64	48	240	286	114	766	514	0.40	0.075
Ergen 2007 [31]	Turkey (Caucasian)	PCR-RFLP	HB	45/59	23	17	5	63	27	23	26	10	72	46	0.39	0.571
Steinbrecher 2010 [34]	Germany (Caucasian)	MS	PB	248/492	163	80	5	406	90	333	133	26	799	185	0.19	0.011
Jing-Xian 2011 [33]	China (Asian)	TaqMan	NS	45/40	5	26	14	36	54	12	21	7	36	35	0.44	0.673
Mandal 2012 [18]	India (Asian)	PCR-RFLP	HB	195/250	105	67	23	277	113	164	72	14	400	100	0.20	0.113
Stoehr 2012 [32]	Germany (Caucasian)	PCR-RFLP	HB	119/232	76	37	6	189	49	166	60	6	392	72	0.16	0.835

SOC – source of control, MAF – minor allele frequency, HWE – Hardy-Weinberg equilibrium, PCR-RFLP – polymorphism chain reaction-restriction fragment length polymorphism, MS – mass spectrometry, PB – population based, HB – hospital based, NS – not stated

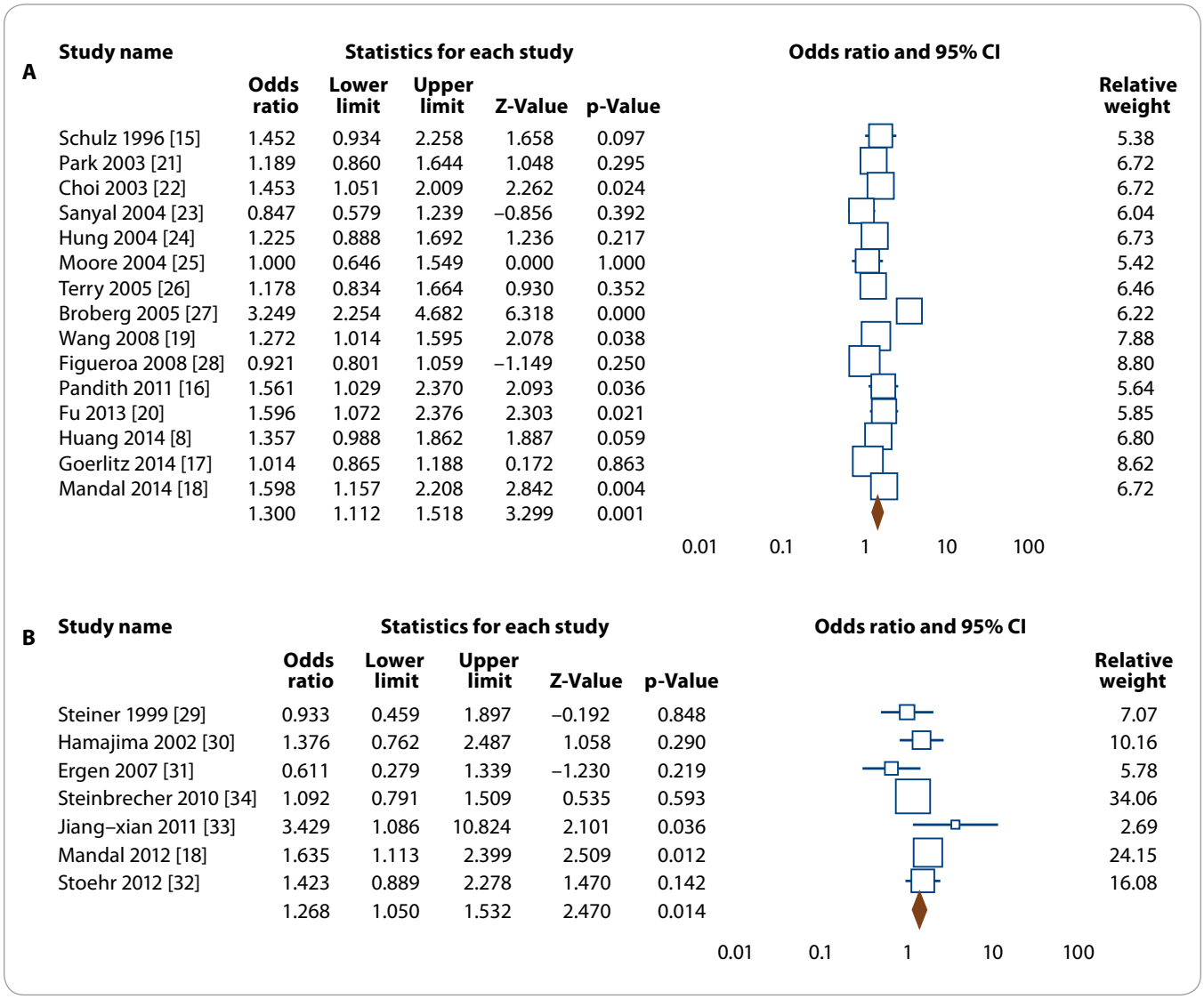

Fig. 2. Forest plot for association of *NQO1* rs1800566 polymorphism with risk of bladder and prostate cancers.
A. Bladder cancer (allele model T vs. C).
B. Prostate cancer (dominant model TT + TC vs. CC).

