Meta Analysis

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PARP1 rs1136410 Val762Ala contributes to an increased risk of overall cancer in the East Asian population: a meta-analysis

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Abstract

Objectives: To investigate the association between poly(ADP-ribose) polymerase 1 (*PARP1*) rs1136410 Val762Ala and cancer risk in Asian populations, as published findings remain controversial.

Methods: The PubMed and EMBASE databases were searched, and references of identified studies and reviews were screened, to find relevant studies. Meta-analyses were performed to evaluate the association between *PARP1* rs1136410 Val762Ala and cancer risk, reported as odds ratio (OR) and 95% confidence interval (CI).

Results: A total of 24 studies with 8926 cases and 15295 controls were included. Overall, a significant association was found between *PARP1* rs1136410 Val762Ala and cancer risk in East Asians (homozygous: OR 1.19, 95% CI 1.06, 1.35; heterozygous: OR 1.10, 95% CI 1.04, 1.17; recessive: OR 1.13, 95% CI 1.02, 1.25; dominant: OR 1.13, 95% CI 1.06, 1.19; and allele comparison: OR 1.09, 95% CI 1.03, 1.15). Stratification analyses by race and cancer type revealed similar results for gastric cancer among the Chinese population.

Conclusion: The findings suggest that *PARP1* rs1136410 Val762Ala may be significantly associated with an increased cancer risk in Asians, particularly the Chinese population.

Keywords

PARP1, Val762Ala, cancer, risk, meta-analysis

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Introduction

Cancer is a major public health problem worldwide and is recognized to rank as the leading cause of death in the 21st century. Incidence and mortality rates of various cancers continue to increase rapidly worldwide, with approximately 18.1 million new cases and 9.6 million cancer-related deaths in 2018.[1] However, about 48% of new cases and 57% of cancer deaths occurred in Asia.[1] Both genetic and environmental factors contribute to carcinogenesis.[2] Environmental agents, including ultraviolet light, inhaled cigarette smoke and incompletely defined diet, can often cause DNA damage that may lead to carcinogenesis. Several pathways exist to monitor and correct such damage, including the base excision repair (BER) system, which plays an important role in excising and replacing the damage mainly arising from endogenous oxidative and hydrolytic decay.[3,4]

Poly(ADP-ribose) polymerase-1 (PARP1), also named adenosine diphosphate ribosyl transferase (ADPRT), is a key component of the BER system.[5] In the presence of DNA breaks, the catalytic activity of PARP1 has been shown to be stimulated more than 500-fold and PARP1 is assumed to play multifunctional roles in various biological functions, including cell survival, cell death programmes, transcriptional regulation, telomere cohesion and mitotic spindle formation.[5] PARP1 deficiency in female mice has been reported to cause mammary carcinogenesis, suggesting PARP1 may be a possible risk factor for breast cancer in humans.[6] Accumulating evidence implicates PARP1 deficiency as a contributing factor to carcinogenesis. The human *PARP1* gene lies in chromosome 1q41-42, spanning 47.3 kb in length and containing 23 exons. To date, more than 1 000 single nucleotide polymorphisms (SNPs) have been identified for *PARP1*. Among them, the Val762Ala (rs1136410 A > G) polymorphism is the most investigated.[7–10] Ala762 has been found to display almost half the activity of Val762, influencing the ability to repair and, thus, possible carcinogenesis.[11]

A number of previous studies have investigated the association between *PARP1* rs1136410 Val762Ala and cancer risk. However, the findings remain controversial and inconclusive. The latest meta-analyses were conducted in 2013 to study the association between this polymorphism and overall cancer risk in all ethnicities.[7,8] No previously published meta-analysis has focused only on Asian populations. Therefore, the aim of the present study was to perform a meta-analysis investigating the association between *PARP1* rs1136410 Val762Ala and cancer risk primarily in an Asian population, and particularly in the Chinese population.

