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Review Article

Association of the AKR1C3 polymorphism with cancer risk: a meta-analysis and systematic review

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Abstract: A number of studies investigating the association between AKR1C3 gene polymorphisms and the risks of cancer have yielded conflicting results. Therefore, we performed a meta-analysis to evaluate the effect of AKR1C3 gene single nucleotide polymorphisms on risk of all cancer types. A literature search was conducted to identify the relevant studies from PubMed, EMbase, OVID, and CMB databases. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. This meta-analysis included a total of 12 studies. In the combined results, no significant association was observed between the AKR1C3 rs12529 polymorphism with cancer risks. But the results of subgroup analysis of rs12529 showed a significant association in Asians (allele G vs allele C, OR=1.64, 95% CI 1.13-2.38, P=0.009; CG+GG vs CC, OR=1.78, 95% CI 1.03-3.07, P=0.04). In addition, significant association was observed between rs3763676 with cancer risk (GA+GG vs AA, OR=1.20, 95% CI 1.03-1.40, P=0.02). In regard to rs4881400, rs2245191 and rs12387, no significant association was observed between these polymorphisms with cancer risk. Results of the current meta-analysis suggest that rs12529 G allele might be associated with increased risk of cancer in Asians but not in other populations. In addition, carrying the rs3763676 G allele may be a potential risk factor of cancer. While rs4881400, rs2245191 and rs12387 polymorphisms were not associated with cancer risk. Further studies with larger sample sizes are needed to confirm these results.

Keywords: AKR1C3, gene, polymorphism, cancer, meta-analysis, systematic review

Introduction

Aldo-keto reductase (AKR) is a member of the oxidoreductase superfamily. The AKR family includes a number of enzymes related monomeric NADPH-dependent oxidoreductases, such as aldehyde reductase, aldose reductase, prostaglandin F synthase, xylose reductase, ρ-crystallin, and many others [1]. It can catalyze the conversion of aldehydes and ketones to a series non-toxic or less toxic alcohols by utilizing NADH or NADPH as cofactors [2-4]. The AKR protein superfamily contains approximately 190 members that fall into 16 families and are found in prokaryotes and eukaryotes. AKR1 is the largest family. Human AKR1Cs gene locus on chromosome 10p15-p14, and encodes 13 kinds of unique protein (AKR1C1-13). Human AKR1C3 gene encodes Aldo-keto reductase family 1 member C3, which consists of more than 40 known enzymes and proteins. The enzymes display overlapping but distinct substrate specificity. This enzyme catalyzes the reduction of prostaglandin (PG) D2, PGH2 and phenanthrenequinone (PQ), and the oxidation of 9α, 11β-PGF2 to PGD2. It may play an important role in the pathogenesis of allergic diseases such as asthma, and may also have a role in controlling cell growth and differentiation.

Sufficient evidences suggest that AKR1C3 is associated with occurrence, diagnosis and treatment of cancers. AKR1C3 was found widespread expression in a variety of tumor cells [5-8], and it often associated with poor prognosis [9-13]. Nakamura et al. [14] found AKR1C3 expression is positively correlated with the clinical stage of prostate cancer. It is associated with prostate cancer aggressiveness, and AKR1C3 overexpression promotes angiogene-

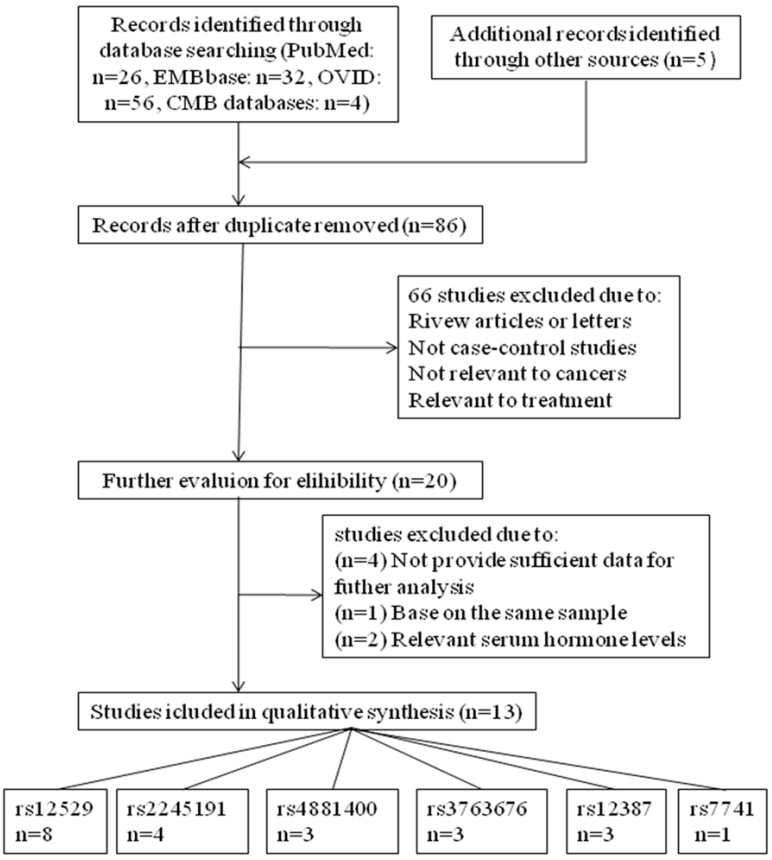

Figure 1. Flow diagram of study selection in this meta-analysis.

sis and aggressiveness of prostate cancer cells [15]. Lin HK et al. [12] detected AKR1C3 expression by immunohistochemistry in sections of paraffin-embedded mammary gland and prostate, and found the cancerous cells were strongly immunoreactive.

The AKR1C3 enzyme is encoded by the gene AKR1C3, and this gene is highly polymorphic. This is mainly due to the presence of single nucleotide polymorphisms (SNPs). Currently, there are more than 100 SNPs were found in gene AKR1C3. SNPs in coding regions can be divided into non-synonymous mutations and synonymous mutations. Non-synonymous mutations can lead to an amino acid sequence change of protein, but synonymous mutations does not affect the expression of genes. Then, is SNPs in AKR1C3 gene influence the risk for cancer? A large number of genetic studies have investigated the association of these SNPs with risk of cancer, but the obtained results were conflicting. In studies of the relation between rs12529 polymorphism and cancer, Lan Q et al. [16] found that Chinese people who carry rs12529 mutation homozygous GG genotype had significantly increased their susceptibility of lung cancer, especially in women who often use smoky coal these effects are more obvious. But N. Ersoy Tunali et al. [17] found that carrying the rs12529 mutation homozygous GG genotype relative to lower bladder cancer risk than carrying wild-type homozygous CC genotype. In other studies, rs12529 polymorphism was not associated with prostate cancer [18, 19], Bladder cancer [20], Breast cancer [21], lymphoma [22] or childhood leukemia [23]. With regard to the association between rs3763676 polymorphism and cancer, Figueroa, J. D. et al. [20] found significant association with increased bladder cancer risk, whereas others [21, 24] reported null association. As to other polymorphisms (rs4881400 [20, 21, 25], rs2245191 [20, 21, 23, 26], rs1238 [20, 21, 27]) of AKR1C3, no significant association with cancer risk was observed in obtained studies. No meta-analysis has been published with a compilation of these studies. Therefore, we performed a meta-analysis in order to provide a more comprehensive and reliable conclusion on the association between the AKR1C3 gene polymorphisms and the risks of cancer.

