

Association between *APEI* Asp148Glu polymorphism and the risk of urinary cancers: a meta-analysis of 18 case–control studies

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Background: Several observational studies suggested that *APEI* Asp148Glu was significantly associated with urinary cancers; however, the results of published studies are inconsistent.

Materials and methods: The PubMed and EMBASE were searched for case–control studies regarding the association between Asp148Glu and the risk of urinary cancers with a time limit of September 12, 2015. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association between Asp148Glu and the risk of developing prostate cancer, kidney cancer, bladder cancer, as well as all urinary cancers combined.

Results: A total of 18 case–control studies were included in the analysis. Our meta-analysis revealed that the inheritance of at least one *APEI* 148Glu among Asian men was associated with a 1.26-fold increase in the risk of developing urinary cancers. Meanwhile, *APEI* Asp148Glu was significantly associated with the risk of prostate cancer. However, there were no significant relationships between the *APEI* SNP (single nucleotide polymorphism) and all urinary cancers combined and bladder cancer and kidney cancer among the men of Caucasian/Asian/African descent or all racial/ethnic groups combined. When stratified by the quality score, no significant association was found in high-quality studies (score ≥ 7), but a significant increased risk of urinary cancers was observed in lower quality studies (score < 7) (dominant model: OR=1.27, 95% CI=1.11–1.45).

Conclusion: Our meta-analysis suggests that *APEI* Asp148Glu was not associated with the risk of urinary cancers but might increase the risk of urinary cancers among Asians. Stratification by cancer type identified a significant association of Asp148Glu with prostate cancer.

Keywords: *APEI*, polymorphism, cancer, meta-analysis

Introduction

Urinary cancers, including kidney cancer, prostate cancer and bladder cancer, are common types of malignancies worldwide.¹ For example, prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% of the total new cancer cases and 6% of the total cancer deaths in males in 2008.¹ Bladder cancer is the seventh most common cancer among men, with ~297,300 new incident cases per year in the world.¹ The estimated probability of developing urinary cancers is based on the average experience of the general population and may over- or underestimate individual risk because of differences in exposure, medical history, and/or genetic susceptibility.²

DNA repair genes play a major role in the DNA mismatch repair pathway, which includes base excision repair (BER), nucleotide excision repair, mismatch repair, and double strand break repair.³ Genetic variations in genes involved in DNA repair

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would confer susceptibility to the tumor and would be associated to disease aggressiveness through the alteration of DNA repair pathways.⁴ Among them, BER pathway is responsible for repairing small lesions such as oxidative damage, alkylation, or methylation.⁵ This pathway is a multistep process that requires the activity of several proteins.⁶ Apurinic/apyrimidinic endonuclease 1 (APE1, also known as APE, APEX, HAP1, and REF-1) is a multifunctional protein that plays a central role in the BER pathway through hydrolyzing the phosphodiester backbone immediately 5' to the AP site.^{5,7} APE1 can act as a 3'-phosphodiesterase to initiate the repair of 3'-blocking damage at DNA single-strand breaks, which are produced either directly by reactive oxygen species or indirectly through the enzymatic removal of damaged bases.^{8,9} It also acts as a transcriptional coactivator for numerous transcription factors (AP-1, p53, Pax-5, and TTF-1) involved in cancer development.¹⁰

The human *APE1* gene (2.6 kb in size) is localized to chromosome 14q11.2-12 and consists of four introns and five exons.^{11,12} A total of 18 polymorphisms in *APE1* have been identified.¹³ But the most extensively studied polymorphism is a T to G transversion, Asp148Glu (rs1130409 and T1349G). It was reported that the Glu was associated with an increased mitotic delay after exposure to ionizing radiation.^{13,14} Functional studies on *APE1* Asp148Glu suggested that the Glu may alter endonuclease and DNA-binding activity, reduce the ability to communicate with other BER proteins, and decrease the capacity to repair DNA oxidative damage.¹⁵ In the study on X-ray exposure to lymphocytes and polymorphisms of DNA repair genes on chromosome aberrations, samples from individuals with the Asp/Glu or Glu/Glu genotype showed higher levels of damage with regard to all the studied measures, including aberrant cells, chromatid breaks, chromatid exchanges, deletions, and dicentric.¹⁶ Although numerous epidemiological studies have been conducted to explore the association between *APE1* Asp148Glu and the risk of urinary cancers,¹⁷⁻³⁷ the results are to some extent inconsistent, which may be due to the limitations in individual studies. In this study, we combined all the published case-control studies regarding the association between *APE1* Asp148Glu and urinary cancers to better explore this genetic variation on the risk of developing urinary cancers.

Materials and methods

Study identification and selection

Case-control studies regarding the *APE1* Asp148Glu and the risk of urinary cancers published before September 12, 2015 were included through searches of PubMed and EMBASE by using the following terms and key words: "apurinic endonuclease" or "apyrimidinic endonuclease" or *APE1*

or *APEX* or *APEX1* or *HAP1* or *REF-1*; polymorphism or variant or variation or mutation; and kidney or renal or urothelial or "transitional cell carcinoma" or bladder or prostatic or prostate. The search was limited to human studies. The criteria used for the study selection were as follows: 1) the articles were concerned about the association between *APE1* Asp148Glu and urinary cancers, including prostate cancer, kidney cancer, and bladder cancer; 2) the studies were designed as case-control studies; 3) detailed genotyping data were available; and 4) there were no overlapping data.

Data extraction

Information was carefully extracted from all the eligible studies independently by three investigators according to the selection criteria listed earlier. The following data were collected: first author's name, publication year, country, ethnicity (categorized as Asians, Caucasians, or the African-Americans), source of controls, genotyping method, numbers of cases and controls, genotype frequency of cases and controls, and the result of Hardy-Weinberg equilibrium (HWE) test. We did not require a minimum number of patients to be included in our meta-analysis.