Materials and methods

Search strategy

To retrieve all relevant studies, the PubMed and EMBASE electronic databases were searched for articles published in Chinese or English, up to June 2020, using the following terms: 'PARP1 or PARP-1 or poly (ADP-ribose) polymerase 1 or ADPRT' or 'polymorphism or variant or variation' or 'cancer or carcinoma or tumor'. In addition, references in review articles and the identified studies were manually screened to identify additional relevant studies. Only the largest or the latest study was included in the meta-analysis. Two independent researchers (YX ad JL) screened titles and abstracts of articles retrieved in the search, followed by full-text evaluation for articles that met the inclusion criteria.

Inclusion and exclusion criteria

For inclusion into the present meta-analysis, studies must have satisfied the following criteria: (1) investigating the

association between the *PARP1* rs1136410 Val762Ala polymorphism and cancer risk in an Asian study population; (2) cohort or case–control design; and (3) enough information for estimation of odds ratios (ORs) and their 95% confidence intervals (CIs). Studies were excluded if the following criteria were met: (1) case only studies; (2) reviews, meta-analyses and comments; or (3) insufficient information for calculation. Studies with genotype frequencies in the controls that departed from Hardy–Weinberg equilibrium (HWE) were also excluded, unless further evidence indicated that other polymorphisms were in HWE.

Data extraction and quality score

Two investigators (YX and JL) independently extracted the following information from each eligible publication: author surname, year of publication, country of origin, cancer type, source of control, and distribution of alleles and genotypes. In case of any disagreement, the issue was resolved by discussion with a third investigator (YL). The quality of each study was evaluated using previously published quality assessment criteria.[12] The quality score ranged from 0–15, with scores of 0–9 considered to be low quality, and scores of 10–15 considered to be high quality.

This work was performed under PRISMA guidelines for conducting systematic reviews and meta-analyses. All analyses were based on previously published studies; therefore, no ethics approval or patient consent were required.

Statistical analyses

Goodness-of-fit χ^2-test was applied to estimate HWE, and a P value < 0.05 was considered significant and indicated that the study departed from HWE. The strength of association between the *PARP1* rs1136410 Val762Ala polymorphism and cancer risk in Asians was evaluated by crude ORs and their corresponding 95% CIs under the five genetic models: homozygous model (Ala/Ala versus Val/Val), heterozygous model (Val/Ala versus Val/Val), recessive model (Ala/Ala versus Val/Ala + Val/Val), dominant model (Val/Ala + Ala/Ala versus Val/Val) and allele comparison model (Ala versus Val). Q-test was performed to assess heterogeneity among the studies. A P value > 0.10 indicated no significant heterogeneity, in which case the fixed-effects model (Mantel–Haenszel method) was used.[13] Otherwise, the random-effects model (DerSimonian and Laird method) was applied.[14] Stratification analyses were also performed to test the association regarding race, cancer type and source of control. Moreover, Begg's funnel plot and Egger's linear regression test was adopted to assess the potential publication bias.[15] All statistical analyses were conducted using STATA software, version 11.0 (Stata Corporation, College Station, TX, USA). A P value less than 0.05 was considered statistically significant.

Trial sequential analysis

Trial sequential analysis (TSA) was used to evaluate whether the quantitative results were reliable. TSA was performed by anticipating a 20% relative risk reduction, a 5% type I error, and a statistical test power of 80%. If the cumulative Z-curve crossed the TSA monitoring boundary, or exceeded the required information size, firm evidence had been reached. Otherwise, more studies were needed.[16]

Genotype-based mRNA expression analysis

Expression quantitative trait loci (eQTL) analysis in the genotype-tissue expression (GTEx) portal (https://www. gtexportal.org/home/)

was used to evaluate correlations between the *PARP1* rs1136410 Val762Ala polymorphism and levels of mRNA expression.