Methods

Literature search

Relevant literature published before Dec 1st, 2015 were identified through a search in PubMed, EMbase, OVID, CMB databases and Cochrane Library using the following search terms: (AKR1C3 OR "Aldo-keto reductase family 1 member C3") AND (polymorphism OR polymorphisms) AND (cancer OR tumor OR carcinoma), last search update: Dec, 2015. Publication date and publication language were not restrict-

Table 1. Main characteristics of included studies

First author, publication year	Cancer type	Country	Ethnic group	Gender	Study design	dbSNP ID	NOS
Mononen, N. 2006	Prostate cancer	Finland	Caucasian	Men	PCC	rs12529	6
Berndt, S. I. 2007	Prostate cancer	USA	Caucasian + African	Men	PCC	rs12529	7
Kwon, E. M. 2012	Prostate cancer	USA	Caucasian + African	Men	PCC	rs4881400	7
Schulze, J. J. 2012	Prostate cancer	Switzerland	Caucasian	Men	PCC	rs3763676	5
Karunasinghe N. 2013	Prostate cancer	Auckland	Caucasian	Men	PCC	rs12529	5
Plourde, M. 2009	Breast cancer	French	Caucasian	Female	HCC	rs12529, rs4881400, rs3763676, rs12387, et al.	5
Reding, K. W. 2009	Breast cancer	USA	Caucasian + African + Asian + other	Female	PCC	rs12387	7
Lan, Q. 2007	Non-Hodgkin lymphom	USA	Caucasian + African + other	Female	PCC	rs12529	7
Kim, C. 2012	Non-Hodgkin Lymphoma	USA	Caucasian + African + other	Female	PCC	rs2245191	7
Figueroa, J. D. 2008	Bladder cancer	Spain	Caucasian	Mixed	HCC	rs12529, rs4881400, rs2245191, rs3763676, rs12387, et al.	7
Lan, Q. 2004	Lung cancer	China	Asian	Mixed	PCC	rs12529	7
Liu, C. Y. 2008	Childhood leukemia	China	Asian	Mixed	PCC	rs12529, rs2245191, et al.	7

HCC: hospital-based case-control; PCC: population-based case-control; NOS: Newcastle-Ottawa quality assessment scale.

Table 2. 1. The genotype data of rs12529 polymorphism

First author, publication year	N (Case genotype)				N (Control genotype)				HWE	Genotyping method
	Total	CC	CG	GG	Total	CC	CG	GG		
Berndt, S. I. 2007	485	177	228	80	614	202	300	112	0.97342204	TaqMan
Figueroa, J. D. 2008	1084	354	540	190	999	292	500	207	0.793047287	TaqMan
KArunasinghe, N. 2013	341	112	167	62	420	171	194	55	0.998394368	TaqMan
Lan, Q. 2004	116	1	21	94	112	1	32	79	0.246101425	Real-time PCR
Lan, Q. 2007	454	162	215	77	534	182	248	104	0.239400257	Real-time PCR
Liu, C. Y. 2008	97	66	28	3	180	143	33	4	0.218722909	TaqMan
Mononen, N. 2006	847	354	394	99	923	379	441	103	0.13329349	Microarray
Plourde, M. 2009	44	26	12	6	70	27	30	13	0.370027714	PCR-RFLP
Total	3468	1252	1605	611	3852	1397	1778	677		

2. The genotype data of rs4881400 polymorphism

First author, publication year	N (Case genotype)				N (Control genotype)				HWE	Genotyping method
	Total	TT	GT	GG	Total	CC	CG	GG		
Figueroa, J. D. 2008	884	558	294	32	873	523	294	56	0.09528152	iPLEX
Kwon, E. M. 2012	1226	716	442	68	1309	760	475	74	0.984555514	TaqMan
Plourde, M. 2009	50	34	15	1	70	43	21	6	0.161406492	PCR-RFLP
Total	2160	1308	751	101	2252	1326	790	136		

3. The genotype data of rs2245191 polymorphism

First author, publication year	N (Case genotype)					N (Control genotype)					HWE	Genotyping method
	Total	CC	CA	AA	CA+AA	Total	CC	CA	AA	CA+AA		
Figueroa, J. D. 2008	1061	533	445	83	528	991	496	411	84	495	0.930055836	TaqMan
Liu, C. Y. 2008	98	55	34	9	43	180	128	40	12	52	0.001290316	TaqMan
Plourde, M. 2009	50	30	17	3	20	70	41	25	4	29	0.941445178	PCR-RFLP
Kim, C. 2012	454	266	NA	NA	188	533	322	NA	NA	211	NA	Real-time PCR
Total	1663	884	496	95	779	1774	987	475	100	787		

4. The genotype data of rs3763676 polymorphism

First author, publication year	N (Case genotype)				N (Control genotype)				HWE	Genotyping method
	Total	AA	AG	GG	Total	AA	AG	GG		
Figueroa, J. D. 2008	1086	443	498	145	1032	471	433	128	0.068809139	GoldenGate
Plourde, M. 2009	50	16	27	7	70	31	32	7	0.762768134	PCR-RFLP
Schulze, J. J. 2012	176	71	72	33	159	63	77	19	0.537698262	PCR-RFLP
Total	1312	530	597	185	1261	565	542	154		

5. The genotype data of rs12387 polymorphism

First author, publication year	N (Case genotype)					N (Control genotype)					HWE	Genotyping method
	Total	AA	AG	GG	AG+GG	Total	AA	AG	GG	AG+GG		
Figueroa, J. D. 2008	962	701	240	21	261	932	687	227	18	245	0.880985226	TaqMan
Plourde, M. 2009	50	33	16	1	17	70	48	21	1	22	0.438832032	PCR-RFLP
Reding, K. W. 2009	1263	838	NA	NA	425	1027	698	NA	NA	329	NA	iPLEX
Total	2275	1572	256	22	703	2029	1433	248	19	596		

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; NA: not applicable.

ed in our search. The references used in eligible articles were also examined manually to further identify potentially relevant studies. If more than one article was published by the same author using the same case series, the study with the most individual investigators was included in our meta-analysis.