excluded. Among these studies, 46 studies were excluded because they did not report useful data for meta-analysis, or were a review, case only study, and not being case-control studies. Finally, 22 case-control studies including 15 studies with 4,413 cases and 4,275 controls for bladder cancer [8,15–28] and 7 studies with 762 cases and 1,813 controls for prostate cancer [18,29–34] were included to the meta-analysis. The main characteristics of the studies are shown in Tab. 1. All included studies were published between 2005 and 2013. The studies have been carried out in Germany (N = 4), USA (N = 2), Sweden (N = 2), India (N = 3), China (N = 2), Taiwan (N = 2), Korea (N = 1), Italy (N = 1), Argentina (N = 1), Spain (N = 1), Egypt (N = 1), Japan (N = 1), and Turkey (N = 1). As for ethnicity, 12 studies were conducted on Caucasians, 9 studies on Asians, and 1 article on Africans. A total of 16 polymerase chain reaction-restriction fragment length polymorphism, 3 mass spectrometry, and 1 TaqMan genotyping approach were used. The genotype and minor allele frequency distributions in the studies considered in the present meta-analysis are shown in Tab. 1. Moreover, the distribution of genotypes in the controls was in agreement with HWE for all selected studies, except for one study for prostate cancer (Tab. 1).

Quantitative synthesis

Bladder cancer

The summary of the meta-analysis of the association of *NQO1* rs1800566 polymorphism with bladder cancer is shown in Tab. 2. Overall, pooled ORs showed that there was a significant association between *NQO1* rs1800566 polymorphism and bladder cancer risk under four genetic models, i.e., allele (T vs. C: OR 1.300, 95% CI 1.112–1.518, P = 0.001) (Fig. 2A), homozygote (TT vs. CC: OR 1.415, 95% CI 1.084–1.847, P = 0.011),

Tab. 2. Summary of meta-analysis for the association of *NQO1* rs1800566 polymorphism with risk of bladder and prostate cancers.