Results

Characteristics of eligible studies

As shown in Figure 1, a total of 519 articles were identified from PubMed, EMBASE, and from manually screening reviews and references. After title and abstract screening, 38 articles satisfied the inclusion criteria and underwent further full text evaluation. Among them, 10 were excluded for no Asian population, two for insufficient information and two deviated from HWE. In order to enlarge the sample size, six articles were included in the final analysis due to other polymorphisms that were in HWE.[17–22] Finally, 24 studies comprising 8 926 cases and 15 295 controls were subjected to the final meta-analysis.[17–40]

The characteristics of all the identified studies are listed in Table 1. There were five studies focused on gastric cancer, four on lung cancer, two each on breast and colorectal cancer, and other cancers represented by only one study. In terms of race, 19 studies were conducted in the Chinese population, three in Japanese participants and two in the Korean population. Thus, all studies involved participants from East Asia. Out of the selected studies, 20 were hospital-based (HB) and four were population-based (PB). A total of 16 studies were considered to be of high quality and eight were of low quality.

Meta-analysis results

Main findings regarding the association between the *PARP1* rs1136410 Val762Ala polymorphism and cancer risk in the East Asian population are shown in Table 2. A significant association was found between

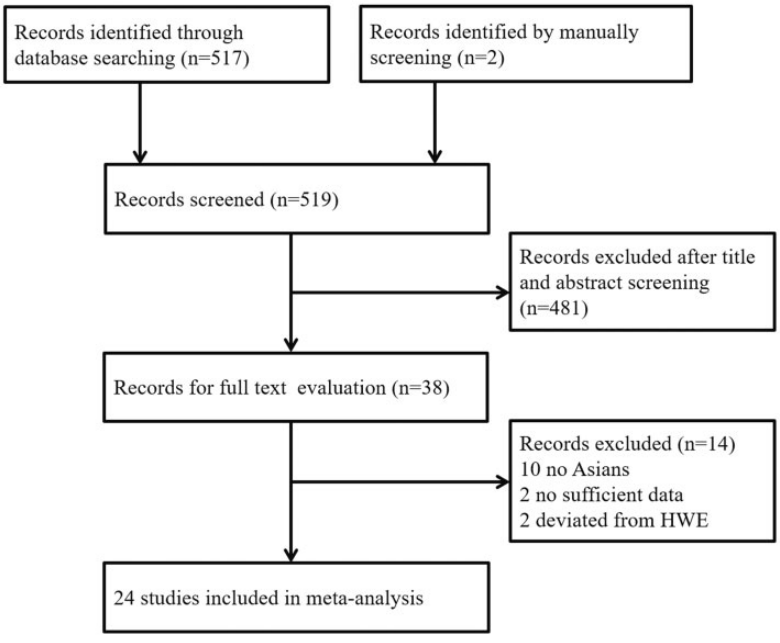

Figure 1. Flow diagram showing selection of studies included in the current meta-analysis.

Table 1. The main characteristics of all studies included in the meta-analysis.