Quality score assessment

The study quality was assessed by using a quality assessment score developed for genetic association studies by Thakkestian et al.³⁸ Total scores range from 0 (worst) to 12 (best). The criteria for quality assessment of genetic associations between the *APE1* Asp148Glu and urinary cancers are described in Table S1.

Statistical analysis

Data in the control group were used to estimate a pooled allelic prevalence. HWE was tested by chi-squared test ($P < 0.05$ was considered representative of statistical significance). The minor allele frequency was also calculated for the controls. The strength of association between *APE1* Asp148Glu and the risk of urinary cancers was measured by odd ratios (ORs) with 95% confidence intervals (CIs). The pooled ORs were calculated for recessive model (Glu/Glu vs Asp/Glu+Asp/Asp), dominant model (Glu/Glu+Asp/Glu vs Asp/Asp), homozygote comparison (Glu/Glu vs Asp/Asp), heterozygote comparison (Asp/Glu vs Asp/Asp) and additive model (Glu vs Asp). Heterogeneity assumption was checked by a chi-square-based Q test, and I^2 statistics was calculated to quantify the proportion of the total variation across studies due to heterogeneity.³⁹ A P -value of > 0.05 for the Q test indicated a lack of heterogeneity among studies, so that the pooled OR estimate of each study

was calculated by the fixed-effects model (the Mantel–Haenszel method).⁴⁰ Otherwise, the random-effects model (the DerSimonian and Laird method) was used.⁴¹ Subgroup analyses were conducted according to ethnicity (ie, Asians, African–Americans, Caucasians), cancer type (ie, all urinary cancers, kidney cancer, prostate cancer, and bladder cancer), genotyping methods (ie, polymerase chain reaction–restriction fragment length polymorphism [PCR–RFLP] and TaqMan), source of control (ie, population based and hospital based), and quality score (score <7 or score ≥7). Sensitivity analyses were performed to test the reliability of results by sequential omission of individual studies.⁴² Publication bias is the tendency on the parts of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings.⁴³ An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was further assessed by the method of Egger’s linear regression test ($P < 0.05$ was considered a significant publication bias).⁴⁴ Statistical analyses were performed by using STATA statistical software (version 11.0).

Results

Extraction process and study characteristics

The selection process of the studies is presented in Figure 1. In total, 419 potentially relevant articles were identified after

the initial search, and 20 of them concentrated on the *APE1* Asp148Glu. Also, four additional articles were identified from retrieved articles. Thus, following implementation of our search criteria, we found 24 publications on the association between *APE1* Asp148Glu and the risk of urinary cancers.^{10,17,19–28,30–37,45–48} Among them, eight studies were excluded because of duplicated data or lack of usable data.^{10,24,26,31,35,45,46,48} Because the two studies by Andrew et al^{18,25} contain overlapping data and the source of control in one of them²⁵ is mixed, the study by Andrew et al¹⁸ was excluded when calculating the pooled OR, while the study by Andrew et al²⁵ was excluded when conducting the subgroup analysis according to the source of controls. Hence, 16 publications including 18 studies (5,539 cases and 7,348 controls) were selected in the meta-analysis. Table 1 lists the studies identified and their main characteristics. Of them, there were ten bladder cancer studies, seven prostate cancer studies, and one kidney cancer study. There were six studies^{32,33,36,37,47} involving Asians, ten studies with Caucasians,^{17,19–23,25,27,28,34} and two studies with African–Americans.^{19,30} The quality of all 18 studies ranged from 3 to 12, with a mean value of 6.9 (standard deviation: 2.18). The distribution of genotypes in the controls of each study was consistent with HWE except for two studies,^{28,34} which were not included in further pooling (Table 2). The pooled prevalence of the Glu were 0.424 (95% CI=0.393–0.456) in control group, while the pooled prevalence of the Glu among Asians were 0.383 (95% CI=0.311–0.456), Caucasians

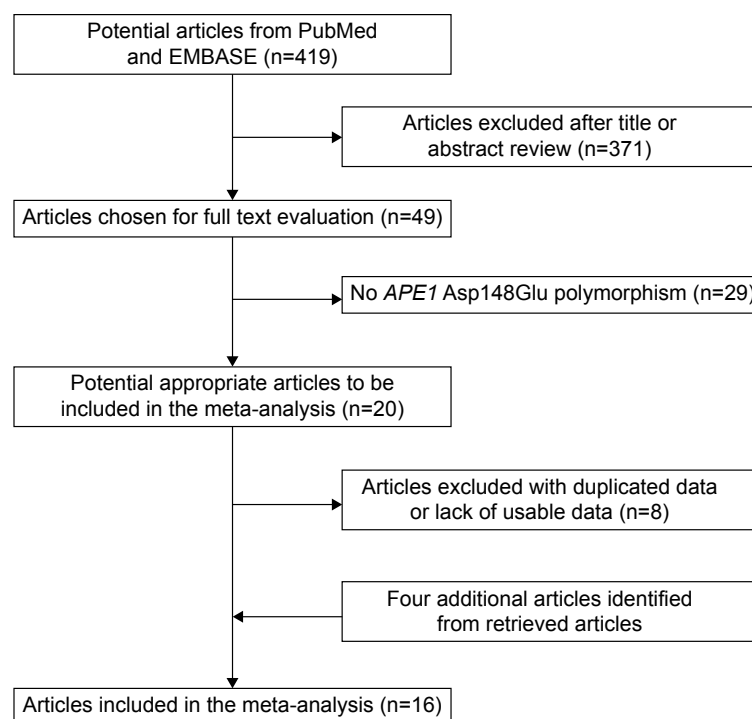


Figure 1 Flow diagram of the studies included in this meta-analysis.