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z-test	POR	P_{Beggs}	P_{Eggers}
Bladder Cancer										
Overall	T vs. C	random	76.45	≤ 0.001	1.300	1.112–1.518	3.299	0.001	0.276	0.014
	TT vs. CC	random	47.96	0.020	1.415	1.084–1.847	2.555	0.011	0.198	0.081
	TC vs. CC	random	79.68	≤ 0.001	1.389	1.111–1.738	2.879	0.004	0.620	0.064
	TT + TC vs. CC	random	81.29	≤ 0.001	1.428	1.145–1.782	3.157	0.002	0.198	0.023
	TT vs. TC + CC	fixed	31.43	0.117	1.169	0.987–1.519	1.838	0.066	0.488	0.209
Ethnicity										
Caucasian	T vs. C	random	84.98	≤ 0.001	1.283	0.963–1.709	1.706	0.088	0.710	0.171
	TT vs. CC	fixed	38.57	0.122	0.986	0.748–1.300	–0.098	0.922	0.018	0.084
	TC vs. CC	random	88.49	≤ 0.001	1.405	0.934–2.115	1.630	0.103	1.000	0.257
	TT + TC vs. CC	random	88.88	≤ 0.001	1.398	0.939–2.082	1.648	0.099	1.000	0.205
	TT vs. TC + CC	fixed	6.630	0.379	0.938	0.714–1.232	–0.459	0.646	0.173	0.178
Asian	T vs. C	fixed	0.00	0.842	1.421	1.249–1.616	5.357	≤0.001	0.259	0.027
	TT vs. CC	fixed	0.00	0.880	1.890	1.445–2.472	4.648	≤0.001	0.259	0.148
	TC vs. CC	fixed	0.00	0.757	1.469	1.208–1.787	3.857	≤0.001	1.000	0.922
	TT + TC vs. CC	fixed	0.00	0.961	1.583	1.318–1.901	4.919	≤0.001	1.000	0.500
	TT vs. TC + CC	fixed	0.00	0.443	1.498	1.183–1.897	3.359	0.001	0.259	0.191
Prostate Cancer										
Overall	T vs. C	random	55.59	0.036	1.194	0.940–1.518	1.453	0.145	1.000	0.909
	TT vs. CC	random	62.56	0.014	1.348	0.689–2.641	0.872	0.383	1.000	0.938
	TC vs. CC	fixed	1.030	0.416	1.276	1.047–1.555	2.410	0.016	1.000	0.942
	TT + TC vs. CC	fixed	38.31	0.137	1.268	1.050–1.532	2.470	0.014	1.000	0.908
	TT vs. TC + CC	random	53.74	0.043	1.171	0.669–2.051	0.553	0.580	0.763	0.867
Ethnicity										
Caucasian	T vs. C	fixed	35.99	0.196	1.017	0.831–1.244	0.163	0.871	1.000	0.812
	TT vs. CC	fixed	50.78	0.107	0.766	0.417–1.406	–0.861	0.389	0.734	0.491
	TC vs. CC	fixed	0.00	0.423	1.146	0.895–1.468	1.081	0.280	0.308	0.170
	TT + TC vs. CC	fixed	14.52	0.320	1.088	0.858–1.380	0.699	0.489	0.308	0.431
	TT vs. TC + CC	fixed	48.03	0.123	0.767	0.423–1.390	–0.875	0.382	0.308	0.409
Asian	T vs. C	fixed	35.19	0.214	1.472	1.174–1.844	3.358	0.001	1.000	0.882
	TT vs. CC	fixed	48.33	0.144	2.063	1.247–3.414	2.818	0.005	1.000	0.722
	TC vs. CC	fixed	0.00	0.533	1.544	1.110–2.148	2.577	0.010	0.296	0.257
	TT + TC vs. CC	fixed	0.00	0.383	1.646	1.207–2.244	3.148	0.002	1.000	0.519
	TT vs. TC + CC	fixed	45.83	0.158	1.568	0.995–2.470	1.940	0.052	1.000	0.890

