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Original Article

Association between angiotensin I-converting enzyme gene polymorphism and susceptibility to cancer: a meta analysis

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Abstract: Background: Angiotensin I-converting enzyme (ACE) gene plays an important role in the pathogenesis of cancers. The association between ACE insertion/deletion (I/D) polymorphism and the risk of various cancers has been studied. However, the results of these studies remain conflicting. Therefore, we performed a meta-analysis to evaluate the association between ACE I/D polymorphism and the risk of cancers. Methods: PubMed, Embase, ScienceDirect, Springer, CNKI, Wanfang, Weipu, CBM databases and Google Scholar were searched for case-control studies on ACE I/D polymorphism and the risk of cancers, published up to Dec 31, 2013. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association between ACE I/D polymorphism and cancer risk. Results: Thirty-five published studies with 5007 cases and 8173 controls were included. Overall, there were no significant association between ACE I/D polymorphism and the risk of cancers (II vs. ID+DD OR = 1.05, 95% CI = 0.89-1.23, I vs. D OR = 1.00, 95% CI = 0.89-1.13). However, when stratified by ethnicity, we found a significant association between this polymorphism and cancer risk in Caucasians (II vs. ID+DD: OR = 1.43, 95% CI = 1.02-2.00, I vs. D: OR = 1.23, 95% CI 1.01-1.49). Conclusion: ACE I/D polymorphism is associated with the cancer risk in Caucasians.

Keywords: ACE I/D, single nucleotide polymorphism, cancer risk, meta-analysis

Introduction

Angiotensin I-converting enzyme (ACE) is a zinc metallopeptidase which converts angiotensin I to angiotensin II. ACE is one of the key enzymes in human renin-angiotensin system (RAS) [1]. It plays an important role in the modulation of vascular homeostasis, inflammation and angiogenesis [2-4]. ACE is expressed in many tissues and systems including lung, vasculature, kidney, heart, and testes [5]. Emerging evidence has shown that the expression of ACE is up-regulated in several types of cancers [6-9]. Moreover, ACE inhibitors are currently considered being used as novel antineoplastic therapies [6, 10].

The ACE gene is located on human's chromosome 17q23 that consists of 26 exons and 25 introns [11]. The ACE insertion/deletion (I/D) polymorphism of 287bp Alu repeat sequence in intron 16 (rs4646994) has been reported [11]. Although the I/D polymorphism is not located in the coding region of the ACE gene, subjects with ACE D allele exhibits a higher plasma ACE level and activity [12]. The I/D polymorphism account for 20% to 50% of the variance in ACE expression or activity in blood and tissues among individuals [13].

Up to now, a number of studies were conducted to evaluate the association between ACE I/D polymorphism and risk of different types of cancers in diverse populations. However, the results from the published studies remain conflicting rather than conclusive. Therefore, we performed a meta-analysis on all eligible case-control studies to clarify the association between ACE I/D polymorphism and cancer risk.