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Quality score	Ethnicity	Region	Cancer type	Genotyping	Control source	Cases/controls
Broberg et al ¹⁷	2005	6	Caucasian	Sweden	BC	TaqMan	PB	61/155
Matullo et al ²⁰	2006	3	Caucasian	Multiple countries	BC	TaqMan	PB	124/1,094
Wu et al ²²	2006	9	Caucasian	USA	BC	TaqMan	HB	596/590
Terry et al ²¹	2006	6	Caucasian	USA	BC	MALDI-TOF	HB	229/207
Chen et al ¹⁹	2006	6	Caucasian	USA	PCa	PCR-RFLP	HB	228/217
Chen et al ¹⁹	2006	6	African	USA	PCa	PCR-RFLP	HB	123/112
Figueroa et al ²³	2007	7	Caucasian	Spain	BC	TaqMan	HB	1,094/1,013
Andrew et al ²⁵	2008	8	Caucasian	USA/Italy	BC	SNP mass-tagging system	Mixed	911/1,165
Michiels et al ²⁷	2009	10	Caucasian	France	BC	Illumina	HB	189/316
Narter et al ²⁸	2009	4	Caucasian	Turkey	BC	PCR-RFLP	NR	75/35
Wang et al ³²	2010	6	Asian	People's Republic of China	BC	PCR-RFLP	HB	234/253
Lavender et al ³⁰	2010	10	African	USA	PCa	TaqMan	HB	186/631
Cao et al ³³	2011	6	Asian	People's Republic of China	KC	TaqMan	HB	612/632
Kuasne et al ³⁴	2011	4	Caucasian	Brazil	PCa	PCR-RFLP	HB	172/172
Mittal et al ³⁶	2012	9	Asian	India	BC	PCR-RFLP and ARMS	PB	212/250
Mittal et al ³⁶	2012	9	Asian	India	PCa	PCR-RFLP and ARMS	PB	195/250
Jing et al ³⁷	2013	10	Asian	People's Republic of China	PCa	PCR-RFLP	HB	198/156
Pournourali et al ⁴⁷	2015	6	Asian	Iran	PCa	PCR-RFLP	HB	100/100

Abbreviations: SNP, single nucleotide polymorphism; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; TaqMan, real-time TaqMan analysis; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; ARMS, amplification refractory mutation specific; BC, bladder cancer; PCa, prostate cancer; KC, kidney cancer; PB, population based; HB, hospital based.

0.467 (95% CI=0.454–0.480), and African–Americans 0.354 (95% CI=0.354–0.378).

Meta-analysis results

Table 3 lists the main results of the meta-analysis for *APE1* Asp148Glu. Overall, no significant association was found between Asp148Glu and the risk of urinary cancers

(dominant model: OR=1.06, 95% CI=0.98–1.15; Figure 2A). In the stratified analysis by ethnicity, we did not find significant associations among Caucasians (dominant model: OR=1.06, 95% CI=0.96–1.17; Table 3). Similarly, no significant associations were observed among the African–Americans (dominant model: OR=1.02, 95% CI=0.77–1.35; Table 3). However, among Asians, the individuals who

Table 2 Genotype distribution of *APE1* Asp148Glu used in the meta-analysis

References	Year	Ethnicity	Cancer type	Control source	Sample size (case/control)	Case (genotype %)			Control (genotype %)			HWE	MAF	
						AA	Aa	aa	AA	Aa	aa			
Broberg et al ¹⁷	2005	Caucasian	BC	PB	61	155	9	35	17	37	79	39	0.81	0.51
Matullo et al ²⁰	2006	Caucasian	BC	PB	124	1,094	31	69	24	309	526	259	0.23	0.48
Wu et al ²²	2006	Caucasian	BC	HB	596	590	176	283	137	166	279	145	0.20	0.48
Terry et al ²¹	2006	Caucasian	BC	HB	229	207	51	133	45	63	104	40	0.80	0.44
Chen et al ¹⁹	2006	Caucasian	PCa	HB	228	217	65	122	41	73	108	36	0.71	0.41
Chen et al ¹⁹	2006	African	PCa	HB	123	112	42	64	17	42	59	11	0.14	0.36
Figueroa et al ²³	2007	Caucasian	BC	HB	1,094	1,013	335	510	249	292	491	230	0.39	0.47
Andrew et al ²⁵	2008	Caucasian	BC	Mixed	911	1,165	259	461	191	333	586	246	0.69	0.46
Michiels et al ²⁷	2009	Caucasian	BC	HB	189	316	53	96	40	94	154	68	0.74	0.46
Narter et al ²⁸	2009	Caucasian	BC	NR	75	35	50	14	11	27	4	4	0.00	0.17
Wang et al ³²	2010	Asian	BC	HB	234	253	78	116	40	84	129	40	0.41	0.41
Lavender et al ³⁰	2010	African	PCa	HB	186	631	82	88	16	274	269	88	0.10	0.35
Cao et al ³³	2011	Asian	KC	HB	612	632	181	292	139	199	329	104	0.10	0.43
Kuasne et al ³⁴	2011	Caucasian	PCa	HB	172	172	84	83	5	106	64	2	0.02	0.20
Mittal et al ³⁶	2012	Asian	BC	PB	212	250	126	82	4	141	92	17	0.71	0.25
Mittal et al ³⁶	2012	Asian	PCa	PB	195	250	108	72	15	136	101	13	0.30	0.25
Jing et al ³⁷	2013	Asian	PCa	HB	198	156	66	98	34	60	73	23	0.92	0.38
Pournourali et al ⁴⁷	2015	Asian	PCa	HB	100	100	15	60	25	30	50	20	0.92	0.45

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; A, major allele; a, minor allele; BC, bladder cancer; PCa, prostate cancer; KC, kidney cancer; PB, population based; HB, hospital based.