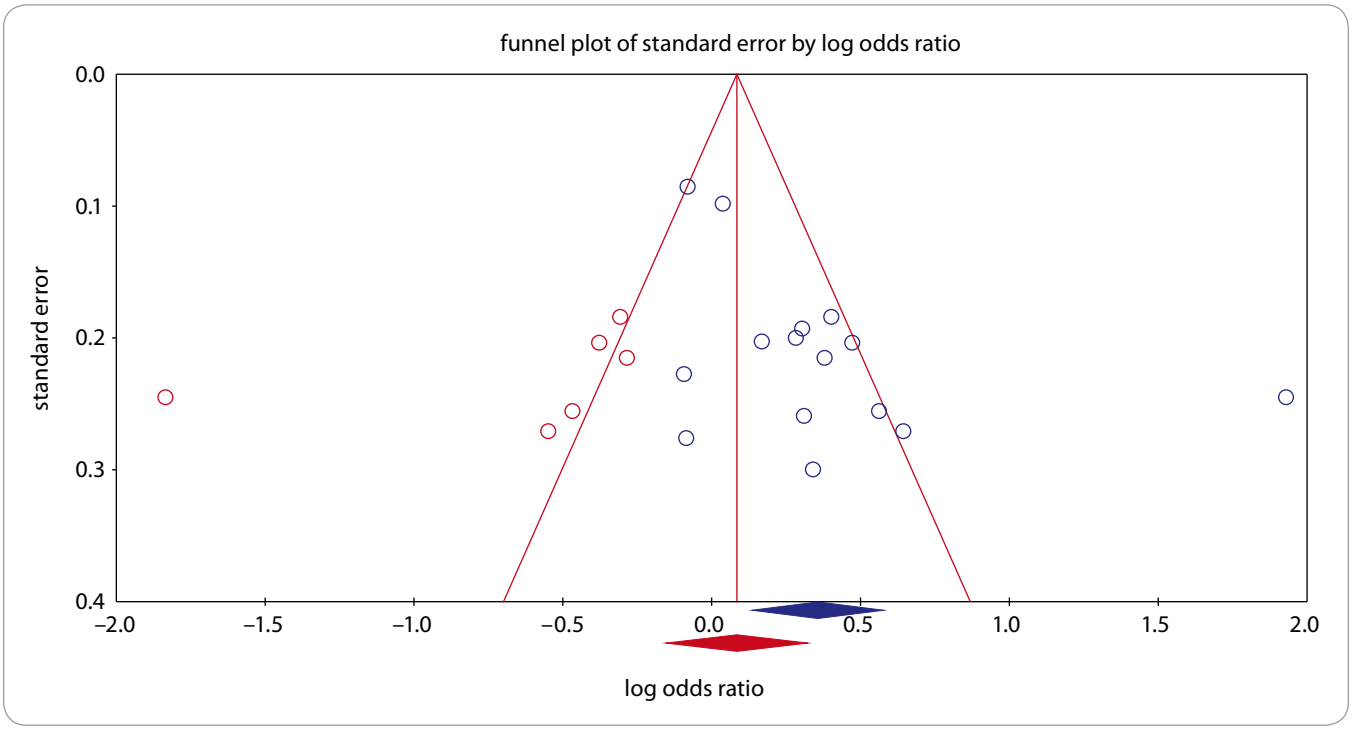

Fig. 3. Funnel plot for publication bias in the meta-analysis of *NQO1* rs1800566 polymorphism with bladder cancer under dominant model (TT + TC vs. CC).

heterozygote (TC vs. CC: OR 1.389, 95% CI 1.111–1.738, P = 0.004), and dominant (TT + TC vs. CC: OR 1.428, 95% CI 1.145–1.782, P = 0.002). Stratified analysis by ethnicity revealed that there was a significant association between *NQO1* rs1800566 polymorphism and bladder cancer among Caucasians using all five genetic models, i.e., allele (T vs. C: OR 1.421, 95% CI 1.249–1.616, P ≤ 0.001), homozygote (TT vs. CC: OR 1.890, 95% CI 1.445–2.472, P ≤ 0.001), heterozygote (TC vs. CC: OR 1.469, 95% CI 1.208–1.787, P ≤ 0.001), dominant (TT + TC vs. CC: OR 1.583, 95% CI 1.318–1.901, P ≤ 0.001), and recessive (TT vs. TC + CC: OR 1.498, 95% CI 1.183–1.897, P = 0.001), but not in Asian population.

Prostate Cancer

The summary of the meta-analysis of the association of *NQO1* rs1800566 polymorphism with prostate cancer is shown in Tab. 2. Overall, pooled ORs showed that there was a significant association between *NQO1* rs1800566 polymorphism and prostate cancer risk under two genetic models, i.e., heterozygote (TC vs. CC: OR 1.276, 95% CI 1.047–1.555, P = 0.016), and dominant (TT + TC vs. CC: OR 1.268, 95% CI 1.050–1.532, P = 0.014) (Fig. 2B). Stratified analysis by ethnicity revealed that there was a significant association between *NQO1* rs1800566 polymorphism and prostate cancer among Asians under all four genetic models, i.e., allele (T vs. C: OR 1.472, 95% CI 1.174–1.844, P = 0.001), homozygote (TT vs. CC: OR 2.063, 95% CI 1.247–3.414, P = 0.005), heterozygote (TC vs. CC: OR 1.544, 95% CI 1.110–2.148, P = 0.010), dominant (TT + TC vs. CC: OR 1.646, 95% CI 1.207–2.244, P = 0.002), but not under Caucasians.

Heterogeneity test and sensitivity analyses

There was a statistically significant heterogeneity for both bladder cancer and prostate cancer in the overall analysis. Thus, we performed subgroup analyses by ethnicity and HWE status to explain the potential source of heterogeneity. As shown in Tab. 2, most heterogeneity disappeared in the subgroup analysis by ethnicity among Asians and Caucasians, indicating that ethnicity might be the major source of heterogeneity in this meta-analysis. Moreover, we performed a sensitivity analysis to assess the influence of each study on pooled results and robustness of our results by sequential omission of each eligible study. However, the pooled results showed that the significance of the OR was not affected by any single study. Then, sensitivity analysis was conducted by excluding those studies departure from the HWE. Therefore, the sensitivity analysis suggested that the current meta-analysis were relatively consistent even when a single study or some studies were excluded.

Publication bias

Publication bias was assessed with Begg's funnel plots and Egger's test (Tab. 2). The shapes of the funnel plots and Egger's test did not show any evidence of publication bias in the overall and subgroup analysis by ethnicity for prostate cancer. However, the results of Begg's funnel plots and Egger's regression test suggested evidence of publication bias for bladder cancer in overall under two genetic models, i.e., allele (P_{Beggs} = 0.276; P_{Eggers} = 0.014) and dominate (P_{Beggs} = 0.198; P_{Eggers} = 0.023; Fig. 3), and by subgroup analysis among Asians under the allele model (P_{Beggs} = 0.259;

P_{Eggers} = 0.027). Thus, to adjust these biases, we used a trim-and-fill method developed by Duval and Tweedie. However, after trimming, we obtained similar results, indicating that the results were statistically reliable.

