# 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 upregulated 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 casecontrol 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.

Author	V	Constant	Curta	Courses		Case	6	Control			I Case		Control	
	Year	Cancer type	Country	Source	Π	ID	DD	п	ID	DD	I	D	Ι	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	Colorecta1	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	Rena1	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	Colorecta1	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 Vasků 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

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

# ACE gene polymorphism and susceptibility to cancer

	Cance	er	Cont	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	M-H. Random, 95% CI
2.4.1 Asians							
1-1.Yaren A 2007	2	57	7	52	0.8%	0.23 [0.05, 1.18]	
1-3.Liu SY 2011	71	241	95	299	4.0%	0.90 [0.62, 1.30]	-
1-4 Nacak M 2010	37	125	29	165	3.2%	1.97 [1.13, 3.44]	
1-7.Namazi S 2010	8	70	7	70	1.5%	1.16 [0.40, 3.40]	
1-8 Yaren A 2006	2	44	6	46	0.8%	0.32 [0.06, 1.67]	
10 Yigit B 2007	4	48	12	51	1.3%	0 30 10 09 0 991	
11 Sugimoto M 2006	54	119	50	132	3.4%	1.36 [0.82, 2.26]	+
12 Koh WP 2003	79	182	282	643	4 2%	0.98 [0.70, 1.37]	
13 Srivastava K 2010	90	232	107	260	4.0%	0.91 [0.63, 1.30]	-+-
14 Yuan F 2012	59	289	84	384	4.0%	0.92 [0.63, 1.33]	-
15 Yaren A 2008	4	75	14	85	1.4%	0 29 [0 09 0 91]	
16 Alves Corréa SA 2009	20	101	53	307	3.1%	1 18 [0 67 2 10]	
17 Gao M 2012	351	684	320	602	4 6%	0.93 [0.75, 1.16]	+
19 Goto X 2005	76	202	209	454	4.0%	0.71 [0.50, 0.99]	-
21 Haiman CA(Janan) 2003	119	284	154	357	4.1%	0.95 [0.69, 1.30]	+
24 Li 7H 2011	67	175	94	279	3.0%	1 22 [0 82 1 81]	
25 Mondizabal Puiz AP2011	4	63	74	288	1 6%	0.20 [0.02, 1.01]	
26 Choop KT 2000	72	219	14	121	2.6%	0.20 [0.07, 0.30]	
27 Ding X I 2008	55	121	40	22	3.0%	0.75 [0.47, 1.19]	
22 Vecki V 2004	10	77	13	202	2.3 /0	1 22 [0.66, 2.26]	
34 Mana HW 2004	19	24	40	203	1 70/	1.22 [0.00, 2.20]	
25 Zhang OZ 2005	10	47	10	50	2.20/	1 37 [0 62, 2 05]	
Subtotal (95% CI)	21	3/88	20	1023	62 0%	0.91 [0.62, 3.05]	
Total evente	1004	5400	1740	4525	02.570	0.51 [0.70, 1.00]	1
Heterogeneity: $Tau^2 = 0.05$ ; Cl Test for overall effect: $Z = 1.15$	hi² = 38.72 9 (P = 0.23	, df = 2 )	1 (P = 0.0	01); l² =	46%		
2.4.2 Caucasians							
1-2.Vairaktaris E 2007	30	160	9	153	2.3%	3.69 [1.69, 8.07]	
1-5.Nikiteas N 2007	15	92	6	102	1.7%	3.12 [1.15, 8.41]	
1-6.Kupcinskas J 2011	27	114	62	238	3.3%	0.88 [0.52, 1.48]	
1-9.Usmani BA 2000	8	58	101	553	2.3%	0.72 [0.33, 1.56]	
18.Lukic S 2011	24	45	30	128	2.5%	3.73 [1.83, 7.63]	
20.Toma M 2009	25	108	30	150	3.0%	1.20 [0.66, 2.20]	
21.Haiman CA(Latin) 2003	73	249	189	652	4.2%	1.02 [0.74, 1.40]	+
21.Haiman CA(USA) 2003	79	292	91	402	4.1%	1.27 [0.89, 1.80]	
28.Holla L 1998	25	40	40	202	2.5%	6.75 [3.26, 13.97]	
29.Rocken C 2005	24	113	41	189	3.1%	0.97 [0.55, 1.72]	
30.Rocken C 2007	37	141	41	189	3.3%	1.28 [0.77, 2.14]	
31.Tunny TJ 1996	16	55	24	80	2.4%	0.96 [0.45, 2.03]	
32.Ozen F 2013	10	52	67	212	2.4%	0.52 [0.24, 1.09]	
Subtotal (95% CI)		1519		3250	37.1%	1.43 [1.02, 2.00]	•
Total events	393		731				
Heterogeneity: Tau <sup>2</sup> = 0.28; Cl Test for overall effect: Z = 2.08	hi² = 52.13 3 (P = 0.04	, df = 1: )	2 (P < 0.0	00001);	l <sup>2</sup> = 77%		
Total (95% CI)		5007		8173	100.0%	1.05 [0.89, 1.23]	•
Total events	1617		2471				
Heterogeneity: $Tau^2 = 0.13$ ; Cl Test for overall effect: $Z = 0.57$ Test for subgroup differences:	hi <sup>2</sup> = 102.9 7 (P = 0.57 Chi <sup>2</sup> = 5.7	4, df = : ) 1. df =	34 (P < 0	.00001	); I <sup>2</sup> = 67%	F	0.01 0.1 1 10 100 avours [experimental] Favours [control]