Table 3 Stratified analyses of Asp148Glu on the risk of urinary cancers

Genetic model Asp148Glu N*	Recessive model			Dominant model			Homozygote			Heterozygote			Additive model			
	Glu/Glu vs Asp/Glu+Asp/Asp			Glu/Glu+Asp/Glu vs Asp/Asp			Glu/Glu vs Asp/Asp			Asp/Glu vs Asp/Asp			Glu vs Asp			
	OR (95% CI)	P _h	I ² (%)	OR (95% CI)	P _h	I ² (%)	OR (95% CI)	P _h	I ² (%)	OR (95% CI)	P _h	I ² (%)	OR (95% CI)	P _h	I ² (%)	
UC	18 (5,539/7,348)	1.03 (0.94–1.13)	0.148	26.2	1.06 (0.98–1.15)	0.176	23.5	1.06 (0.95–1.19)	0.072	34.9	1.07 (0.98–1.16)	0.236	18.2	1.04 (0.98–1.09)	0.173	23.8
Ethnicity																
Caucasian	10 (3,679/4,964)	0.98 (0.88–1.10)	0.952	0	1.06 (0.96–1.17)	0.105	37.9	1.02 (0.89–1.16)	0.678	0	1.08 (0.97–1.19)	0.120	36.0	1.02 (0.96–1.09)	0.303	15.3
Asian	6 (1,551/1,641)	1.26 (1.03–1.54)	0.085	48.3	1.08 (0.93–1.25)	0.197	31.8	1.25 (0.84–1.84)	0.047	55.5	1.03 (0.89–1.21)	0.260	23.2	1.10 (1.00–1.22)	0.169	35.7
African	2 (309/743)	0.77 (0.50–1.20)	0.063	71.1	1.02 (0.77–1.35)	0.589	0	1.06 (0.95–1.19)	0.081	67.1	1.09 (0.81–1.46)	0.982	0	0.95 (0.78–1.09)	0.203	38.3
Source of control																
PB	4 (592/1,749)	0.85 (0.67–1.07)	0.114	46.4	1.00 (0.84–1.19)	0.500	0	0.90 (0.69–1.17)	0.079	52.2	1.05 (0.87, 1.26)	0.482	0	0.96 (0.85–1.08)	0.484	0
HB	12 (3,961/4,399)	1.06 (0.95–1.19)	0.233	21.5	1.08 (0.98–1.19)	0.089	37.9	1.09 (0.96–1.24)	0.099	36.5	1.07 (0.97, 1.18)	0.127	33.0	1.05 (0.99–1.12)	0.113	34.6
Quality score																
≥7	8 (3,581/4,371)	0.95 (0.85–1.07)	0.152	34.6	0.97 (0.88–1.07)	0.933	0	1.06 (0.95–1.19)	0.072	34.9	0.99 (0.98–1.16)	0.929	0	0.97 (0.91–1.04)	0.173	23.8
<7	10 (1,958/2,977)	1.20 (1.02–1.41)	0.580	0	1.27 (1.11–1.45)	0.341	11.1	1.37 (1.14–1.66)	0.718	0	1.23 (1.07–1.42)	0.197	26.8	1.17 (1.07–1.28)	0.646	0
BC	10 (3,725/5,078)	0.96 (0.86–1.07)	0.598	0	1.01 (0.92–1.11)	0.407	3.6	0.98 (0.86–1.11)	0.386	6.0	1.03 (0.93–1.14)	0.392	5.3	0.99 (0.93–1.06)	0.636	0
Ethnicity																
Caucasian	8 (3,279/4,575)	0.97 (0.87–1.09)	0.972	0	1.02 (0.92–1.14)	0.269	20.3	0.99 (0.87–1.14)	0.772	0	1.04 (0.93–1.16)	0.226	25.4	1.00 (0.94–1.07)	0.657	0
Asian	2 (446/503)	0.59 (0.15–2.37)	0.020	81.7	0.94 (0.72–1.22)	0.660	0	0.58 (0.15–2.30)	0.025	80.1	0.98 (0.75–1.30)	0.916	0	0.93 (0.76–1.13)	0.226	31.8
Source of control																
PB	3 (397/1,499)	0.80 (0.63–1.02)	0.161	41.8	1.01 (0.83–1.23)	0.347	9.2	0.84 (0.63–1.12)	0.077	56.2	1.09 (0.89–1.34)	0.433	0	0.94 (0.83–1.07)	0.347	3.7
HB	5 (2,342/2,379)	0.99 (0.86–1.13)	0.970	0	0.99 (0.87–1.12)	0.292	19.3	0.98 (0.83–1.15)	0.718	0	0.99 (0.91–1.14)	0.262	23.9	0.99 (0.91–1.07)	0.655	0
PCa	7 (1,202/1,638)	1.08 (0.85–1.38)	0.270	21.0	1.21 (1.03–1.42)	0.155	35.8	1.23 (0.94–1.61)	0.127	39.7	1.12 (1.03–1.44)	0.236	25.3	1.12 (1.00–1.26)	0.177	32.9
Ethnicity																
Caucasian	2 (400/389)	1.19 (0.74–1.90)	0.342	0	1.45 (1.08–1.94)	0.350	0	1.42 (0.84–2.39)	0.313	1.7	1.44 (1.06–1.94)	0.410	0	1.26 (1.02–1.56)	0.225	32.0
Asian	3 (493/506)	1.31 (0.90–1.92)	0.889	0	1.21 (0.93–1.58)	0.070	62.4	1.61 (1.05–2.46)	0.497	0	1.16 (0.88–1.53)	0.063	63.9	1.18 (0.98–1.43)	0.359	2.3
African	2 (309/743)	0.77 (0.50–1.20)	0.063	71.1	1.02 (0.77–1.35)	0.589	0	0.80 (0.50–1.29)	0.081	67.1	1.09 (0.81–1.46)	0.982	0	0.95 (0.78–1.17)	0.203	38.3
Source of control																
PB	1 (195/250)	1.52 (0.71–3.27)	–	–	0.96 (0.66–1.40)	–	–	1.45 (0.66–3.18)	–	–	0.90 (0.61–1.33)	–	–	1.04 (0.77–1.41)	–	–
HB	6 (1,007/1,388)	1.04 (0.81–1.34)	0.234	26.7	1.27 (1.07–1.52)	0.179	34.3	1.20 (0.91–1.60)	0.081	48.9	1.30 (1.08–1.56)	0.381	5.6	1.14 (1.01–1.29)	0.124	42.1