Inclusion and exclusion criteria

Abstracts of all citations and retrieved studies were reviewed. Studies included in our meta-analysis must meet the following criteria: (1) A case-control design was used; (2) Association between AK1C3 and cancer was examined; (3)

Table 3. Summary of ORs and Heterogeneity tests for various contrasts on the association between AKR1C3 rs12529 polymorphism and cancer risk

Gene models	OR	95% CI	P	P^{het}	I^2 (%)
G vs C	1.01	(0.88-1.17)	0.89	0.001	70
GG vs CC+CG	1.00	(0.83-1.21)	0.98	0.09	44
CG+GG vs CC	0.98	(0.82-1.18)	0.84	0.01	61
GG vs CC	0.94	(0.75-1.18)	0.59	0.06	48
CG vs CC	0.99	(0.84-1.16)	0.86	0.06	48
GG vs CG	0.98	(0.86-1.12)	0.8	0.32	14

OR = odds ratio; CI = confidence interval; P^{het} = *P* value for heterogeneity based on Q test.

All patients diagnosed with cancers should be confirmed by pathological or histological examinations; (4) Available genotype data and the calculation of odds ratios (ORs) with the corresponding 95% confidence interval (95% CI) were provided. Studies were excluded when one of the following was: (1) Genotype frequency was not reported or provided; (2) There was insufficient information for meta-analysis even after requesting from authors; (3) Meta-analyses, letters, reviews or editorial articles.

Data extraction

The data was extracted independently by two reviewers according to the inclusion criteria listed above. In case of conflicting evaluations, disagreements were resolved by discussion between the two reviewers. For each study, the following characteristics and numbers were collected: first author, year of publication, country of sample, ethnicity, gender of samples, cancer type, number of cases and controls, genotyping methods, as well as study design and genotyping frequencies in both cases and controls, evidence of Hardy-Weinberg equilibrium (HWE) in controls.

Quality assessment of included studies

Two authors independently assessed the quality of papers according to NOS (Newcastle-Ottawa Scale) quality score systems. Eight assessment items related to the quality appraisal were used in this meta-analysis with scores ranging from 0 to 9. Scores of 0-3 was defined as low, moderate and high quality, respectively. Disagreements were also resolved through discussion between the authors. The supporting NOS quality score system is available in Supplementary 1.

Statistical analysis

All statistical analyses were conducted with Review Manager (RevMan) V.5.2 (Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2015) and Microsoft Excel (V.2007, Microsoft Corporation, Redmond, Washington, USA).

The test for heterogeneity

The fixed-effects model (Mantel-Haenszel method) or the random-effects model (DerSimonian-Laird method) was used for meta-analysis according to the heterogeneity among the pooled studies. Heterogeneity among studies was examined with χ^2-based Q testing and I^2 statistics. $P < 0.1$ was considered significant for the χ^2-based Q testing, if significant heterogeneity was observed ($P < 0.10$ or $I^2 > 50\%$), a random-effects model was applied; otherwise, the fixed-effects model was utilised. Moreover, we minimised the influence of heterogeneity by classifying the enrolled studies into subgroups based on cancer type, ethnicity, gender, genotyping method, and study design.

Effect evaluation

We calculated the strength of the association between AKR1C3 gene polymorphism and risk of cancers by ORs corresponding to 95% CIs. Pooled ORs were calculated for allele frequency comparison (X^+ vs X^-), recessive model ($X^+ X^-$ + $X^+ X^+$ vs $X^- X^-$), dominant model ($X^+ X^-$ + $X^- X^-$ vs $X^+ X^+$), co-dominant model of homozygote effect ($X^+ X^+$ vs $X^- X^-$), and co-dominant model of heterozygote effect ($X^+ X^+$ vs $X^+ X^-$ and $X^+ X^-$ vs $X^- X^-$), respectively. Wherein X^+ represents a mutant allele which occurs single nucleotide polymorphism, X^- represents a wild-type allele. The significance of pooled ORs was determined by Z-test, and $P < 0.05$ was considered statistically significant.

Sensitivity analysis

HWE in the controls was tested by the χ^2 test for goodness of fit using a previous meta-analysis

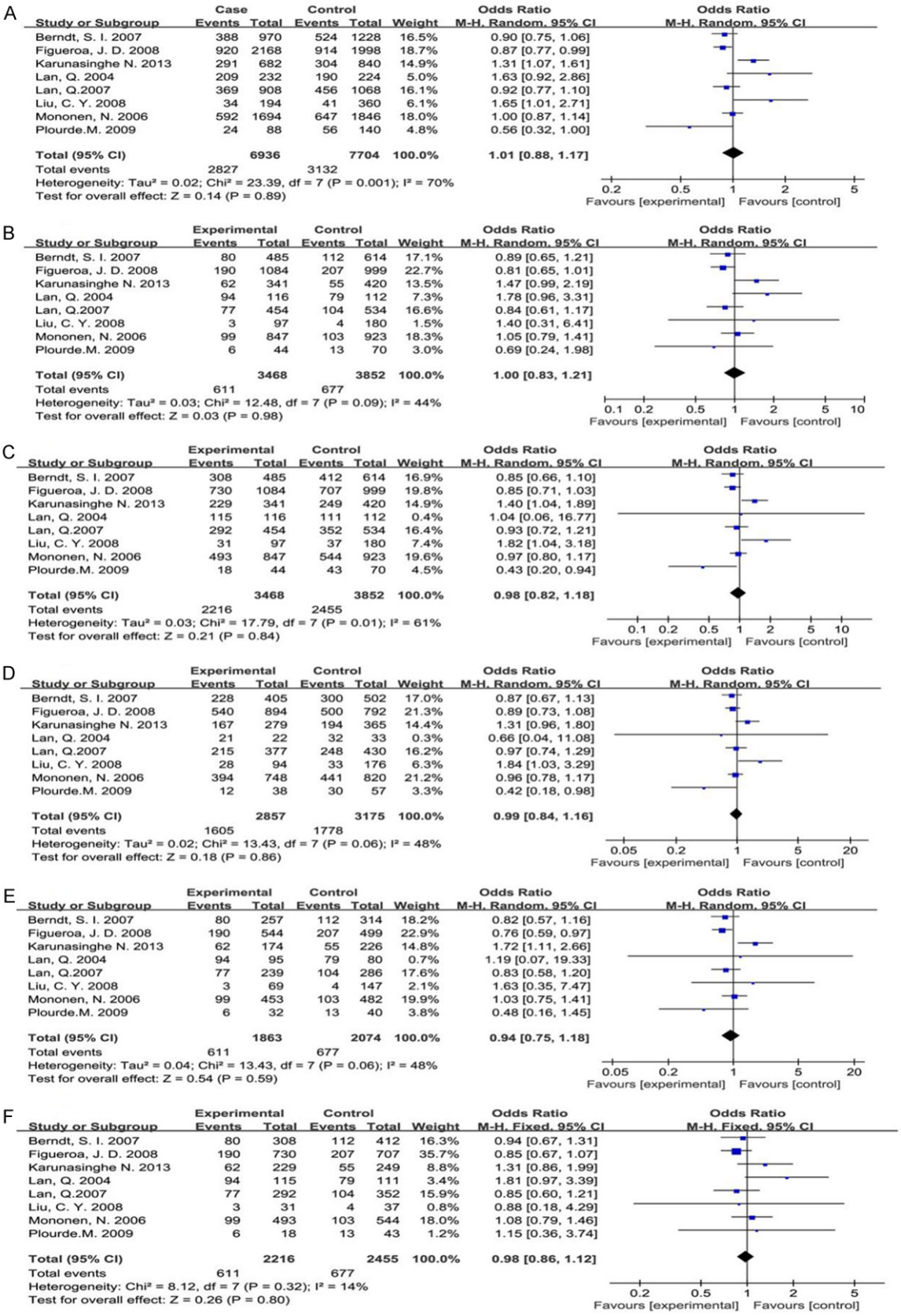

Figure 2. Forest plots of association between rs12529 and cancer risk (A. representative G vs C, B. representative GG vs CC+CG, C. representative CG+GG vs CC, D. representative GG vs CC, E. representative CG vs CC, F. representative GG vs CG).