Author and reference No.	Publication Year	Country	Race	Cancer type	Control source	Sample size		Case genotypes			Control genotypes			MAF	HWE	Score
						Cases	Controls	AA	AG	GG	AA	AG	GG			
Hao et al.[23]	2004	China	Chinese	Esophageal	HB	414	479	125	212	77	168	230	81	0.41	0.880	13
Zhang et al.[24]	2005	China	Chinese	Lung	HB	1000	1000	307	509	184	359	504	137	0.39	0.057	12
Miao et al.[17]	2006	China	Chinese	Gastric	HB	500	1000	150	257	93	396	492	112	0.36	0.026	11
Zhai et al.[25]	2006	China	Chinese	Breast	HB	302	639	100	153	49	197	331	111	0.43	0.164	10
Zhang et al.[22]	2006	China	Chinese	Gastric	HB	236	708	76	109	51	258	367	83	0.38	0.006	8
Stern et al.[26]	2007	Singapore	Chinese	Colorectal	PB	307	1173	93	150	64	381	564	228	0.43	0.457	13
Chiang et al.[27]	2008	China	Chinese	Thyroid	HB	283	469	86	139	58	168	221	80	0.41	0.616	11
Jin et al.[28]	2010	Korea	Korean	NHL	PB	573	721	189	279	105	221	354	146	0.45	0.845	12
Wang et al.[29]	2010	China	Chinese	Bladder	HB	234	253	68	120	46	78	127	48	0.44	0.771	10
Kim et al.[30]	2011	Korea	Korean	Gastric	HB	151	320	42	70	39	102	161	57	0.43	0.635	7
Nakao et al.[18]	2012	Japan	Japanese	Pancreatic	HB	185	1465	61	90	34	550	657	258	0.40	0.012	11
Pan et al.[19]	2012	China	Chinese	Gastric	PB	176	308	60	79	37	105	132	71	0.44	0.020	9
Wen et al.[20]	2012	China	Chinese	Gastric	HB	307	307	96	154	57	105	132	70	0.44	0.024	9
Yuan et al.[31]	2012	China	Chinese	Head and neck	HB	395	883	138	193	64	300	431	152	0.42	0.895	10
Zhang et al.[32]	2012	China	Chinese	Cervical	HB	80	176	25	39	16	54	83	39	0.46	0.508	8
Hosono et al.[33]	2013	Japan	Japanese	Endometrial	HB	91	261	29	47	15	100	121	40	0.39	0.734	8
Li et al.[34]	2013	China	Chinese	Colorectal	HB	451	626	134	228	89	222	319	85	0.39	0.078	9
Tang et al.[35]	2013	China	Chinese	Breast	HB	793	845	250	405	138	275	419	151	0.43	0.694	11
Xue et al.[36]	2013	China	Chinese	Lung	HB	410	410	129	202	79	138	205	67	0.41	0.531	10
Zeng et al.[21]	2013	Japan	Japanese	Cholangiocarcinoma	HB	94	94	40	11	43	35	11	48	0.57	< 0.001	6
Wang et al.[37]	2015	China	Chinese	Lung	HB	500	500	151	252	97	140	251	109	0.47	0.860	10
Yu et al.[38]	2015	China	Chinese	Lung	HB	373	360	163	164	46	162	164	34	0.32	0.415	10
Cheng et al.[39]	2019	China	Chinese	Neuroblastoma	PB	469	998	136	244	89	330	482	186	0.43	0.669	13
Deng et al.[40]	2019	China	Chinese	Glioma	HB	602	1300	185	303	114	432	641	227	0.42	0.684	13

HB, hospital based; PB, population based; NHL, non-Hodgkin lymphoma; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

Table 2. Meta-analysis of the association between the poly(ADP-ribose) polymerase 1 (*PARP1*) rs1136410 Val762Ala and cancer risk in East Asians.

	Homozygous		Heterozygous		Recessive		Dominant		Allele comparison	
	Ala/Ala versus Val/Val		Val/Ala versus Val/Val		Ala/Ala versus (Val/Ala + Val/Val)		(Val/Ala + Ala/Ala) versus Val/Val		Ala versus Val	
Variable	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}
East Asians	1.19 (1.06, 1.35)	0.001	1.10 (1.04, 1.17)	0.920	1.13 (1.02, 1.25)	0.002	1.13 (1.06, 1.19)	0.371	1.09 (1.03, 1.15)	0.006
Race										
Chinese	1.22 (1.07, 1.39)	0.001	1.11 (1.04, 1.19)	0.894	1.15 (1.02, 1.29)	0.002	1.14 (1.07, 1.21)	0.403	1.10 (1.04, 1.17)	0.011
Korean	1.14 (0.59, 2.21)	0.034	0.95 (0.76, 1.18)	0.608	1.16 (0.65, 2.07)	0.030	0.97 (0.79, 1.19)	0.225	1.06 (0.77, 1.46)	0.041
Japanese	1.08 (0.78, 1.49)	0.480	1.23 (0.93, 1.62)	0.744	0.99 (0.74, 1.33)	0.718	1.16 (0.90, 1.48)	0.384	1.06 (0.88, 1.28)	0.323
Cancer type										
Lung	1.22 (0.90, 1.66)	0.045	1.07 (0.94, 1.22)	0.552	1.19 (0.93, 1.52)	0.088	1.11 (0.99, 1.26)	0.232	1.09 (0.95, 1.25)	0.065
Gastric	1.46 (0.98, 2.18)	0.003	1.20 (1.03, 1.39)	0.535	1.34 (0.91, 1.98)	< 0.001	1.28 (1.11, 1.47)	0.345	1.19 (1.01, 1.41)	0.020
Breast	0.96 (0.76, 1.21)	0.573	1.01 (0.84, 1.21)	0.421	0.95 (0.77, 1.18)	0.827	1.00 (0.84, 1.18)	0.407	0.98 (0.88, 1.10)	0.506
Colorectal	1.41 (0.94, 2.11)	0.116	1.14 (0.93, 1.39)	0.682	1.30 (0.92, 1.85)	0.117	1.20 (0.99, 1.45)	0.403	1.17 (0.99, 1.39)	0.176
Others	1.08 (0.96, 1.22)	0.653	1.11(1.01, 1.22)	0.835	1.02 (0.92, 1.14)	0.943	1.10 (1.00, 1.21)	0.574	1.05 (0.99, 1.12)	0.503
Control source										
HB	1.24 (1.08, 1.42)	0.001	1.11 (1.04, 1.19)	0.908	1.17 (1.03, 1.32)	0.002	1.15 (1.08, 1.22)	0.388	1.11 (1.04, 1.18)	0.009
PB	1.02 (0.85, 1.21)	0.447	1.07 (0.93, 1.23)	0.467	0.98 (0.84, 1.14)	0.739	1.05 (0.92, 1.20)	0.355	1.01 (0.93, 1.11)	0.381