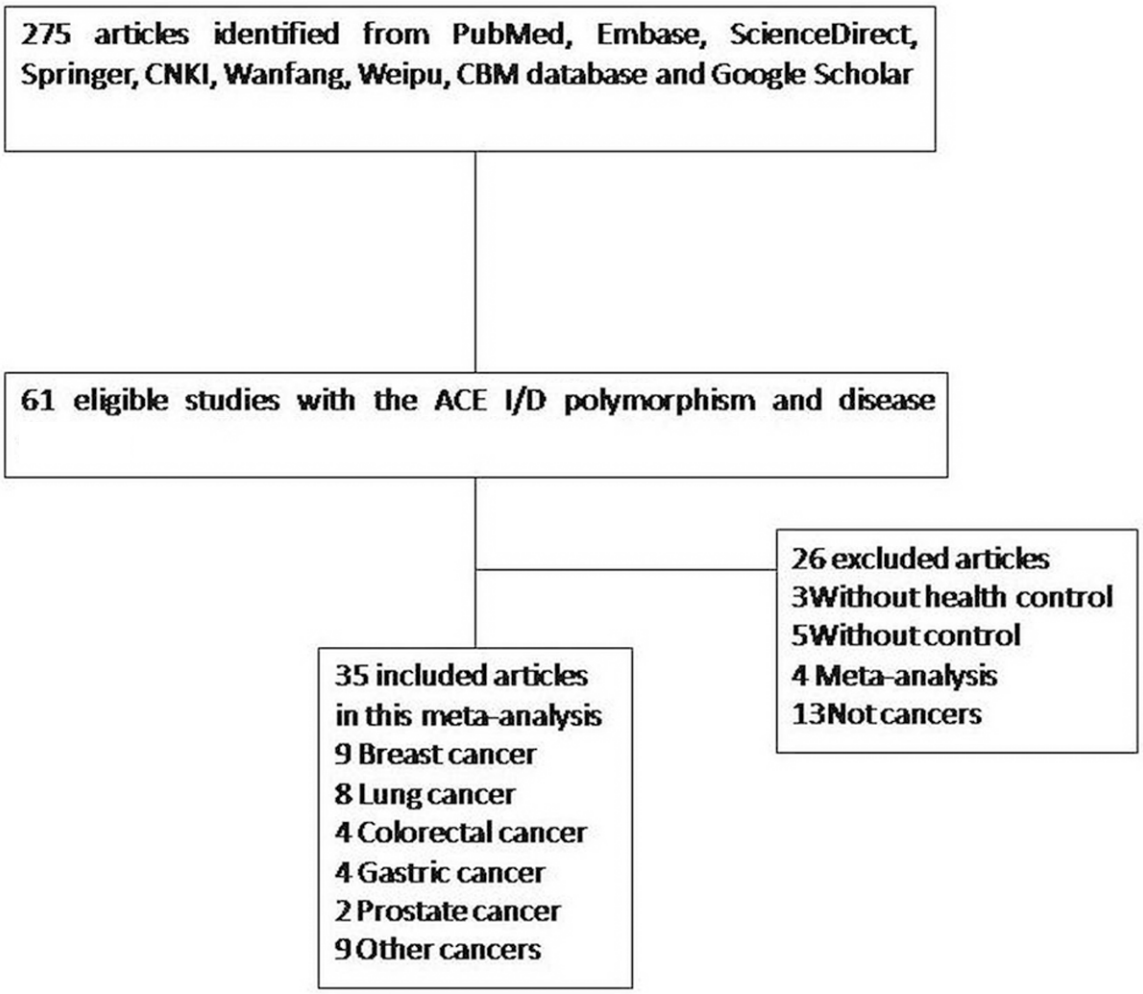

Figure 1. Flow diagram of study selection.

Methods

Literature search

We conducted the literature search by using the PubMed, Embase, ScienceDirect, Springer, CNKI, Wanfang, Weipu, CBM databases and Google Scholar for relevant articles published (update to Dec 31, 2013) with the following search terms: "ACE" or "angiotensin I converting" and "polymorphism" or "insertion/deletion" and "cancer" or "carcinoma" or "tumor". In addition, the studies were identified by manual search of the reference lists of reviews and retrieved studies. The inclusion criteria were: (1) the study evaluated the association between ACE polymorphism and cancer risk in human; (2) a case-control study; (3) genotype distributions in both cases and controls were available for estimating an odds ratio with 95% confidence interval (CI) and *P* value, (4) genotype distributions of controls must be consistent with Hardy-Weinberg equilibrium (HWE). Main exclusion criteria of studies were as follows: (1) case reports, reviews, letters and editorial articles; (2) only case population; (3) duplicate of previous publication; and (4) the distribution of genotypes among controls are consistent with HWE.

Data extraction

Two investigators (Zhang and Cheng) extracted the data from all eligible studies independently. We checked all potentially relevant studies and reached a consensus on all items. From each study, the following information was extracted: first author's name, year of publication, country of origin, ethnicity, definition of case, source of control selection and the genotype frequencies in cases and controls.

Table 1. Distribution of ACE genotype and allele among cancer patients and controls