Notes: P_h, P-values for heterogeneity from Q test. Random-effects model was used when P-value for heterogeneity test was less than 0.05, otherwise, fixed-effects model was used. *N= numbers of comparisons and the sample size (case/control).

Abbreviations: UC, urinary cancers; BC, bladder cancer; PCa, prostate cancer; PB, population based; HB, hospital based.

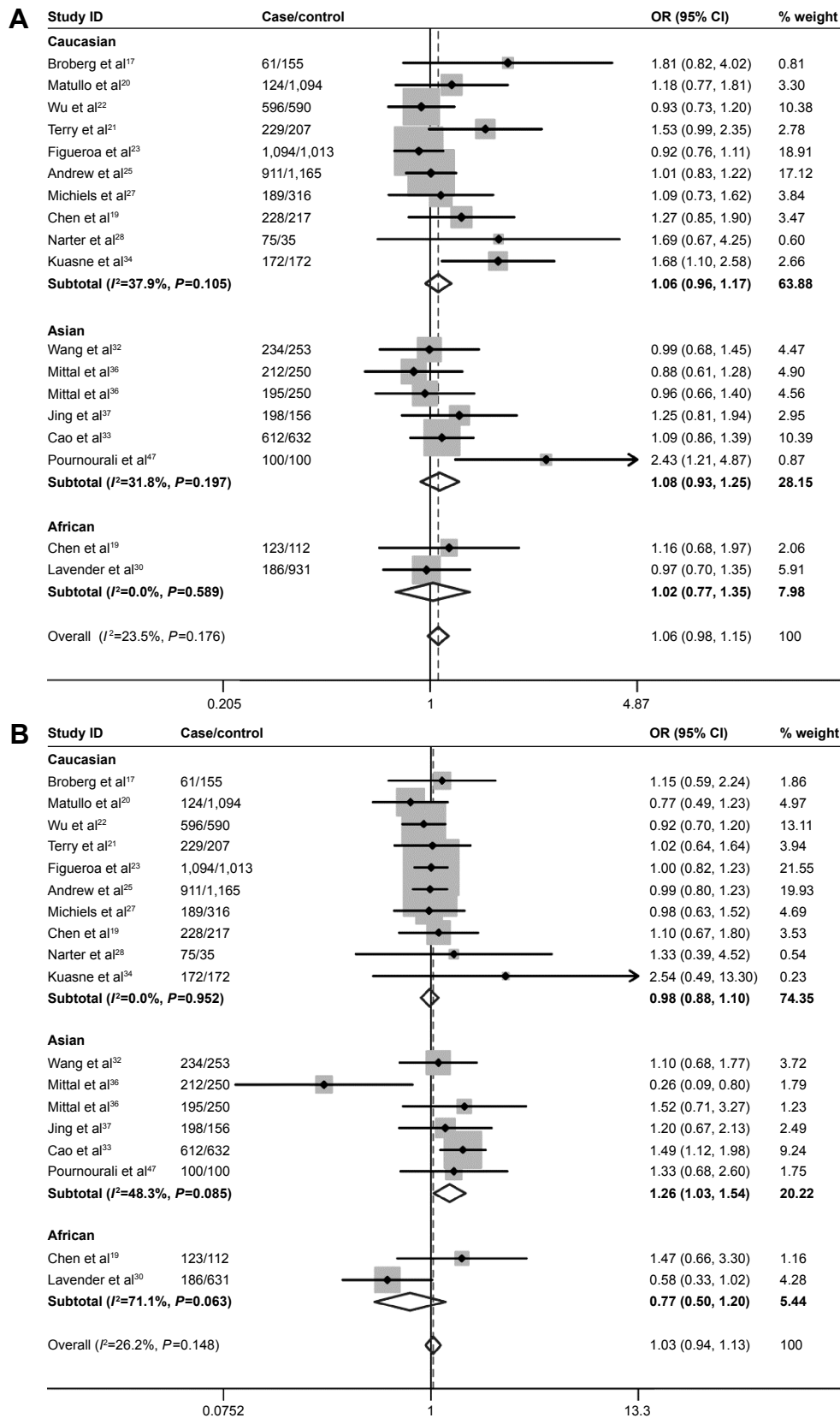


Figure 2 Forest plots of ORs with 95% CI for APEI Asp148Glu and the risk of urinary cancers observed in subgroup analyses by ethnicity (fixed effects).

Notes: The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. **(A)** Dominant model and **(B)** recessive model.