Table 4. Summary of ORs and Heterogeneity tests for various contrasts on the association between AKR1C3 rs3763676 polymorphism and cancer risk

Gene models	OR	95% CI	P	P^{het}	I^2 (%)
G vs A	0.99	(0.76-1.30)	0.95	0.08	60
GG vs AA+AG	1.18	(0.93-1.48)	0.17	0.39	0
GA+GG vs AA	1.20	(1.03-1.40)	0.02	0.42	0
GG vs AA	1.27	(0.99-1.62)	0.06	0.62	0
GA vs AA	1.18	(1.00-1.39)	0.05	0.23	33
GG vs GA	1.09	(0.85-1.39)	0.49	0.21	36

OR = odds ratio; CI = confidence interval; P^{het} = *P* value for heterogeneity based on Q test.

as reference (Verhagen et al. 2010), and P < 0.01 was considered as significant deviation from HWE. As deviations from HWE in control subjects may bias the estimates of genetic effects in a meta-analysis (Zintzaras, 2010), sensitivity analysis was conducted by comparing results including studies with significant HWE deviations in control subjects with results excluding these studies.

The publication bias

Publication bias was examined with funnel plots, where the presence of publication bias was illustrated in the asymmetric shape of funnel plots [28].

Results

The characteristics of included studies

A total of 86 studies were collected after the first search, and 66 records were excluded because they were review articles, letters, not case-control studies, or were not relevant to the current analysis. Of the remaining studies under evaluation, 4 did not provide sufficient data for further analysis, 2 investigated the association between the gene polymorphisms and the serum hormone levels, 1 base on the same sample. Finally, 13 studies were considered eligible for this meta-analysis, but just 1 study investigated the AKR1C3 rs7741 polymorphism [29], so this study is excluded. A flow chart outlining study selection and reasons for exclusion are presented in **Figure 1**. Among these studies, 8 studies with 3,468 cases and 3,852 controls investigated the AKR1C3 rs12529 polymorphism [16, 18-23, 30]. 4 studies with 1,663 cases and 1,774 controls investigated rs2245191 polymorphism [20, 21, 23, 26]. 3 studies with 2,160 cases and 2,252 controls investigated rs4881400 polymorphism [20, 21, 25]. 3 studies with 1,312 cases and 1,261 controls investigated rs3763676 polymorphism [20, 21, 24]. 3 studies with 2,275 cases and 2,029 controls investigated rs12387 polymorphism [20, 21, 27]. The cancer types in the 12 studies included prostate cancer (5 studies [18, 19, 24, 25, 30]), breast cancer (2 studies [21, 27]), bladder cancer (1 study [20]), lung cancer (1 study [16]), non-Hodgkin lymphoma (2 studies [22, 26]), childhood leukemia (1 study [23]). Among these studies, 5 studies consisted of Caucasian samples, 2 studies with Asian samples, 4 studies with both African and Caucasian samples, and 1 study with both Asian, Caucasian and African samples. Characteristics of all studies included in the meta-analysis are presented in **Table 1**, and the genotype data of all studies are presented in **Table 2**.

Overall analysis

There were 8 studies containing 3468 cases and 3852 controls included in the analysis of AKR1C3 rs12529 polymorphism. As show in **Table 3** and **Figure 2**, no significant association was observed between rs12529 polymorphism and the cancer risk under all genetic models. Significant heterogeneity was observed with P < 0.1 in most models (**Table 3**).

The association of rs3763676 in the AKR1C3 gene with cancer was investigated in 3 studies with a total of 1312 cases and 1261 controls. As show in **Table 4** and **Figure 3**, significant association was observed under dominant model (GA+GG vs AA, OR=1.20, 95% CI 1.03-1.40, P=0.02), and there was not significant heterogeneity was observed in this genetic models. No significant association was observed in other genetic model in the overall analysis (**Table 4**).

The results of the analysis for the association between AKR1C3 rs4881400, rs2245191 polymorphisms and the cancer risk were presented in **Tables 5** and **6** respectively. No sig-

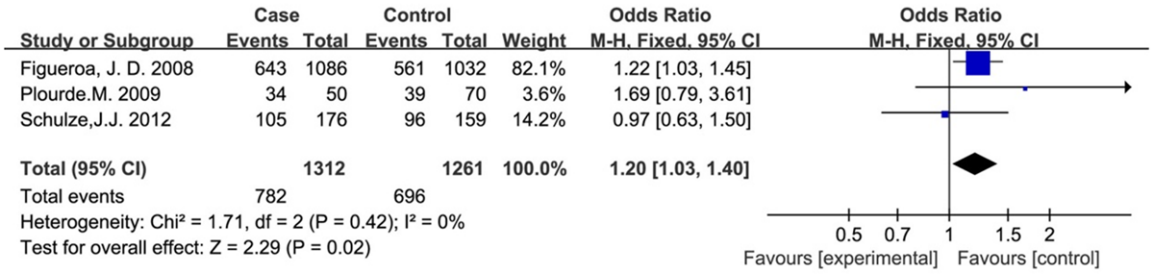

Figure 3. Forest plots of association between rs3763676 and cancer risk (GA+GG vs AA).

Table 5. Summary of ORs and Heterogeneity tests for various contrasts on the association between AKR1C3 rs4881400 polymorphism and cancer risk

Gene models	OR	95% CI	P	P^{het}	I^2 (%)
G vs T	1.05	(0.95-1.17)	0.31	0.42	0
GG vs TT+TG	0.69	(0.39-1.22)	0.2	0.06	64
GT+GG vs TT	0.93	(0.83-1.05)	0.26	0.54	0
GG vs TT	0.68	(0.38-1.21)	0.19	0.06	65
GT vs TT	0.97	(0.85-1.09)	0.58	0.91	0
GG vs GT	0.72	(0.43-1.22)	0.22	0.1	56

OR = odds ratio; CI = confidence interval; P^{het} = *P* value for heterogeneity based on Q test.