	Author	Year	Cancer type	Country	Source	Case			Control			Case		Control	
						II	ID	DD	II	ID	DD	I	D	I	D
1	Yaren A	2007	Breast	Turkey	hospital-based	2	24	31	7	12	33	28	86	26	78
2	Vairaktaris E	2007	Oral	Greece	hospital-based	30	70	60	9	66	78	130	190	84	222
3	Liu SY	2011	Colorectal	China	hospital-based	71	138	32	95	158	46	280	202	348	250
4	Nacak M	2010	Lung	Turkey	hospital-based	37	50	38	29	72	64	124	126	130	200
5	Nikiteas N	2007	Colorectal	Greece	hospital-based	15	27	50	6	44	52	57	127	56	148
6	Kupcinskas J	2011	Gastric	Germany	hospital-based	27	59	28	62	110	66	113	115	234	242
7	Namazi S	2010	Breast	Iranian	hospital-based	8	42	20	7	34	29	58	82	48	92
8	Yaren A	2006	Breast	Turkey	hospital-based	2	17	25	6	12	28	21	67	24	68
9	Usmani BA	2000	Renal	USA	hospital-based	8	29	21	101	295	157	45	71	497	609
10	Yigit B	2007	Prostate	Turkey	hospital-based	4	19	25	12	24	15	27	69	48	54
11	Sugimoto M	2006	Gastric	Japan	hospital-based	54	53	12	50	60	22	161	77	160	104
12	Koh WP	2003	Breast	Singapore	population-based	79	80	23	282	305	56	238	126	869	417
13	Srivastava K	2010	Gall Bladder	Indian	population-based	90	116	26	107	131	22	296	168	345	175
14	Yuan F	2012	Hepatocellular	China	hospital-based	59	214	16	84	211	89	332	246	379	389
15	Yaren A	2008	Lung	Turkey	hospital-based	4	39	32	14	37	34	47	103	65	105
16	Alves Corrêa SA	2009	Breast	Brazilian	hospital-based	20	20	61	53	113	141	60	142	219	395
17	Gao M	2012	Lung	China	hospital-based	351	271	62	320	253	29	973	395	893	311
18	Lukic S	2011	Pancreatic	Serbia	hospital-based	24	17	4	30	72	26	65	25	132	124
19	Goto Y	2005	Gastric	Japan	population-based	76	98	28	209	189	56	250	154	607	301
20	Toma M	2009	Colorectal	Romanian	hospital-based	25	50	33	30	73	47	100	116	133	167
21	Haiman CA	2003	Breast	Japan	population-based	119	128	37	154	160	43	366	202	468	246
21	Haiman CA	2003	Breast	Latin	population-based	73	127	49	189	301	162	273	225	679	625
21	Haiman CA	2003	Breast	USA	population-based	79	129	84	91	187	124	287	297	369	435
24	Li ZH	2011	Nasopharyngeal	China	hospital-based	67	78	30	94	142	43	212	138	330	228
25	Mendizabal-Ruiz AP	2011	Breast	Mexico	hospital-based	4	6	53	74	151	63	14	112	299	277
26	Cheon KT	2000	Lung	Korea	hospital-based	72	116	30	48	50	23	260	176	146	96
27	Ding XJ	2008	Lung	China	hospital-based	55	56	10	19	10	4	166	76	48	18
28	Holla L	1998	Leukemia	Czech	hospital-based	25	11	4	40	86	76	61	19	166	238
29	Rocken C	2005	Gastric	Germany	hospital-based	24	57	32	41	95	53	105	121	177	201
30	Rocken C	2007	Colorectal	Germany	hospital-based	37	69	35	41	95	53	143	139	177	201
31	Tunny TJ	1996	Aldosterone-producing adenoma	Australia	hospital-based	16	25	14	24	34	22	57	53	82	78
32	Ozen F	2013	Lung	Greece	population-based	10	30	12	67	105	40	50	54	239	185
33	Vaskù V	2004	T-cell lymphoma	Turkey	hospital-based	19	37	21	43	103	57	75	79	189	217
34	Wang HW	2000	Lung	China	hospital-based	10	6	18	13	18	7	26	42	44	32
35	Zhang QZ	2005	Lung	China	hospital-based	21	21	5	20	30	4	63	31	70	38