OR, odds ratio; CI, confidence interval; HB, hospital-based; PB, population-based.

the *PARP1* rs1136410 Val762Ala polymorphism and cancer risk in the East Asian population (homozygous model: OR 1.19, 95% CI 1.06, 1.35, $P = 0.004$; heterozygous model: OR 1.10, 95% CI 1.04, 1.17, $P = 0.001$; recessive model: OR 1.13, 95% CI 1.02, 1.25, $P = 0.024$; dominant model: OR 1.13, 95% CI 1.06, 1.19, $P < 0.001$; and allele comparison model: OR 1.09, 95% CI 1.03, 1.15, $P = 0.002$).

In the analyses of data stratified by race, a total of 19 studies with 7832 cases 12434 controls focused on the Chinese population. *PARP1* rs1136410 Val762Ala was found to be significantly associated with an increased risk of cancer in the Chinese population under all five genetic modes (homozygous model: OR 1.22, 95% CI 1.07, 1.39, $P = 0.004$; heterozygous model: OR 1.11, 95% CI 1.04, 1.19, $P = 0.001$; recessive model: OR 1.15, 95% CI 1.02, 1.29, $P = 0.023$; dominant model: OR 1.14, 95% CI 1.07, 1.21, $P < 0.001$; and allele comparison model: OR 1.10, 95% CI 1.04, 1.17, $P = 0.002$; Figure 2 and Table 2). These associations were not observed in the Korean and Japanese populations (Figure 2).

In the analysis of data stratified by cancer type, *PARP1* rs1136410 Val762Ala was found to be significantly associated with an increased risk of gastric cancer (heterozygous model: OR 1.20, 95% CI 1.03, 1.39, $P = 0.018$; dominant model: OR 1.28, 95% CI 1.11, 1.47, $P = 0.001$; and allele comparison model: OR 1.19, 95% CI 1.01, 1.41, $P = 0.039$) and other cancers (oesophageal, thyroid, non-Hodgkin lymphoma, bladder, pancreatic, head and neck, cervical,