Table 6. Summary of ORs and Heterogeneity tests for various contrasts on the association between AKR1C3 rs2245191 polymorphism and cancer risk

Gene models	OR	95% CI	P	P^{het}	I^2 (%)
A vs C	1.39	(0.75-2.59)	0.29	0.0004	87
AA vs CC+CA	0.96	(0.72-1.29)	0.8	0.67	0
AC+AA vs CC	1.06	(0.93-1.22)	0.38	0.12	49
AA vs CC	0.99	(0.73-1.34)	0.93	0.44	0
AC vs CC	1.21	(0.77-1.89)	0.41	0.07	62
AA vs AC	0.92	(0.67-1.25)	0.58	0.97	0

OR = odds ratio; CI = confidence interval; P^{het} = *P* value for heterogeneity based on Q test.

nificant association was observed in all genetic models in the overall analysis.

With respect to the analysis AKR1C3 rs12387 polymorphism. Because one included study [21] provide the sample size of genotype AA and total AG+GG, so we only analyze the associations between rs12387 polymorphism and the cancer risk under one genetic model (GA+GG vs AA). As show in **Figure 4**, neither significant association (OR=1.06, 95% CI 0.93-1.21, P=0.35) nor significant heterogeneity was observed in this genetic models.

Subgroup analysis

Results of subgroup meta-analysis and heterogeneity test of the association between AKR1C3 rs12529 polymorphism and cancer risk are shown in **Table 7**.

When studies were stratified according to cancer type. Only one study was included in childhood leukemia subgroup. Significant association was observed in childhood leukemia under three genetic models (allele G vs allele C, OR=1.65, 95% CI 1.01-2.71, P=0.05; CG+GG vs CC OR=1.82, 95% CI 1.04-3.18, P=0.04; CG vs CC OR=1.84, 95% CI 1.03-3.29, P=0.04). In other cancer types, no significant association was observed between rs12529 and cancer risk.

As show in **Figures 5** and **6**, When studies were stratified according to ethnicity of subjects, significant associations were observed in Asians under two genetic models (allele G vs allele C, OR=1.64, 95% CI 1.13-2.38, P=0.009; CG+GG vs CC, OR=1.78, 95% CI 1.03-3.07, P=0.04). No significant heterogeneity (P > 0.1) was observed in Asians subgroups. There was no significant association observed in other ethnic subgroups.

When studies were stratified according to genotyping methods, study design or gender of subjects, no significant association was found between rs12529 and cancer risk under all genetic models.

We did not perform the subgroup analysis of AKR1C3 rs4881400, rs2245191, rs3763676,

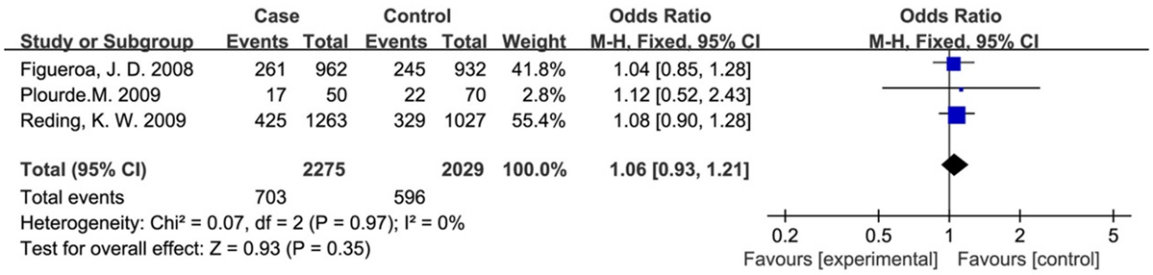

Figure 4. Forest plots of association between rs12387 and cancer risk (GA+GG vs AA).

rs12387 polymorphisms due to the limitations of the studies included.

Sensitivity analysis

To assess the influence of each individual study on the pooled ORs, sensitivity analysis was performed by omission of individual studies. In the analysis of rs4881400, when removing the study (Kwon, E. M. 2012), the pooled ORs of genetic models (GG vs TT+TG, GG vs TT, GG vs GT) changed obviously. In the analysis of rs2245191, when removing the study (Figueroa, J. D. 2008), the pooled ORs of genetic models (A vs C) changed obviously. When removing any individual study, no significant influence of pooled ORs was observed under all genetic models of AKRA1C3 rs12529, rs3763676, rs12387 polymorphisms. The exclusion of the studies (Liu, C. Y. 2008) that deviated from HWE did not change the results significantly.

Publication bias

The funnel plots of the publication bias are presented in **Figure 7**. As shown by symmetric funnel plots, no significant publication bias was observed under all studied models was noted.

Discussion

A large number of studies have addressed the association of AKR1C3 polymorphisms with cancer risk. Overall, the reported effects are of small amplitude and many studies have reported contradictory results. In this study, we performed a comprehensive literature search, and included a total of 13 studies for the analyses between the SNPs of AKR1C3 gene with the risk of cancer. In the combined results, we did not find any significant association between rs12529, rs4881400, rs2245191 and rs12387 polymorphisms with cancer risk. But the results of subgroup analysis of rs12529 polymorphism showed a significant association in Asians under allele frequency comparison model and dominant model (allele G vs allele C, OR=1.64, 95% CI 1.13-2.38, P=0.009; CG+GG vs CC, OR=1.78, 95% CI 1.03-3.07, P=0.04). In regard to rs3763676 polymorphisms, the combined results show significant associations in dominant model (GA+GG vs AA, OR=1.20, 95% CI 1.03-1.40, P=0.02).

The AKR1C3 gene encodes for NADPH-dependent oxidoreductases which catalyze a variety of substrate spectrum: aldehydes, ketones and many xenobiotic compounds. DNA adducts or oxidative DNA damage caused by ROS and the by-products generated in the metabolic processes are associated with carcinogenesis [31]. Previous studies found that the rs12529 polymorphism on exon 1 of AKR1C3 gene is associated with lung cancer [16], but not with prostate cancer [18, 19], Bladder cancer [20], Breast cancer [21], lymphoma [22] or childhood leukemia [23]. In the combined results, we found that the rs12529 polymorphism did not increase the risk of cancer, the result is in accord with most previous studies. When studies were stratified according to cancer type, ethnic, gender, genotyping methods, and study design, significant association was observed in Asians but not in Caucasian, and carrying G allele may be a risk factor for cancer. The inconformity may relate with several factors, the allele frequency data from the dbSNP database for AKR1C3 rs12529 from HapMap show that the most common genotype in Caucasians is the minor allele in Asians (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs5rs12529). There for, the difference may be attributed partially to the ethnicity-related distribution of the geno-

Table 7. Results of subgroup meta-analysis and heterogeneity test of the association between AKR1C3 rs12529 polymorphism and cancer risk