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 Pearson'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% Cls. 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 populationbased 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 sub-

group 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  $l^2$  showed stable variation under the comparisons (II vs. DD: P < 0.00001,  $l^2 =$ 74%; ID vs. DD P < 0.00001,  $l^2 = 76\%$ ; II+ID vs. DD P < 0.00001,  $l^2 = 79\%$ ; II vs. ID+DD P <0.00001,  $l^2 = 67\%$ ; I vs. D P < 0.00001,  $l^2 =$ 78%). In the subgroup analyses of ethnicity, the  $l^2$  showed inconsistent with the former, the  $l^2$  of II vs. ID+DD are 46% and 77%. While there is no notable difference of  $l^2$  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**).

# ACE gene polymorphism and susceptibility to cancer

Study or Subgroup         Events         Total         Events         Total         Weight         M.H. Random, 95% Cl           25.1 Asians		Canc	er	Cont	rol		Odds Ratio	Odds Ratio
2.5.1 Asians 1.1 Yaren A 2007 28 114 26 104 20% 0.98 [0.53, 1.81] 1.3 Jiu SY 2011 280 482 348 598 3.5% 1.00 [0.78, 1.27] 1.4 Nacak M 2010 124 250 130 330 3.1% 1.51 [1.09, 2.11] 1.7 Namazi S 2010 58 140 48 140 2.5% 1.36 [0.84, 2.00] 1.8 Yaren A 2006 21 88 24 92 1.8% 0.89 [0.45, 1.75] 1.8 Yaren A 2006 161 238 160 264 3.0% 1.36 [0.94, 1.96] 1.2 Kch WP 2003 238 364 669 1266 3.4% 0.91 [0.71, 1.16] 1.3 Srivastava K 2010 296 464 395 520 3.4% 0.89 [0.69, 1.16] 1.4 Yuan F 2012 332 578 379 768 3.6% 1.39 [1.11, 1.72] 1.5 Yaren A 2008 47 150 65 170 2.6% 0.74 [0.46, 1.77] 1.6 Alves Corrês SA 2009 60 202 219 614 3.0% 0.76 [0.54, 1.08] 1.7 Gao M 2012 973 1368 693 1204 3.7% 0.88 [0.72, 1.02] 1.9 Goto Y 2005 250 404 607 908 3.5% 0.81 [0.63, 1.03] 24 Li ZH 2011 2913 366 568 468 714 3.5% 0.85 [0.63, 1.02] 24 Li Haima CA(Japan) 2003 366 568 468 714 3.5% 0.81 [0.63, 1.03] 24 Li ZH 2011 291 575 216 0.02 (0.64, 1.50] 25 Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.95 [0.76, 1.20] 24 Li ZH 2011 291 575 4189 406 2.9% 0.82 [0.45, 1.50] 33 Vaski V 2004 75 154 189 406 2.9% 0.82 [0.45, 1.50] 33 Vaski V 2004 75 154 189 406 2.9% 0.82 [0.45, 1.50] 33 Vaski V 2004 75 154 189 406 2.9% 0.80 [0.76, 1.03] 43 Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 34 Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35 Zhang G2 2005 6.3 9.47 (106 2.1% 0.89 [0.76, 1.03] 41 -5 Niticas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-5 Niticas N 2007 57 184 56 204 2.7% 1.20 [0.74, 1.39] 4.1 Cal events 4077 5755 Heterogeneity: Tau" = 0.09; Chi" = 95.22, df = 21 (P < 0.00001); P = 78% Test for overall effect: Z = 1.54 (P = 0.12) 25.2 Caucaaians 1-2 Variatis E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5 Niticas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6 KupcintsAs 2011 159 61 80 166 404 2.2% 4.60 [2.65, 7.99] 24 Haima CA[Lini) 2003 275 544 369 804 3.6% 1.12 [0.91, 1.37] 25 Rocken C 2005 113 22 147 77 378 3.2% 1.17 (0.86, 1.59] 21 Haiman CA[Ushi) 2003 275 448 69 2.2% 1.23 [1.01, 1.49] 24 Haiman CA[Ushi) 2003 275 448 69 3025	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
1-1 Yaren A 2007 28 114 26 104 20% 0.98 [0.53, 1.81] 1-3 Jui SV 2011 280 482 348 55% 1.00 [0.78, 1.27] 1-4 Nacak M 2010 124 250 130 330 3.1% 1.51 [1.09, 2.11] 1-7 Namazi S 2010 58 140 48 140 2.5% 1.36 [0.84, 2.20] 1-7 Namazi S 2010 58 140 48 140 2.5% 1.36 [0.84, 2.20] 1-7 Namazi S 2010 7 27 96 48 102 2.1% 0.48 [0.24, 0.79] 1. Suginoto M 2006 161 2.38 160 264 3.0% 1.36 [0.44, 1.96] 1. Suginoto M 2006 161 2.38 160 264 3.0% 1.38 [0.94, 1.96] 1. Skovastava K 2010 2.96 464 345 520 3.4% 0.91 [0.71, 1.16] 1. Skovastava K 2010 2.96 464 345 520 3.4% 0.91 [0.71, 1.16] 1. Svava A 2008 47 150 65 170 2.6% 0.74 [0.46, 1.17] 1. Gave M 2012 973 1368 893 1204 3.0% 0.76 [0.54, 1.08] 1. Gave M 2012 973 1368 893 1204 3.7% 0.86 [0.72, 1.02] 1. Gave M 2012 973 1368 893 1204 3.7% 0.86 [0.72, 1.02] 2. Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 2. Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 2. Haiman CA(Japan) 2003 366 568 466 2.1% 0.12 [0.06, 0.21] 2. Kondrizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 2. Mondrizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 2. Mondrizabal-Ruiz AP2011 14 126 299 575 2.1% 0.48 [0.63, 0.88 [0.45, 1.50] 3. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 3. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 3. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 3. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 3. Wang HW 2000 36 590 132 2.56 2.3% 0.24 [1.45, 4.12] 2. Scaucasians 1Sivisticas N 2007 75 184 56 204 2.7% 1.19 [0.77, 1.84] 1Sivisticas N 2007 57 184 56 2.2% 0.78 [0.52, 1.15] 3. Wang HW 2000 327 584 649 59 N0 3.8% 0.78 [0.52, 1.16] 3. Wang HW 2000 327 584 679 1304 3.6% 1.12 (0.91, 1.37] 3. School 2.05 Chi <sup>2</sup> = 2.12 (2 < 0.00001); F = 78% Test for overall effect: Z = 2.08 (77 378 3.2% 1.17 (0.86, 1.59] 3. Untotil (95% Ch) 3.03 6500 37.9% 1.23 [1.01, 1.49] 3. Bokock C 2005 116 222 177 378 3.2% 1.17 (0.86, 1.59] 3. Chool 71 33 20 44 2.2% 4.60 [2.55, 7.99] 3. Chool 71 34 282 177 378 3.2% 1.17 (0.86, 1.59] 3. Cho	2.5.1 Asians							
	1-1.Yaren A 2007	28	114	26	104	2.0%	0.98 [0.53, 1.81]	
	1-3.Liu SY 2011	280	482	348	598	3.5%	1.00 [0.78, 1.27]	+
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1-4.Nacak M 2010	124	250	130	330	3.1%	1.51 [1.09, 2.11]	-
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1-7.Namazi S 2010	58	140	48	140	2.5%	1.36 [0.84, 2.20]	
10. Vigit B 2007 27 96 48 102 2.1% 0.44 [0.24, 0.79] 11. Sugimoto M 2006 161 233 160 264 3.0% 1.36 [0.94, 1.96] 12. Kch WP 2003 238 364 869 1286 3.4% 0.91 [0.71, 1.16] 13. Srivastava K 2010 296 464 345 520 3.4% 0.98 [0.69, 1.16] 14. Viuan F 2012 332 578 379 768 3.6% 1.39 [1.11, 1.72] 15. Yaren A 2008 47 150 65 170 2.6% 0.74 [0.46, 1.17] 16. Alves Coréa SA 2009 60 202 219 614 3.0% 0.76 [0.54, 1.08] 17. Gao M 2012 973 1368 893 1204 3.7% 0.66 [0.72, 1.02] 19. Gotto Y 2005 250 404 607 908 3.5% 0.91 [0.63, 1.03] 21. Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 24. Li ZH 2011 212 350 330 558 3.3% 1.06 [0.81, 1.39] 25. Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.66, 0.21] 25. Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.66, 0.21] 25. Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.75, 1.58] 34. Wang HW 2000 260 63 94 70 108 2.1% 1.09 [0.76, 1.03] 33. Vaski V 2004 75 154 189 406 2.9% 1.09 [0.76, 1.03] 34. Vang HW 2000 26 68 444 76 1.8% 0.45 [0.23, 0.88] 35. Zhang 02 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] 7 Loi events 4077 575 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.00001); P = 78% Test for overall effect Z = 1.54 (P = 0.12) 2.5. Zaucasians 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nixitas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmani BA 2000 45 116 497 1106 2.8% 0.078 [0.52, 1.15] 18. Likkic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Tom M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Ushi) 2003 287 584 369 804 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Ushi) 2003 287 584 369 804 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Ushi) 2003 287 584 369 804 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Ushi) 2003 287 584 369 804 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Ushi) 2003 287 584 369 804 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Ushi) 2003 287 584 369 804 3.6% 1.12 [0.91, 1.14] 21. Haiman CA(Ushi)	1-8.Yaren A 2006	21	88	24	92	1.8%	0.89 [0.45, 1.75]	