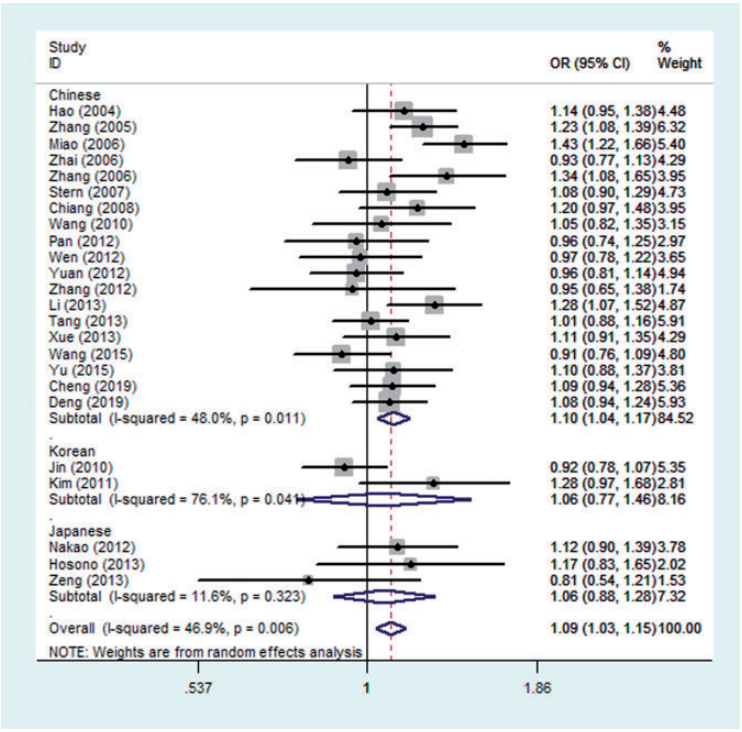

Figure 2. Stratification analysis by race showing odds ratios (ORs) and 95% confidence intervals (CIs) of the association between the poly(ADP-ribose) polymerase 1 (*PARP1*) rs1136410 Val762Ala polymorphism and cancer risk in the allele comparison model.

endometrial, cholangiocarcinoma, neuroblastoma, and glioma combined), but not lung, breast and colorectal cancer (Table 2).

In stratification analyses by control source, hospital-based studies were revealed to show a significant association between *PARP1* rs1136410 Val762Ala and increased cancer risk (homozygous model: OR 1.24, 95% CI 1.08, 1.42, $P = 0.001$; heterozygous model: OR 1.11, 95% CI 1.04, 1.19, $P = 0.002$; recessive model: OR 1.17, 95% CI 1.03, 1.32, $P = 0.013$; dominant model: OR 1.15, 95% CI 1.08, 1.22, $P < 0.001$; and allele comparison model: OR 1.11, 95% CI 1.04, 1.18, $P = 0.001$; Table 2).

Heterogeneity and sensitivity analyses

Substantial heterogeneities were observed among all studies investigating the association between the *PARP1* rs1136410 Val762Ala polymorphism and cancer risk in East Asians, under the homozygous model, $P = 0.001$; the recessive model, $P = 0.002$; and the allele comparison model, $P = 0.006$. The heterogeneities were not observed with the heterozygous model, $P = 0.920$ and the dominant model, $P = 0.371$. Therefore, the random-effects model was applied to evaluate the pooled ORs and their 95% CIs.

Publication bias

A funnel plot and the findings from Egger's linear regression analysis suggested that no evidence of publication bias was observed (homozygous model, $P = 0.644$; heterozygous model, $P = 0.615$; recessive model, $P = 0.755$; dominant model, $P = 0.429$; and allele comparison model, $P = 0.430$).

Trial sequential analysis results

As shown in Figure 3, TSA showed that the cumulative z-curve crossed the trial sequential monitoring boundary before reaching the required information size, suggesting that the cumulative evidence was sufficient and no further evidence was needed to verify the conclusions.

Effect of PARP1 *rs1136410 Val762Ala polymorphism on expression of* PARP1

A further assessment of the effect of *PARP1* rs1136410 Val762Ala polymorphism on