Abbreviations: CI, confidence interval; ORs, odds ratios.

carried the Glu/Glu genotype had an increased risk of urinary cancers (recessive model: OR=1.26, 95% CI=1.03–1.54, $P=0.022$; Table 3, Figure 2B). When stratified by the source of controls, no significant associations were found in both population-based studies and hospital-based studies (Table 3). When stratified by the quality score, no significant association was found in high-quality studies (score ≥ 7), but a significant increased risk of urinary cancers was observed in lower quality studies (score < 7) (dominant model: OR=1.27, 95% CI=1.11–1.45). Subgroup analyses based on cancer type also showed that there was no significant association of bladder cancer. However, significant association was found between Asp148Glu and the risk of prostate cancer (dominant model: OR=1.21, 95% CI=1.03–1.42, Figure 3A; heterozygote comparison: OR=1.12, 95% CI=1.03–1.44, Figure 3B; additive model: OR=1.12, 95% CI=1.00–1.26). Meanwhile, a significant increased risk of prostate cancer was observed among Caucasians (dominant model: OR=1.45, 95% CI=1.08–1.94; heterozygote comparison: OR=1.44, 95% CI=1.06–1.94; additive model: OR=1.26, 95% CI=1.02–1.56) and Asians (homozygote comparison: OR=1.61, 95% CI=1.05–2.46) but not African-Americans.

Test of heterogeneity and sensitivity analyses

The heterogeneity test showed that there was no significant heterogeneity in overall comparisons (Table 3). Although the genotype distributions in two studies^{28,34} did not follow the HWE, the corresponding pooled ORs were not materially altered by including or excluding the studies. Additionally, we also assessed the influence of each individual study on the pooled ORs by sequential omission of individual studies. The results showed that the pooled ORs of this polymorphism were altered by omission of the study by Figueroa et al²³ (Figure 4).

Publication bias

Begg's funnel plot and Egger's test were conducted to estimate the publication bias of studies. It was showed that Egger's test was significant for publication bias in heterozygote comparison ($P<0.001$), additive model ($P=0.04$), and dominant model ($P=0.001$). However, the Egger's test was not statistically significant for publication bias in recessive model ($P=0.893$) and homozygote comparison ($P=0.237$). It suggested that a possibility of publication bias could have existed in the studies.

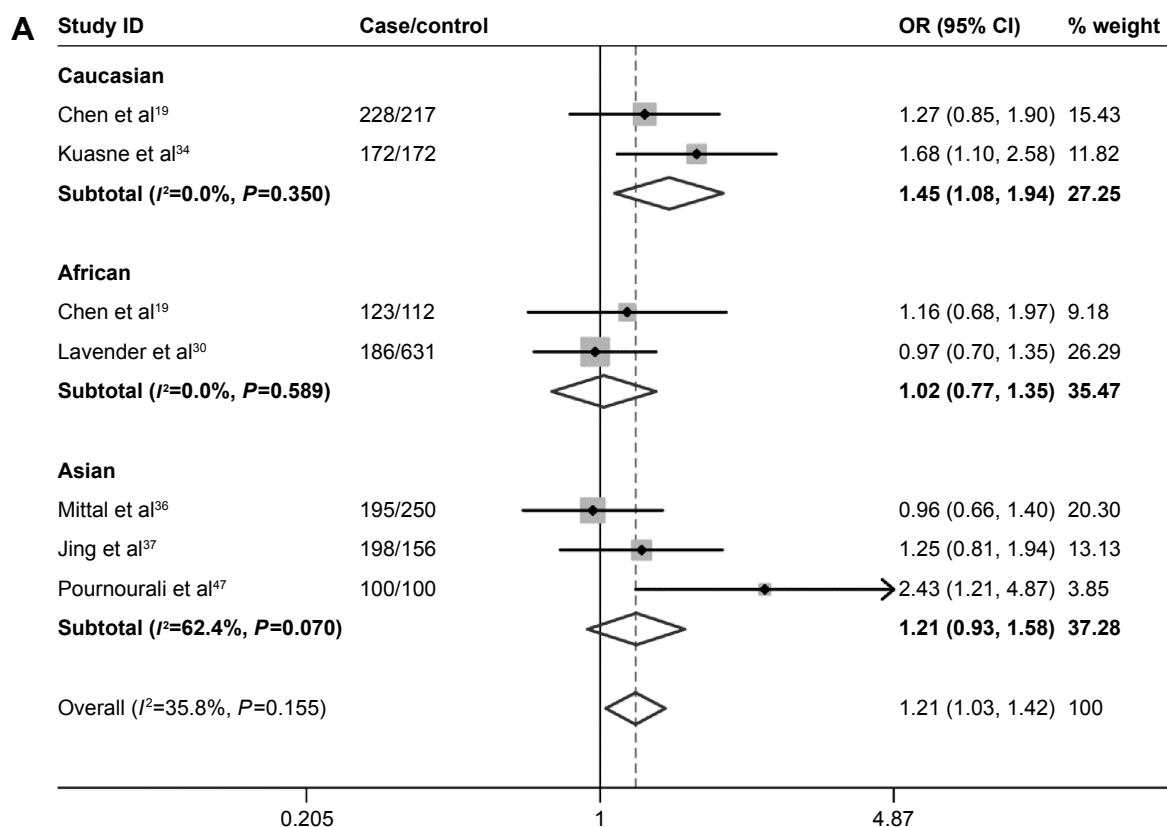


Figure 3 (Continued)