Subroup	N[a]	Test of association		Heterogeneity		Test of association		Heterogeneity		Test of association		Heterogeneity	
		G VS C				GG vs CC+CG				CG+GG vs CC			
		OR (95% CI)	P	I^2 (%)	P^{het}	OR (95% CI)	P	I^2 (%)	P^{het}	OR (95% CI)	P	I^2 (%)	P^{het}
Overall	8	1.01 (0.88-1.17)	0.89	70	0.001	0.96 (0.84-1.09)	0.98	44	0.09	0.98 (0.82-1.18)	0.84	61	0.01
Cancer type													
Prostate cancer	3	1.04 (0.86-1.27)	0.67	75	0.04	1.07 (0.89-1.29)	0.49	49	0.14	1.04 (0.80-1.34)	0.79	70	0.04
Bladder cancer	1	0.87 (0.77-0.99)	0.03	NA	NA	0.81 (0.65-1.01)	0.06	NA	NA	0.85 (0.71-1.03)	0.09	NA	NA
Lung cancer	1	1.63 (0.92-2.86)	0.09	NA	NA	1.78 (0.96-3.31)	0.07	NA	NA	1.04 (0.06-16.77)	0.98	NA	NA
Non-Hodgkin lymphom	1	0.92 (0.77-1.10)	0.36	NA	NA	0.84 (0.61-1.17)	0.31	NA	NA	0.93 (0.72-1.21)	0.6	NA	NA
Childhood leukemia	1	1.65 (1.01-2.71)	0.05	NA	NA	1.40 (0.31-6.41)	0.66	NA	NA	1.82 (1.04-3.18)	0.04	NA	NA
Breast cancer	1	0.56 (0.32-1.00)	0.05	NA	NA	0.69 (0.24-1.98)	0.49	NA	NA	0.43 (0.20-0.94)	0.03	NA	NA
Ethnic group													
Asian	2	1.64 (1.13-2.38)	0.009	0	0.97	1.73 (0.97-3.05)	0.06	0	0.77	1.78 (1.03-3.07)	0.04	0	0.7
Caucasian	4	0.97 (0.79-1.20)	0.8	79	0.002	1.01 (0.76-1.36)	0.93	60	0.06	0.95 (0.72-1.25)	0.71	75	0.008
Caucasian + African	2	0.91 (0.80-1.03)	0.12	0	0.84	0.87 (0.69-1.09)	0.21	0	0.84	0.89 (0.74-1.07)	0.21	0	0.63
Gender													
Men	3	1.04 (0.86-1.27)	0.67	75	0.02	1.09 (0.83-1.42)	0.54	49	0.14	1.04 (0.80-1.34)	0.79	70	0.04
Female	2	0.78 (0.49-1.23)	0.28	60	0.11	0.83 (0.61-1.13)	0.24	0	0.72	0.70 (0.34-1.44)	0.33	70	0.07
Mixed	3	1.26 (0.76-2.09)	0.37	80	0.007	1.16 (0.62-2.16)	0.65	66	0.05	1.17 (0.61-2.22)	0.64	68	0.04
Genotyping methods													
TaqMan	4	1.07 (0.85-1.36)	0.57	82	0.001	1.00 (0.74-1.34)	0.98	57	0.07	1.09 (0.81-1.49)	0.56	78	0.003
Real-time PCR	2	1.15 (0.66-1.97)	0.63	72	0.06	1.17 (0.57-2.42)	0.67	77	0.04	0.93 (0.72-1.21)	0.6	0	0.94
Microarray	1	1.00 (0.87-1.14)	0.95	NA	NA	1.05 (0.79-1.41)	0.73	NA	NA	0.97 (0.80-1.17)	0.75	NA	NA
PCR-RFLP	1	0.56 (0.32-1.00)	0.05	NA	NA	0.69 (0.24-1.98)	0.49	NA	NA	0.43 (0.20-0.94)	0.03	NA	NA
Study design													
PCC	6	1.09 (0.92-1.28)	0.33	68	0.008	1.09 (0.87-1.36)	0.47	42	0.12	1.07 (0.87-1.30)	0.54	55	0.05
HCC	2	0.77 (0.52-1.14)	0.19	53	0.14	0.81 (0.65-1.00)	0.05	0	0.77	0.68 (0.36-1.27)	0.22	64	0.1

Subroup	N[a]	Test of association		Heterogeneity		Test of association		Heterogeneity		Test of association		Heterogeneity	
		GG vs CC				CG vs CC				GG vs CG			
		OR (95% CI)	P	I^2 (%)	P^{het}	OR (95% CI)	P	I^2 (%)	P^{het}	OR (95% CI)	P	I^2 (%)	P^{het}
Overall	8	0.94 (0.75-1.18)	0.59	48	0.06	0.99 (0.84-1.16)	0.86	48	0.06	0.98 (0.86-1.12)	0.8	14	0.32
Cancer type													
Prostate cancer	3	1.11 (0.75-1.64)	0.61	71	0.03	1.01 (0.82-1.25)	0.94	52	0.12	1.07 (0.88-1.31)	0.49	0	0.48
Bladder cancer	1	0.76 (0.59-0.97)	0.03	NA	NA	0.89 (0.73-1.08)	0.25	NA	NA	0.85 (0.67-1.07)	0.17	NA	NA

Lung cancer	1	1.19 (0.07-19.33)	0.9	NA	NA	0.66 (0.04-11.08)	0.77	NA	NA	1.81 (0.97-3.39)	0.06	NA	NA
Non-Hodgkin lymphom	1	0.83 (0.58-1.20)	0.32	NA	NA	0.97 (0.74-1.29)	0.85	NA	NA	0.85 (0.60-1.21)	0.37	NA	NA
Childhood leukemia	1	1.63 (0.35-7.47)	0.53	NA	NA	1.84 (1.03-3.29)	0.04	NA	NA	0.88 (0.18-4.29)	0.88	NA	NA
Breast cancer	1	0.48 (0.16-1.45)	0.19	NA	NA	0.42 (0.18-0.98)	0.05	NA	NA	1.15 (0.36-3.74)	0.81	NA	NA
Ethnic group													
Asian	2	1.51 (0.40-5.76)	0.54	0	0.85	1.76 (1.00-3.12)	0.05	0	0.48	1.64 (0.92-2.94)	0.09	0	0.41
Caucasian	4	0.99 (0.66-1.49)	0.95	75	0.007	0.96 (0.76-1.21)	0.72	63	0.05	1.00 (0.82-1.23)	0.97	20	0.29
Caucasian + African	2	0.82 (0.64-1.06)	0.13	0	0.94	0.92 (0.76-1.11)	0.37	0	0.56	0.90 (0.71-1.14)	0.38	0	0.07
Gender													
Men	3	1.11 (0.75-1.64)	0.61	71	0.03	1.01 (0.82-1.25)	0.94	52	0.12	1.07 (0.88-1.31)	0.49	0	0.48
Female	2	0.79 (0.56-1.11)	0.18	0	0.35	0.70 (0.31-1.58)	0.4	71	0.06	0.87 (0.63-1.22)	0.43	0	0.63
Mixed	3	0.78 (0.61-0.99)	0.04	0	0.6	1.17 (0.63-2.15)	0.62	63	0.07	0.93 (0.75-1.15)	0.52	60	0.08
Genotyping methods													
TaqMan	4	1.02 (0.67-1.56)	0.92	73	0.01	1.08 (0.82-1.42)	0.58	68	0.02	0.94 (0.79-1.13)	0.54	5	0.37
Real-time PCR	2	0.84 (0.58-1.20)	0.33	0	0.8	0.97 (0.73-1.28)	0.83	0	0.79	1.19 (0.57-2.47)	0.65	76	0.04
Microarray	1	1.03 (0.75-1.41)	0.86	NA	NA	0.96 (0.78-1.17)	0.66	NA	NA	1.08 (0.79-1.46)	0.64	NA	NA
PCR-RFLP	1	0.48 (0.16-1.45)	0.19	NA	NA	0.42 (0.18-0.98)	0.05	NA	NA	1.15 (0.36-3.74)	0.81	NA	NA
Study design													
PCC	6	1.04 (0.80-1.35)	0.78	43	0.12	1.05 (0.88-1.25)	0.61	41	0.13	1.06 (0.88-1.28)	0.52	14	0.32
HCC	2	0.74 (0.58-0.95)	0.02	0	0.43	0.69 (0.34-1.39)	0.03	65	0.09	0.86 (0.68-1.08)	0.19	0	0.62