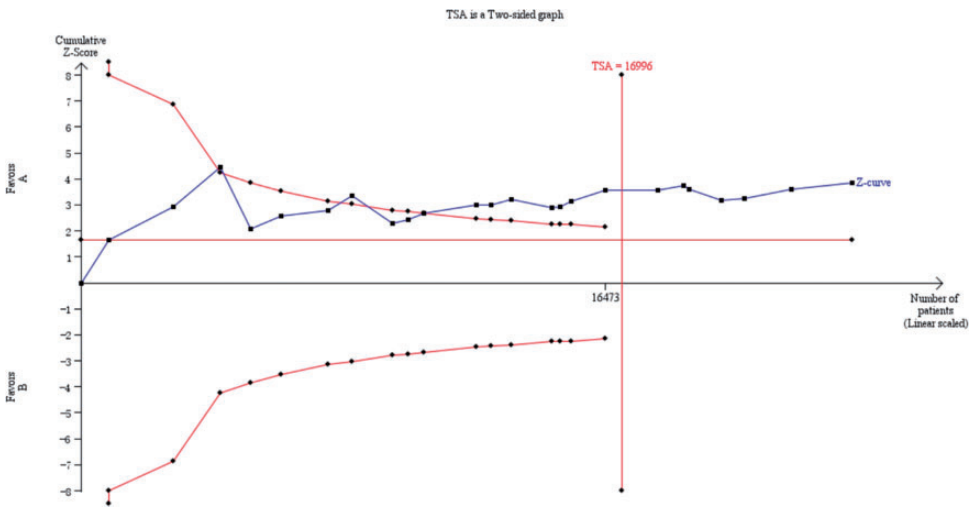

Figure 3. Trial sequential analysis (TSA) of the poly(ADP-ribose) polymerase 1 (*PARP1*) rs1136410 Val762Ala polymorphism under the dominant model.

PARP1 mRNA expression, using the GTEx web tool, showed that the 762Val allele was significantly associated with higher levels of *PARP1* expression in whole blood (Figure 4).

Discussion

DNA repair pathways play a key role in maintaining genome integrity and then protecting against carcinogenesis.[41] PARP1 is a molecular sensor of DNA strand breaks and its activation has an important role in the regulation of their repair.[5] In response to DNA damage, PARP1 is capable of using NAD^+ to synthesize long and branched polymers of ADP-ribose on several acceptor proteins.[5] There are three functional domains within PARP1 polymerase, two zinc-finger motifs that are important for binding to DNA-strand breaks and a third one for coupling damage-induced changes to alterations in its catalytic activity.[42] In addition, there is growing evidence to show that deficiency of PARP1 leads to DNA repair defects and chromatin structure instability, thereby contributing to carcinogenesis.[43]

The human *PARP1* gene is located on chromosome 1q41-42. To date, more than 1 000 SNPs have been identified in the *PARP1* gene. Among them, the most investigated is the Val762Ala polymorphism, an A to G nucleotide transition at codon 762 in exon 17 that results in Val762Ala substitution in the catalytic domain of PARP1.[42] A body of evidence suggests that this polymorphism is associated with altered PARP1