11 Sugimoto M 2006 161 238 160 264 3.0% 1.36 [0.94, 1.96] 12.Koh WP 2003 238 364 869 1286 3.4% 0.91 [0.71, 1.16] 13.Srivastav K 2010 296 464 345 520 3.4% 0.95 [0.68, 1.16] 14.Yuan F 2012 332 578 379 768 3.6% 1.39 [1.11, 1.72] 15.Yaren A 2008 47 150 65 170 2.6% 0.74 [0.46, 1.17] 16.Alves Corréa SA 2009 60 202 219 614 3.0% 0.76 [0.54, 1.08] 17.Gao M 2012 973 1368 983 1204 3.7% 0.66 [0.72, 1.02] 19.Goth Y 2005 250 404 607 908 3.5% 0.81 [0.63, 1.03] 21.Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 24.Li ZH 2011 212 350 330 558 3.3% 1.06 [0.81, 1.39] 25.Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 26.Cheor KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27.Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33.Vaski V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34.Wang HW 2000 26 63 94 70 108 2.1% 1.01 [0.62, 1.98] 35.Zhang QZ 2005 63 94 70 108 2.1% 1.00 [0.76, 1.58] 34.Wang HW 2000 26 63 94 70 108 2.1% 1.00 [0.76, 1.58] 34.Wang HW 2000 26 63 94 70 108 2.1% 0.89 [0.76, 1.03] 7.Ding XJ 2005 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikibas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.44] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-5.Vinkibas N 2007 57 184 366 2.4% 0.78 [0.52, 1.15] 21.Tolal events 4077 5755 Heterogeneity: Tau'= 0.09; Chi'' = 95.22, df = 21 (P < 0.00001); P = 78% Test for overall effect: Z = 1.54 (P = 0.12) 2.52 Caucasians 1-5.Vinkibas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.48] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-5.Vinkibas N 2007 57 184 65 204 2.2% 4.06 [2.52, 1.15] 1-5.Vinkibas N 2007 57 184 56 204 2.2% 4.06 [2.52, 1.15] 1-5.Vinkibas N 2007 57 184 56 204 2.2% 4.14 [4.54, 1.2] 2.1 fram CA(USA) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 2.1 Haiman CA(USA) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 2.1 Haiman CA(USA) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 2.1 Haiman CA(USA) 2003 275 544 369 804 3.6% 1.12 [0.91, 1.37] 2.1 Haiman CA(USA) 2003 277 548 509 3025 Heterogeneity: Tau' = 0.07; Chi'	10.Yigit B 2007	27	96	48	102	2.1%	0.44 [0.24, 0.79]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	11.Sugimoto M 2006	161	238	160	264	3.0%	1.36 [0.94, 1.96]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	12.Koh WP 2003	238	364	869	1286	3.4%	0.91 [0.71, 1.16]	-
14 Yuan F 2012 332 578 379 768 3.6% 1.39 [1.11, 1.72] 15.Yaren A 2008 47 150 65 170 2.6% 0.74 [0.54, 1.08] 17.Gao M 2012 973 1368 893 1204 3.7% 0.68 [0.54, 1.08] 17.Gao M 2012 973 1368 893 1204 3.7% 0.68 [0.72, 1.02] 19.Goto Y 2005 250 404 607 908 3.5% 0.81 [0.63, 1.03] 21.Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 24.Li ZH 2011 212 350 330 558 3.3% 1.06 [0.81, 1.39] 25.Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 26.Cheon KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27.Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33.Vaski V 2004 75 154 189 406 2.2% 1.09 [0.75, 1.58] 34.Wang HW 2000 26 68 444 76 1.8% 0.45 [0.23, 0.88] 35.Zhang QZ 2005 63 94 70 108 2.1% 0.45 [0.23, 0.88] 35.Zhang QZ 2005 63 94 70 108 2.1% 0.46 [0.24, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 95.22; df = 21 (P < 0.00001); P = 78% Test for overall effect: Z = 1.54 (P = 0.12) 2.5.2 Caucasians 1-2.Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikitas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 328 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18.Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20.Torm M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 24.Haiman CA(Lush) 2003 273 498 650 37.9% 1.23 [1.01, 1.49] 4.Heterogeneity: Tau <sup>2</sup> 0.05; Chi <sup>2</sup> = 45.53; df = 12 (P < 0.00001);	13.Srivastava K 2010	296	464	345	520	3.4%	0.89 [0.69, 1.16]	-