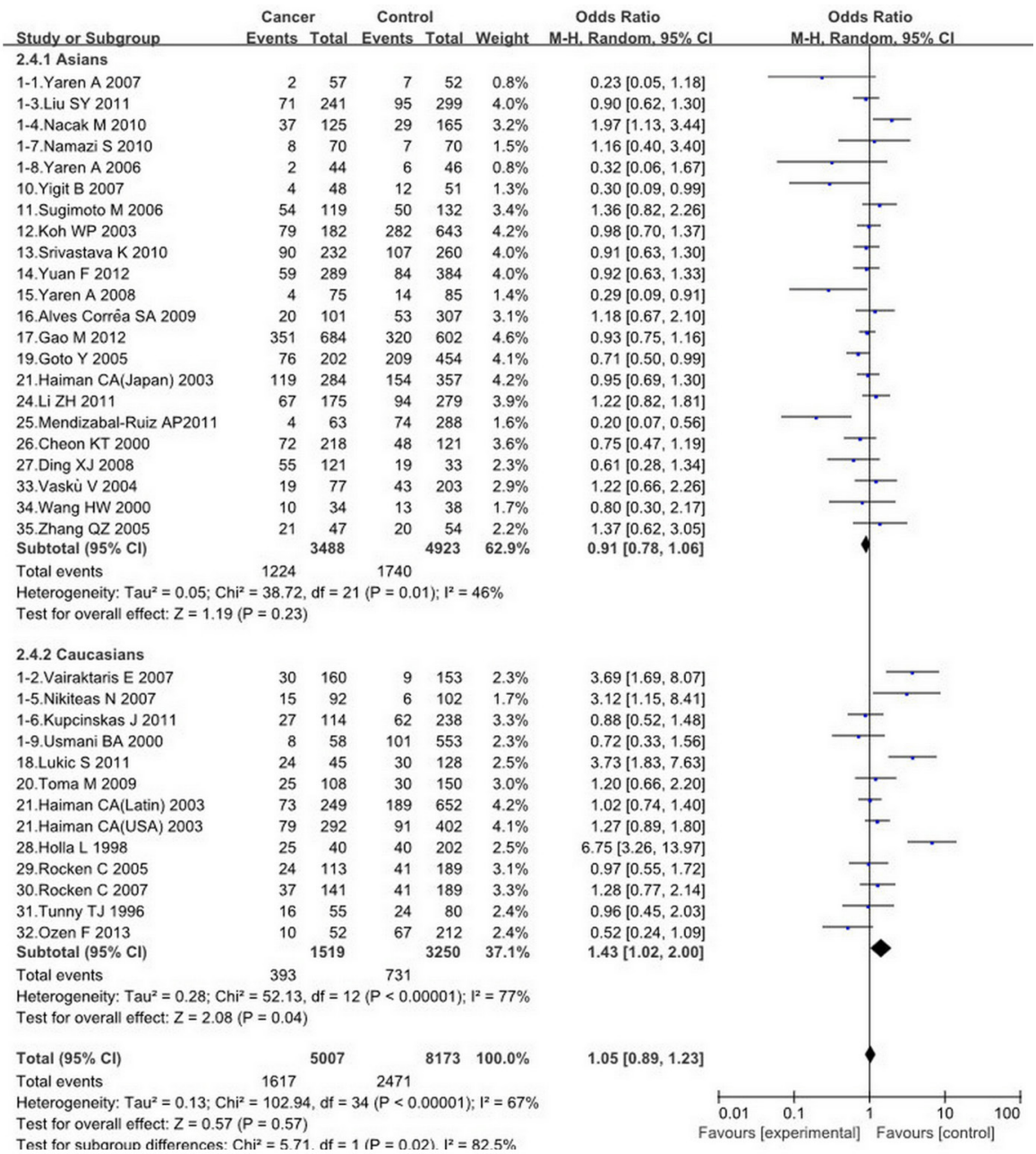

Figure 2. The association between ACE I/D polymorphism and cancer risk in subgroup analysis by ethnicity (II VS. ID+DD).

Statistical analysis

For each case-control study, we first examined whether the genotype distributions in control group were consistent with Hardy-Weinberg equilibrium by *P*earson's X^2 test. Heterogeneity was evaluated by the X^2 based Q statistic and was considered statistical significant at *P* value < 0.10. I^2 value was also used to measure the percentage of variability in studies that due to heterogeneity rather than chance. When the effects were assumed to be homogenous, fixed-effects model was used (the Mantel-Haenszel method); otherwise, it was more appropriate to use random-effects model (DerSimonian and Laird method) [14-16]. The strength of associations between ACE I/D polymorphism and cancer risk were measured by ORs with 95% CIs. The pooled ORs were evaluated for the homozygote comparison (II vs. DD),