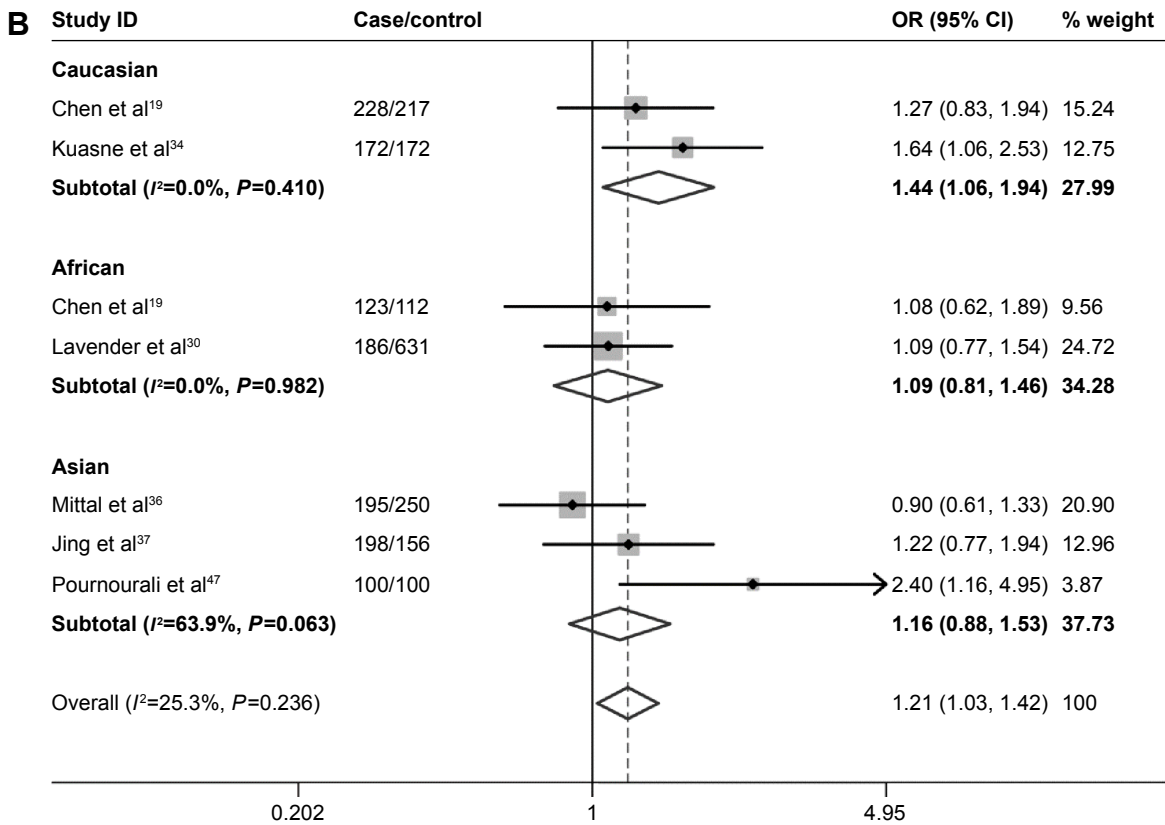


Figure 3 Forest plot of ORs with 95% CI for *APE1* Asp148Glu and the risk of prostate cancer in subgroup analyses by ethnicity (fixed effects).
Notes: The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. **(A)** Dominant model and **(B)** heterozygote comparison.
Abbreviations: CI, confidence interval; ORs, odds ratios.

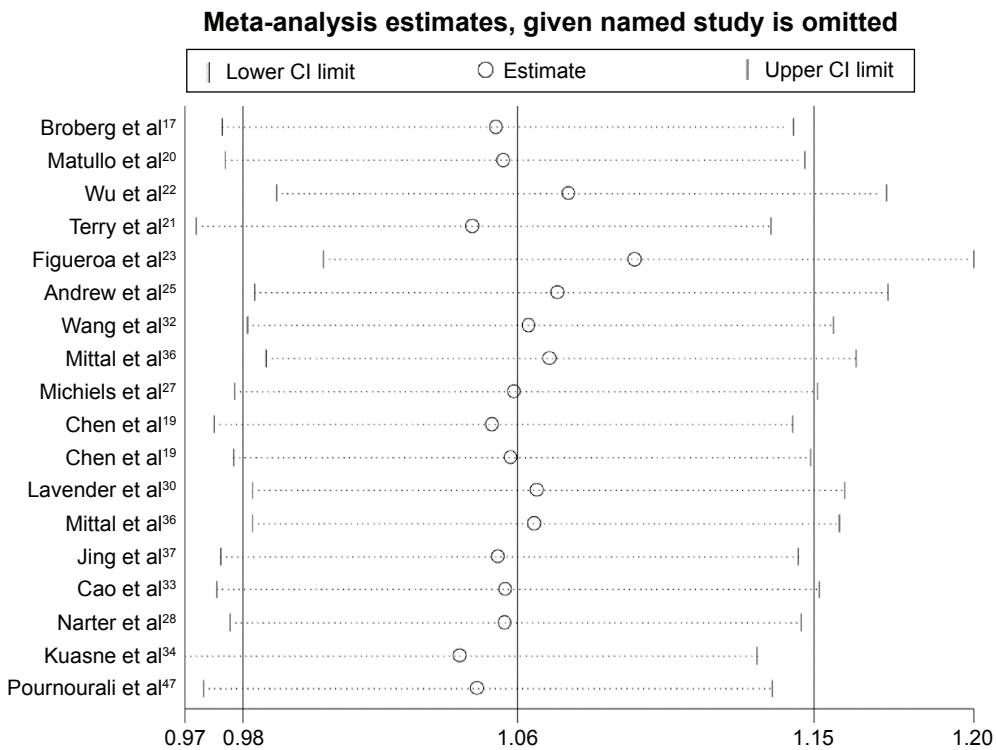


Figure 4 Sensitivity analyses for the robustness of association between *APE1* polymorphism and the risk of urinary cancers.
Note: The vertical line corresponds to the combined relative risk from the fixed effects model.
Abbreviation: CI, confidence interval.