Discussion

In this meta-analysis, a total of 22 case-control studies including 15 studies on bladder cancer and 7 on prostate cancer were selected to provide the most comprehensive assessment of the association of *NQO1* rs1800566 polymorphism with bladder cancer and prostate cancer risk. The current meta-analysis results showed that the *NQO1* rs1800566 polymorphism is significantly associated with bladder and prostate cancers. Moreover, stratified analysis by ethnicity showed that the *NQO1* rs1800566 polymorphism was significantly associated with an increased risk of bladder and prostate cancers in Caucasians and Asians, respectively. In view of the complex effect of genetic variations on tumorigenesis, the lack of an increased risk of bladder and prostate cancers with *NQO1* rs1800566 polymorphism in other populations might be attributed to genetic backgrounds and environmental factors of those populations.

The current meta-analysis results are inconsistence with previous meta-analysis investigating the association between *NQO1* rs1800566 polymorphism in the prostate cancer risk. In 2014, Zhang et al., in a meta-analysis of 6 case-control studies with 717 cases and 1,794 controls, failed to show a significant association between the *NQO1* rs1800566 polymorphism and prostate cancer risk in overall population. However, similarly to our results, they reported that the *NQO1* rs1800566 polymorphism might be a risk factor for development of prostate cancer in Asians [35]. However, Zhang et al., in meta-analysis of urinary system cancer including 5 case-controls on prostate cancer found that the *NQO1* rs1800566 polymorphism conferred genetic susceptibility to urinary system cancer including bladder cancer, prostate cancer, and renal cell carcinoma [11]. Moreover, our results are inconsistent with previous meta-analysis only focused on the role of *NQO1* rs1800566 polymorphism in the bladder cancer risk [36,37]. Recently, Wang et al. performed a meta-analysis on effects of *NQO1* rs1800566 polymorphism and smoking as an environment-related factor on bladder cancer susceptibility. Their meta-analysis included seven case-control studies with 1,341 cases and 1,346 controls, and showed that the *NQO1* rs1800566 polymorphism in smokers significantly increased risk of bladder cancer compared with non-smokers [12]. However, their estimates were based on crude pooled ORs, not adjusted OR values, such as ethnicity, which might be the cause of inaccurate results. Similarly, in 2014, Goerlitz et al., in a case-control study of 902 cases with bladder cancer and 804 population-based healthy subjects in Egypt found that the *NQO1* rs1800566 polymorphism plays an important role in the susceptibility to bladder cancer by modulating the effects of known contributing factors, such as smoking and also schistosoma haematobium infection [17].

Meta-analysis is an ideal tool to identify genetic association [38]. However, between-study heterogeneity can distort the results of a meta-analysis [39,40]. Several factors, such as diversity in study design, sample size, ethnicity, source of controls, genotyping method, and deviation from HWE might contribute to results heterogeneity [41,42]. To identify possible factors that contributed to high heterogeneity, we performed subgroup analysis by ethnicity. The overall heterogeneity no longer existed in subgroup analysis, thus we hypothesized that ethnicity was the main source of between-study heterogeneity in this meta-analysis.

Some limitations in this meta-analysis must be addressed. First, the small sample size for prostate cancer was the major defect in this meta-analysis. Thus, well-designed studies with large sample size are needed to further investigate the association between *NQO1* rs1800566 polymorphism and prostate cancer risk. Second, we mostly focused on studies published in English and Chinese, which might have led to publication bias. Third, the study populations were dominantly Caucasian and Asian. The subgroup meta-analysis for ethnicity had little or no information for other ethnic groups, such as Africans and mixed populations. Forth, several important confounding factors, such as age, gender (for bladder cancer), drinking, smoking, and disease stages were not considered for stratified analysis because relevant data were insufficient in the selected studies. Finally, bladder and prostate cancers are mainly caused by gene-gene and gene-environment interactions. However, no appropriate information was available for further analysis and data sorting. Therefore, further large-scale studies in different populations with more detailed data, with different environmental background are required to validate gene-gene and gene-environment interactions on *NQO1* rs1800566 polymorphism with risk of bladder and prostate cancers.

In summary, the results of meta-analysis suggested that the *NQO1* rs1800566 polymorphism was significantly associated with an increased risk of bladder and prostate cancers. Moreover, *NQO1* rs1800566 polymorphism was significantly associated with risk of bladder cancer and prostate cancer in Caucasians and Asians, respectively. However, well-designed and large studies are needed to further investigate the association of these polymorphisms with breast cancer susceptibility.

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