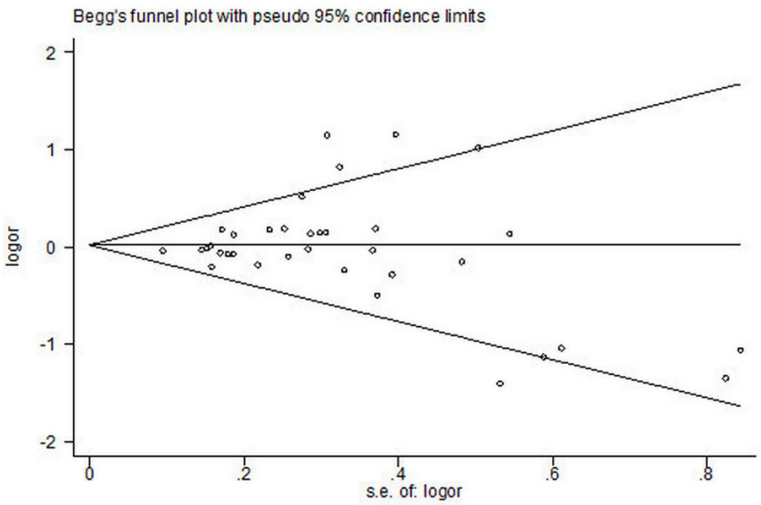

Figure 3. Begg's funnel plot for publication bias in selection of studies on ACE I/D polymorphism (II VS. ID + DD; bias = 0.871).

heterozygote comparison (ID vs. DD), dominant model (II+ID vs. DD) recessive model (II vs. ID+DD), and haploid model (I vs. D) comparison. The funnel plots as well as Begg's tests and Egger's test were used to investigate publication bias [17]. Sensitivity analysis was performed to assess the stability of the results by sequentially excluding each study [18]. All statistical analyses were performed by using the Revman 5.2 software (Cochrane Library Software, Oxford, UK) and STATA11.0 (STATA Corporation, College Station, TX, USA).

Results

Studies characteristics

Overall, 35 publications [13, 19-52] including 5007 cases and 8137 controls were available for this meta-analysis based on the inclusion and exclusion criteria (**Figure 1**). The main characteristics of these studies are summarized in **Table 1**. There were 22 studies of Asian populations, 13 studies of Caucasians population. Of the 35 studies, 7 articles were population-based and 28 articles were hospital-based. The diagnosis of most of the cases was based on pathology. Healthy subjects matched for age and sex were used as controls. Polymerase chain reaction (PCR) was performed for genotyping.

Meta-analysis

A summary of the meta-analysis results of the association between ACE I/D polymorphism and cancer risk is shown, there are no significant association was found between ACE I/D polymorphism and the risk of cancers (II vs. DD OR = 0.97, 95% = CI 0.76-1.24, ID vs. DD OR = 0.98, 95% CI = 0.79-1.21, II+ID vs. DD OR = 0.99, 95% CI = 0.80-1.23, II vs. ID+DD OR = 1.05, 95% CI = 0.89-1.23, I vs. D OR = 1.00, 95% CI = 0.89-1.13). However, in the subgroup analyses by ethnicity, there was a significant association between this ACE I/D polymorphism and cancer risk in Caucasians (II vs. ID+DD: OR = 1.43, 95% CI = 1.02-2.00, I vs. D: OR = 1.23, 95% CI 1.01-1.49) (**Figures 2**, **4**). In the subgroup analyses by cancer types, no significant association was found under different genetic models.

Test of heterogeneity

For the overall analysis, the Q-statistic was significant and I^2 showed stable variation under the comparisons (II vs. DD: $P < 0.00001$, $I^2 = 74\%$; ID vs. DD $P < 0.00001$, $I^2 = 76\%$; II+ID vs. DD $P < 0.00001$, $I^2 = 79\%$; II vs. ID+DD $P < 0.00001$, $I^2 = 67\%$; I vs. D $P < 0.00001$, $I^2 = 78\%$). In the subgroup analyses of ethnicity, the I^2 showed inconsistent with the former, the I^2 of II vs. ID+DD are 46% and 77%. While there is no notable difference of I^2 in I vs. D, the former is 78%, the latter are 78% and 76 % (**Figures 2**, **4**).

Sensitivity analysis

The influence of a single study on the overall meta-analysis estimate was investigated by excluding each study at a time. The omission of any study made no significant difference. This is indicating that the results of our meta-analysis were statistically reliable.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literatures. Egger's test did not show any evidence of publication bias (t = 0.16, $P = 0.871$ for II vs. ID+DD and t = -0.78, $P = 0.440$ for I vs. D, respectively) (**Figures 3**, **5**).