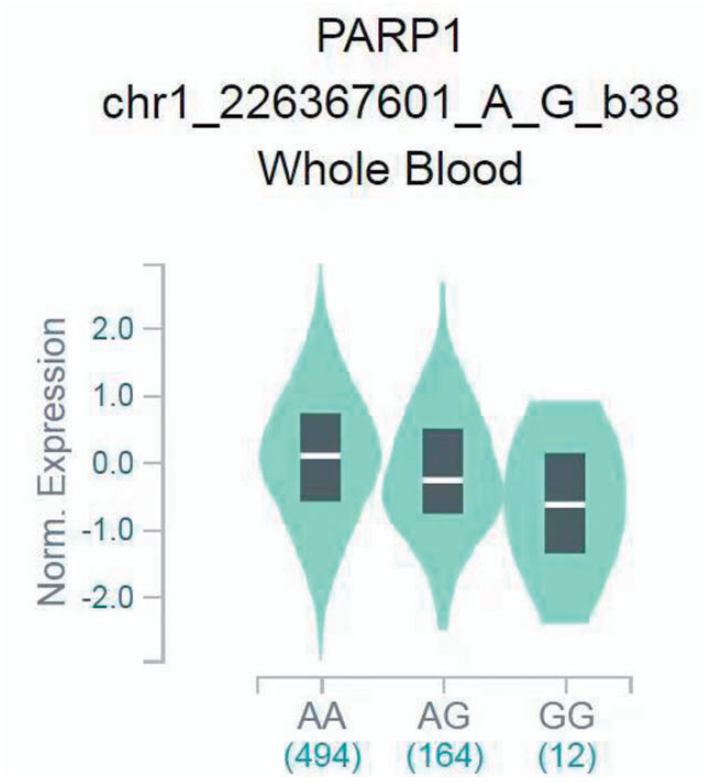

Figure 4. Effect of poly(ADP-ribose) polymerase 1 (*PARP1*) rs1136410 Val762Ala polymorphism on the expression of *PARP1* extracted from the genotype-tissue expression (GTEx) database. The 762Val allele was significantly associated with higher levels of *PARP1* expression in whole blood ($P = 1.4 \times 10^{-5}$).

activity. For example, Wang et al.[11] found that Ala762 displays almost half of the activity of Val762, and thereby may contribute to carcinogenesis.

A total of 24 studies comprising 8 926 cases and 15 295 controls were subjected to meta-analysis in the current study. The results indicated that the *PARP1* rs1136410 Val762Ala polymorphism was significantly associated with an increased cancer risk in the East Asian population. In the analysis of data stratified by race, Ala762 allele was also found to be associated with an increased risk of cancer among the Chinese population, but not in the Japanese and Korean population. The discrepancy in race may be attributed to the number of studies and the number of subjects. 19 studies were conducted in Chinese participants, whereas only three were conducted in a Japanese population and two in a Korean population. More studies need to be conducted within Japanese and Korean populations so that they may be considered for further analyses. In the analysis of data stratified by cancer type, Val762Ala was only found to be significantly associated with an increased risk of gastric cancer.[7,8] The results are consistent with previous meta-analyses in the pooled analysis of overall population. All four lung-cancer studies involved Chinese populations, and no association with this polymorphism and increased lung-cancer risk was found in the present meta-analysis. However, in the study by Qin et al.,[8] the *PARP1* rs1136410 Val762Ala polymorphism was found to be associated with an increased risk of lung cancer in the overall population. This suggests that the polymorphism may play a different role in different races. Moreover, the discrepancy in cancer type may be attributed to high or low *PARP1* expression levels in different tissues, and different functions of PARP1 in different cancer types with different mechanisms of carcinogenesis.[8]

To the best of the authors' knowledge, the current meta-analysis is the first study to investigate the association between the *PARP1* rs1136410 Val762Ala polymorphism and cancer risk in Asians. The two most recent previous meta-analyses, published in 2014, explored the association among all races and included 18 studies in Asians.[7,8] Six additional articles have been included in the present study, thus reaching a total of 24 articles in the meta-analysis. In accordance with previously published findings,[7,8] the present study also found that the *PARP1* rs1136410 Val762Ala polymorphism was significantly associated with an increased cancer risk in Asians. Importantly, this is the first meta-analysis to show that this polymorphism is significantly related to an increased risk of cancer in the Chinese, but not in the Japanese and Korean population. In addition, the present study is the first to find a significant association between the polymorphism and an increased risk of gastric cancer in Asians.

Several potential limitations of the current meta-analysis should also be addressed. First, in the stratification analysis, the number of studies and sample sizes were relatively small, for example, among the Japanese and Korean population. Secondly, as the original information was lacking, the present findings were based on unadjusted ORs. A more precise analysis should be conducted to explore whether individual information, such as age, sex, smoking and drinking status, and other environmental factors, are available to adjust for confounding factors. Thirdly, heterogeneity was observed among some genetic models, and the random-effects model was adopted to estimate the association. Finally, due to the lack of original data, assessment of the possible gene-gene and gene-environment interaction effects on cancer risk was limited.

In conclusion, the current meta-analysis is the first to focus on Asian populations

and provide more precise evidence that the *PARP1* rs1136410 Val762Ala polymorphism is significantly associated with an increased cancer risk in the East Asian population. The same results were observed for gastric cancer in the cancer-type stratification analysis, particularly in the Chinese population. Large-scale and well-designed studies are warranted to validate the findings of this meta-analysis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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