Discussion

Numerous epidemiological studies have been conducted to explore the association between *APEI* Asp148Glu and the risk of urinary cancers.^{17,19–23,25,27,28,30–34,36,37} However, the results are to some extent inconsistent, which may be due to the limitations in individual studies. Meta-analysis has been widely used in epidemiological research, especially for evaluating genetic polymorphisms in cancer susceptibility. It can improve statistical power, subsequently drawing a more reliable conclusion.⁴⁹ Therefore, we performed a meta-analysis to explore the association between *APEI* Asp148Glu and the risk of urinary cancers. Our results indicated that the individuals who carried the Glu/Glu genotype have an increased risk of urinary cancers among Asians. Meanwhile, significant association was found between Asp148Glu and the risk of prostate cancer.

Several genome-wide association studies have identified susceptibility variants,^{50–52} providing evidence in support of the role of genetic susceptibility in developing urinary cancers. As for prostate cancer, the prostate carcinogenesis is a result of multiple environmental and hereditary risk factors, and genetic factors play important roles in the development of prostate cancer.⁵³ Functional studies on *APEI* Asp148Glu suggested that the Glu may alter endonuclease and DNA-binding activity, reduce the ability to communicate with other BER proteins, and decrease the capacity to repair DNA oxidative damage.¹⁵ In the study on X-ray exposure to lymphocytes and polymorphisms of DNA repair genes on chromosome aberrations, samples from individuals with the Asp/Glu or Glu/Glu genotype showed higher levels of damage with regard to all the studied measures, including aberrant cells, chromatid breaks, chromatid exchanges, deletions, and dicentrics.¹⁶

The combined results based on all the studies showed that no significant association was found between Asp148Glu and the risk of urinary cancers. Meanwhile, no significant associations were observed among Caucasians and African-Americans. However, a significant association was found among Asians. The discrepancy suggested a possible role of ethnic difference in genetic background and the environment. The same polymorphisms play different roles in cancer susceptibility among different ethnic populations, because cancer is a complicated multi-genetic disease, and different genetic background may contribute to the discrepancy.⁵⁴ Meanwhile, when stratified by the quality score, no significant association was found in high-quality studies (score ≥ 7) but a significant increased risk of urinary cancers risk was observed in lower quality studies (score < 7). The combined results based on all the high-quality studies further supported the previous conclusion that no significant association was found between Asp148Glu and the risk of urinary cancers.

One recent meta-analysis by Liu et al⁴⁶ estimated the association between Asp148Glu and the risk of bladder cancer, which was basically in accordance with our opinion that Asp148Glu may not contribute to the susceptibility to bladder cancer. However, another published meta-analysis by Zhou et al⁴⁸ showed that no significant association was found between Asp148Glu and the risk of prostate cancer, which is contrast with our results. One possible explanation of the contrast may be that different studies were included in the meta-analysis. As shown in the selection process of the studies, we mentioned that the studies by Mandal et al³⁵ and Mittal et al³⁶ were reported from the same organization. Actually, these two studies may contain partial overlapping data when carefully reading the full texts, and only the larger study³⁶ should be selected for the analysis. However, the meta-analysis by Zhou et al⁴⁸ included the studies by Mandal et al³⁵ and Mittal et al,³⁶ which might be biased by not taking into account the effects of overlapping data. Meanwhile, the study by Zhou et al⁴⁸ was not included in the previous meta-analysis. Thus, the results of our meta-analysis are more accurate and reliable. However, in our meta-analysis, only two or three studies on prostate cancer were available for each specific ethnicity, and they had limited sample size; hence, larger studies are needed to explore the association between Asp148Glu and prostate cancer risk among Africans, Asians, and Caucasians.

Some limitations of our meta-analysis should be considered. First, the number of published studies included in our meta-analysis was not large enough for subgroup analyses by ethnicity and cancer type. Second, our results were unadjusted estimates because of lack of detailed data, such as age, sex, and environmental factors in the studies included. Third, some inevitable publication bias might exist in the results because only published studies were available to be included.

Conclusion

Our meta-analysis suggests that Asp148Glu was not associated with the risk of urinary cancers but might increase the risk of urinary cancers among Asians. Stratification by cancer type identified a significant association of Asp148Glu with prostate cancer. Additional larger studies, stratified by gene–gene and gene–environmental interactions, are needed to further explore the association between Asp148Glu and the susceptibility to urinary cancers.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Criteria for quality assessment of genetic associations of the *APE1* Asp148Glu polymorphism with the risk of urinary cancers

Criteria	Quality score
Representativeness of cases	
A. Consecutive/randomly selected from case population with clearly defined random frame	2
B. Consecutive/randomly selected from case population without clearly defined random frame or with extensive inclusion criteria	1
C. Method of selection not described	0
Representativeness of controls	
D. Controls were consecutive/randomly drawn from the same area (ward/community) as cases with the same criteria	2
E. Controls were consecutive/randomly drawn from a different area than cases	1
F. Not described	0
Ascertainment of cancer cases	
G. Clearly described objective criteria for diagnosis of cancer	1
H. Not described	0
Ascertainment of controls	
I. Clinical examinations were performed on controls to prove that controls did not have cancer	2
J. Article merely stated that controls were subjects who did not have cancer; no proof provided	1
K. Not described	0
Ascertainment of genotyping examination	
L. Genotyping done under "blind" conditions	1
M. Unblinded or not mentioned	0
Test for Hardy-Weinberg equilibrium	
N. Hardy-Weinberg equilibrium in control group	2
O. Hardy-Weinberg disequilibrium in control group	1
P. Hardy-Weinberg equilibrium not checked	0
Association assessment	
Q. Assessed association between genotypes and cancer with appropriate statistic and adjusting confounders	2
R. Assessed association between genotypes and cancer with appropriate statistic without adjusting confounders	1
S. Inappropriate statistic used	0

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