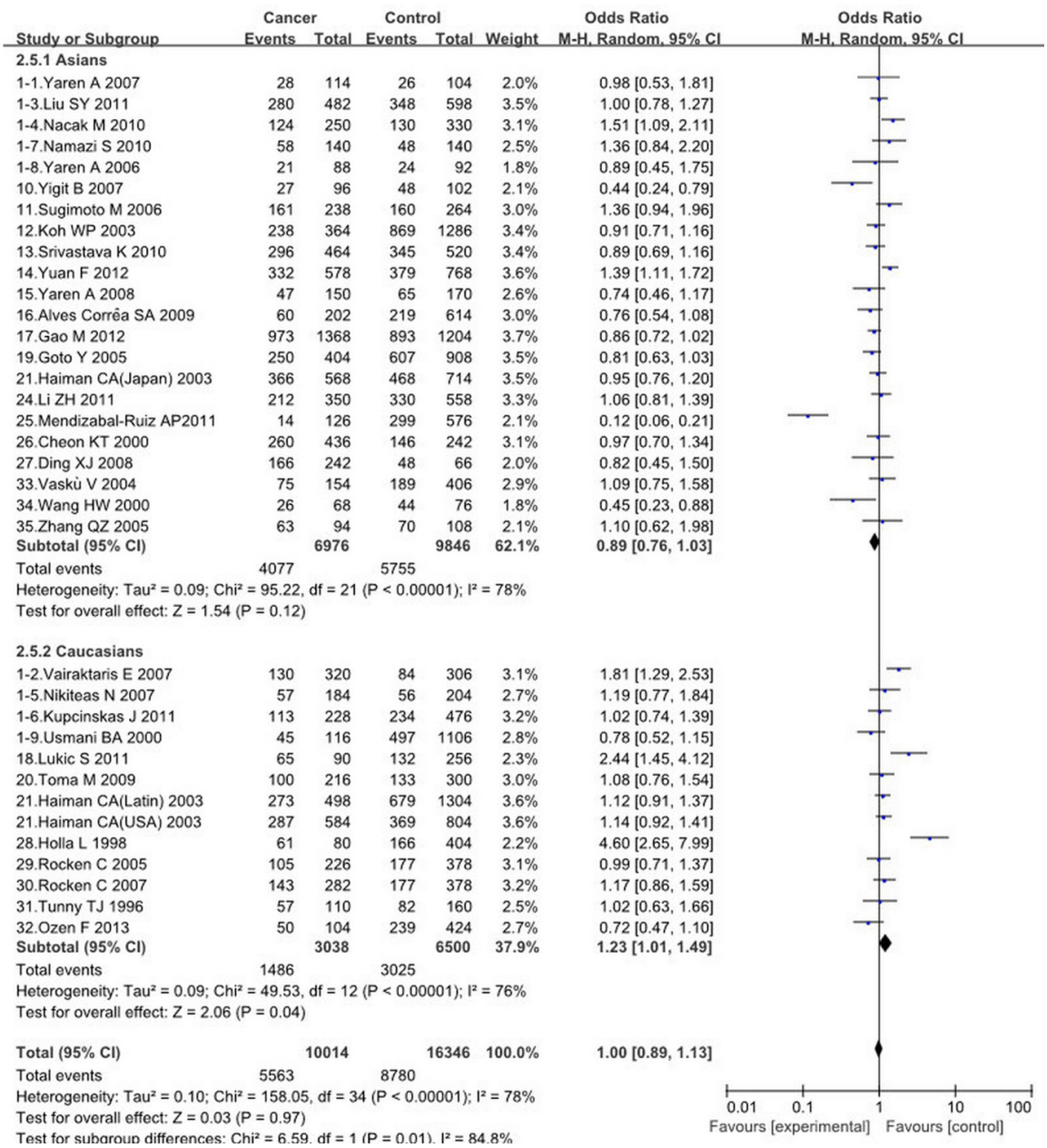

Figure 4. The association between ACE I/D polymorphism and cancer risk in subgroup analysis by ethnicity (I VS. D).