N^a = Number of studies; OR = odds ratio; CI = confidence interval; P^{het} = *P* value for heterogeneity based on Q test; NA: not applicable.

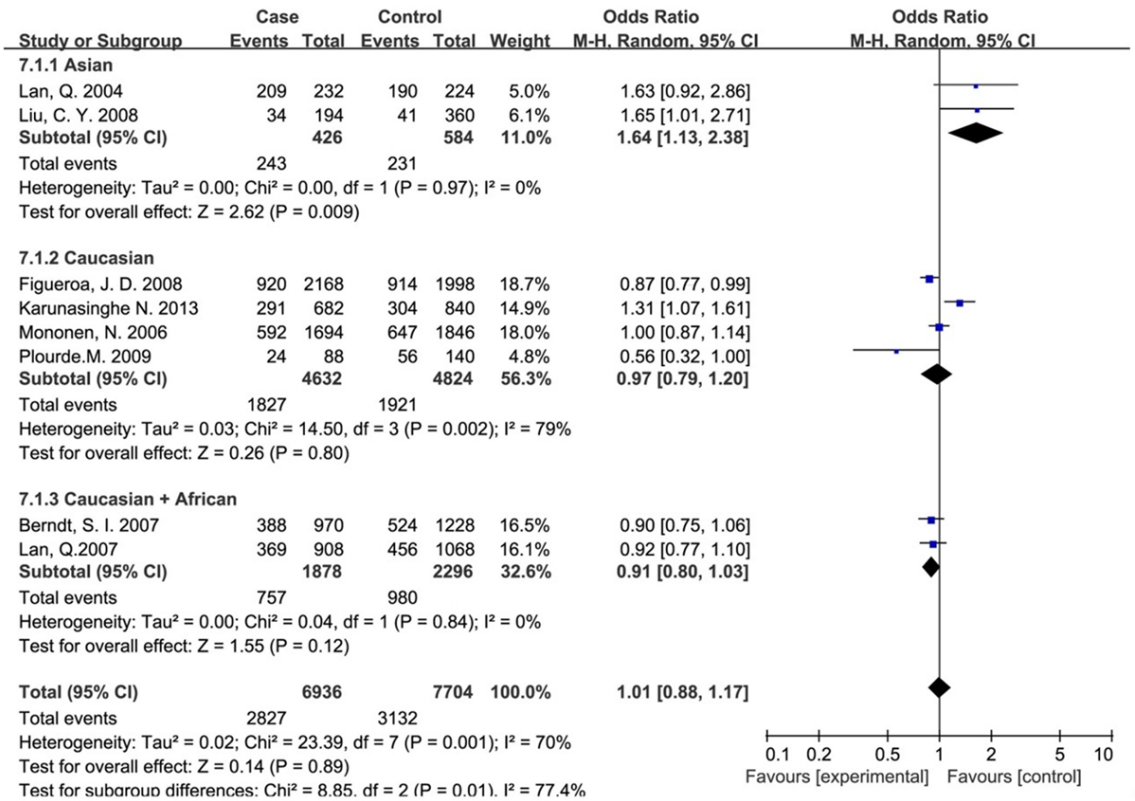

Figure 5. Forest plots of association between rs12529 and cancer risk when studies were stratified by ethnicity (G vs C).

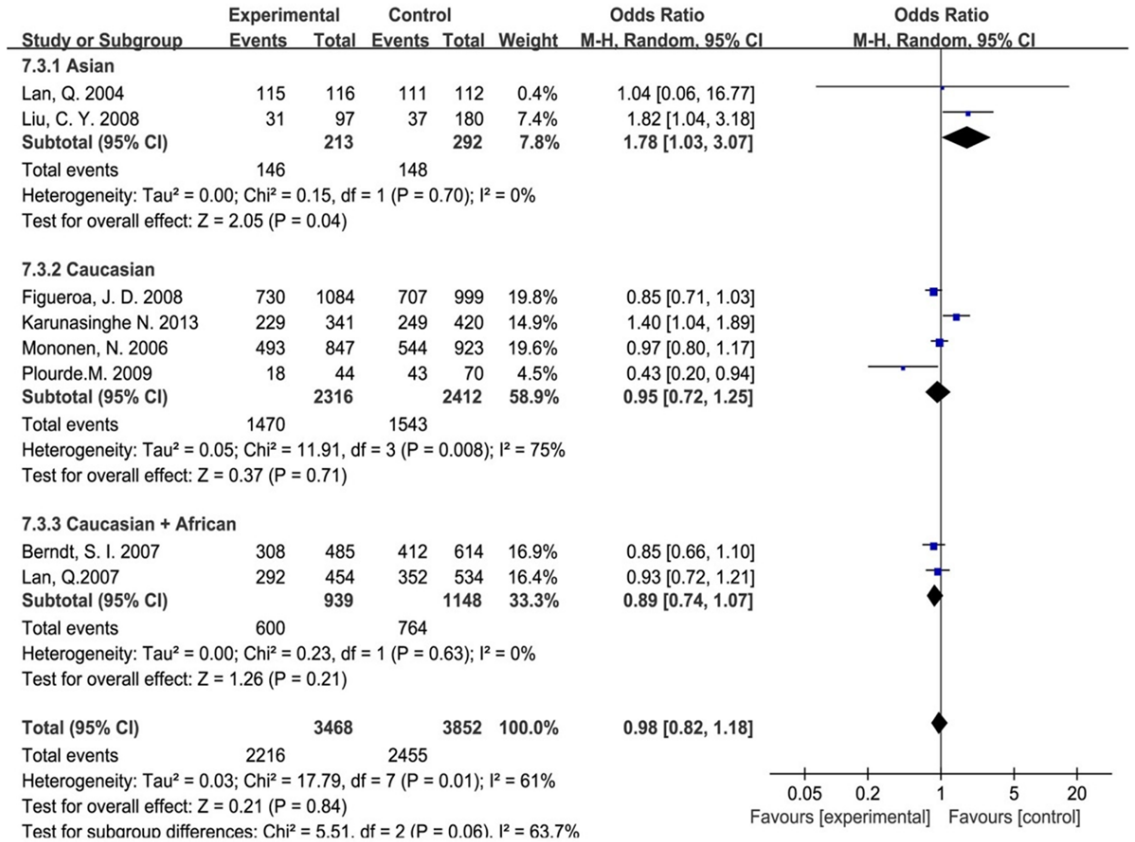

Figure 6. Forest plots of association between rs12529 and cancer risk when studies were stratified by ethnicity (CG+GG vs CC).