Discussion

Human ACE is the key enzyme in the renin-angiotensin system, which works in the regulation of blood pressure, the number of red blood cell, cardiovascular homeostasis and serum electrolytes. In recent years there were more evidences indicating that ACE was associated with the pathogenesis of cancer, even it was the trigger events at least in some group of patients with cancer. It may influence tumor cell adhesion, proliferation, migration, angiogenesis and metastatic behaviors [53]. Some studies showed that the ACE inhibitor could lower the breast cancer risk [10]. But in some meta-analyses, show that there were no significant association between the ACE I/D polymorphisms and breast cancer risk. In different cancer studies, have the inconsistent and conflict result. On the other hand, there are some studies about the risk of ACE gene polymorphism with variety of cancers, for example, in prostate

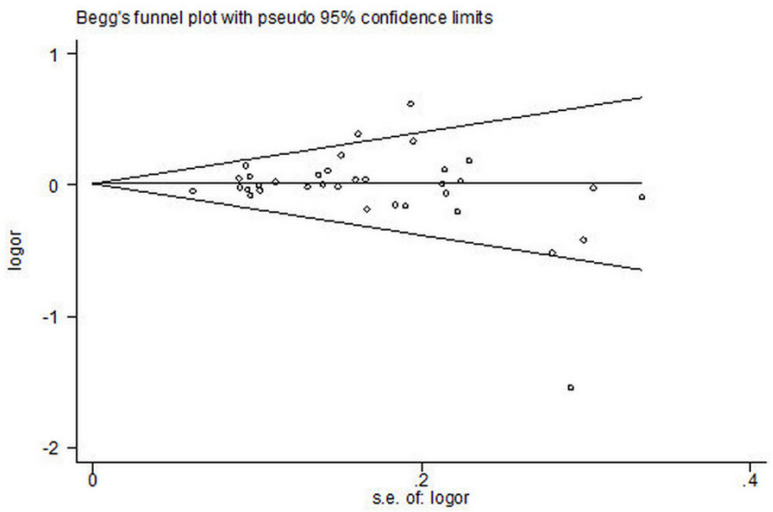

Figure 5. Begg's funnel plot for publication bias in selection of studies on ACE I/D polymorphism (I VS. D; bias = 0.440).

cancer, it has been reported that the ACE gene polymorphism is associated with clinical outcome parameters [54]. It is noteworthy that RAS inhibitors caused reductions in growth and angiogenesis in tumor cell lines [55, 56]. Also it have been demonstrated that the ACE, besides angiotensin II production, is the inactivation of bradykinin [57]. That is known to established role in tumor formation through its ability to stimulate growth and increase vascular permeability [57]. In these sex hormone-related neoplasias cancers, oestrogens increase hepatic synthesis of the renin substrate angiotensinogen, which is converted to angiotensin I, the substrate of ACE [58].

In short, the ACE gene plays an important role in the pathogenesis of cancers. Up to now, a number of original studies have been carried out to investigate whether ACE I/D polymorphism confer individual's susceptibility to cancer. However, the results from the published studies were conflicting. We conducted an updated meta-analysis including with 5007 cases and 8173 controls from 35 case-control studies to evaluate the association between ACE I/D polymorphism and the cancer risk.

There are no significant association between ACE I/D polymorphism and cancer risks under any genetic model in the total population. However, in the subgroup analyses by ethnicity, we found that the ACE I/D polymorphism were associated with increased cancers risk in Caucasians. There was an aggregated OR of 1.43 (95% CI = 1.02-2.00) for increased cancer susceptibility under recessive comparison. This indicates that the ACE I/D polymorphism may contribute to pathogenesis of cancers in Caucasians. Even though the D genotype has been reported that associated coronary heart disease and hypertension. No associations were found between this polymorphism and the cancers risk in Asians, which was consistent with previous reports [13, 28, 30, 31].

One of the unique of meta-analysis is heterogeneity. The heterogeneity was found in almost all comparisons in our meta-analysis. To get more full and accurate detail of the precious date, we used the random-effect models. The results are stable with the sensitivity analysis which did not change the results of the meta-analysis. Meanwhile, there are no publication bias for the risk of cancer in the ACE I/D polymorphism studies.

There were some limitations of our meta-analysis. First, the control subjects were not uniformly defined because of some study only including unitary gender and some reproductive system cancer such as prostatic cancer. Second, in several studies, the larger tumor sizes and lymph node metastases were significantly associated with the DD genotype. Third, all the included studies were from European, Asian and Latino populations, further studies are necessary to contain more findings for other ethnic populations. Fourth, cancer is a multifactorial disease. Due to lack of original data, we could not evaluate the potential interactions of gene-gene and gene-environment.

In conclusion, the I allele of ACE I/D genotype may confer the risk of cancer in Caucasians, but not in Asian. More studies would be of great value to explore the interaction between the ACE I/D polymorphism and cancer risk.

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Disclosure of conflict of interest

None.

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