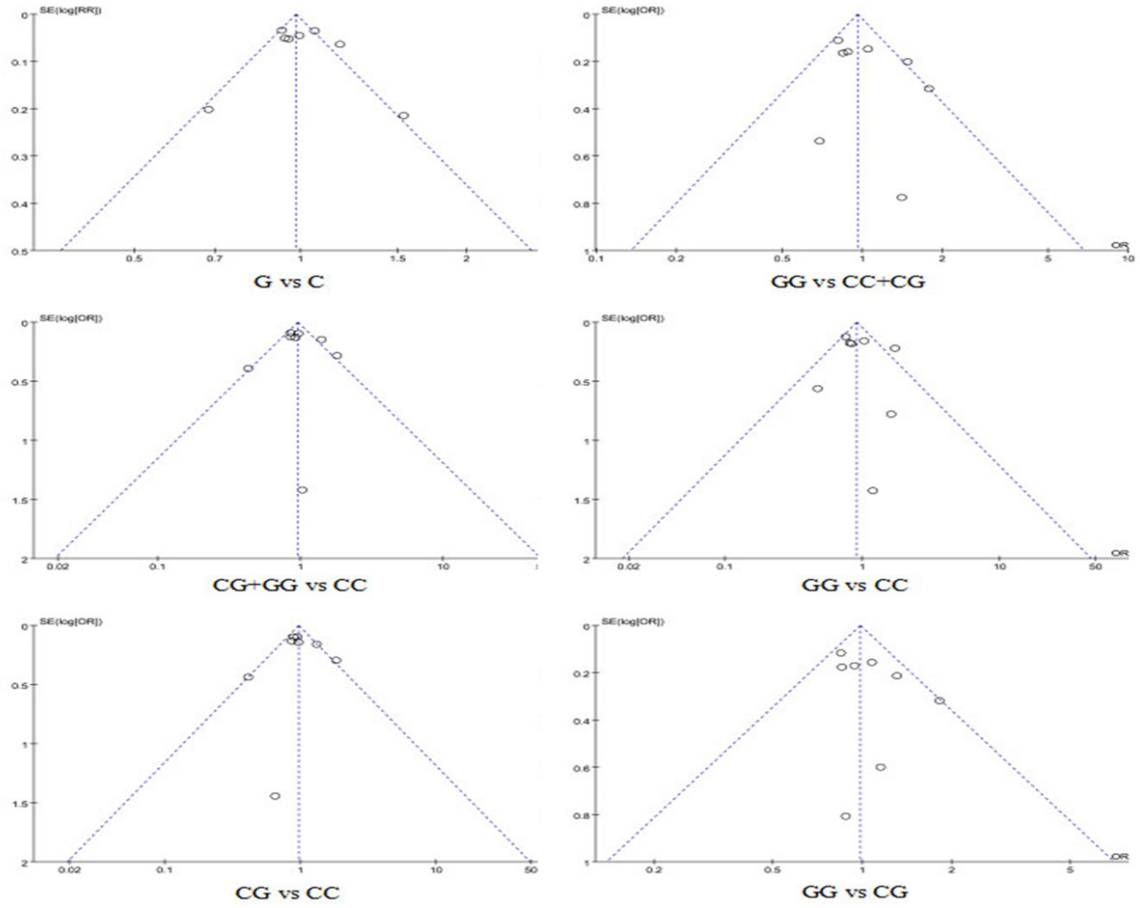

Figure 7. The funnel plots of the publication bias for rs12529.

type frequency. And then, environments, different matching criteria and selection biases might contribute to the diverse results. Furthermore, the Asians subgroup analysis was based on a small sample (213 cases and 296 controls). Further studies with larger sample sizes are needed before the difference in risk estimates between cancers in different populations can be explained.

We also found significant associations between rs3763676 polymorphism with cancer risk under dominant model (GA+GG VS AA). Someone who carrying the AKR1C3 rs3763676 locus GA or GG genotype was more susceptible to cancer than AA genotype. This results may be due to the influence of the SNPs to enzyme metabolic pathways [24]. However, there were only a few studies concentrate on the function of rs3763676 polymorphism, so the accurate function of this SNP is undefined. Further studies are needed before this result explained.

Some limitations of this meta-analysis should be noted in interpreting the results. First, the sample size is still too small to provide sufficient statistical power to estimate the correlation between AKR1C3 polymorphisms and cancer risk. Second, in some cases, heterogeneity was still present after subgroup analysis, it indicates that we have not detect all heterogeneous factors. Third, this meta-analysis was based on unadjusted data, because not all published provide adjusted ORs and 95% CI. It is well acknowledged that many other factors, such as gene-gene or gene-environment interaction may affect the risk of cancer. We was not able to obtain the relevant data. And thus the

potential roles of the above gene polymorphisms might be masked or magnified by other gene-gene or gene-environment interactions. Fourth, only published studies were included, so it is impossible to excluded the selection bias completely. In spite of these limitations, our meta-analysis still has some advantages. We have searched multiple databases based on computer-assisted program and manual search in order to include all eligible studies. And we did not find obvious publication bias in this meta-analysis. Furthermore, the sensitivity analysis indicated that the results are statistically robust.

In conclusion, as the first meta-analysis of the association between SNPs in AKR1C3 gene with overall cancer risk. Our study did not find significant association between rs12529, rs4881400, rs2245191 and rs12387 polymorphisms with cancer risk. In stratification analysis, rs12529 polymorphism might be associated with increased risk of cancer in Asians with the variable alleles as risk alleles. We also observed that rs3763676 polymorphism of AKR1C3 gene were significantly associated with cancer risk, and carrying the rs3763676 locus GA or GG genotype was more susceptible to cancer. But the mechanism to explain the result is ambiguous. Further studies with larger sample sizes and well-designed based on different ethnic groups are needed to confirm these results.

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Disclosure of conflict of interest

None.

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Newcastle-Ottawa quality assessment scale case control studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
a) yes, with independent validation ★
b) yes, eg record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases ★
b) potential for selection biases or not stated
3) Selection of controls
a) community controls ★
b) hospital controls
c) no description
4) Definition of controls
a) no history of disease (endpoint) ★
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor.) ★
b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) ★
b) structured interview where blind to case/control status ★
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes ★
b) no
3) Non-response rate
a) same rate for both groups ★
b) non respondents described
c) rate different and no designation