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	14.Yuan F 2012	332	578	379	768	3.6%	1.39 [1.11, 1.72]	-
16 Alves Corrêa SA 2009 60 202 219 614 3.0% 0.76 [0.54, 1.08] 17.Gao M 2012 973 1368 893 1204 3.7% 0.68 [0.72, 1.02] 9.Got Y 2005 250 404 607 908 3.5% 0.81 [0.63, 1.03] 21.Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 24.Li ZH 2011 212 350 330 558 3.3% 1.06 [0.81, 1.39] 25.Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 26.Cheon KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27.Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33.Vaskù V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34.Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35.Zhang 02 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.0001); P = 78% Test for overall effect: Z = 1.54 (P = 0.12) 25.2 Caucasians 1-2 Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 14.Lukic S 2011 65 90 132 256 2.3% 2.244 [1.45, 4.12] 20.Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.71, 1.37] 21.Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 21.Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 23.Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 24.Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 23.Rocken C 2007 143 282 177 378 3.1% 0.99 [0.71, 1.37] 24.Rocken C 2007 143 282 177 378 3.1% 0.99 [0.71, 1.49] 70al events (1486 3025 Heterogeneity: Tau <sup>2</sup> 2.06, (P1 = 49.5, 3.166] 20.Zoen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] 30.Rocken C 2007 143 6.01 14 2(P < 0.00001); P = 76% Test for overall effect: Z = 2.06 (P = 0.04)	15.Yaren A 2008	47	150	65	170	2.6%	0.74 [0.46, 1.17]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	16.Alves Corrêa SA 2009	60	202	219	614	3.0%	0.76 [0.54, 1.08]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	17.Gao M 2012	973	1368	893	1204	3.7%	0.86 [0.72, 1.02]	-
21. Haiman CA(Japan) 2003 366 568 468 714 3.5% 0.95 [0.76, 1.20] 24. Li ZH 2011 212 350 330 558 3.3% 1.06 [0.81, 1.39] 25. Mendizaba-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 26. Cheon KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27. Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33. Vaski V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% C1) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau" = 0.09; Ch <sup>2</sup> = 95.22, df = 21 (P < 0.00001); P = 78% Test for overall effect: Z = 1.54 (P = 0.12) 2.5.2 Caucasins 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nikiteas N 2007 57 184 56 204 2.7% 1.09 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmain BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18. Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Latin) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 21. Haiman CA(Latin) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28. Hola L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31. Tuny TJ 1996 57 110 82 160 2.5% 10.2 [0.63, 1.66] 32. Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Total events 1486 3025 Heterogeneity: Tau" = 0.09; Ch <sup>2</sup> = 9.53, df = 12 (P < 0.00001); P = 76% Test for overall effect: Z = 2.06 (P = 0.04)	19.Goto Y 2005	250	404	607	908	3.5%	0.81 [0.63, 1.03]	-
24. Li ZH 2011 212 350 330 558 3.3% 1.06 [0.81, 1.39] 25. Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 26. Cheon KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27. Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33. Vaskù V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtoal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.00001); l <sup>2</sup> = 78% Test for overall effect: Z = 1.54 (P = 0.12) 2.5.2 Caucasians 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nikiteas N 2007 57 184 56 204 2.7% 1.09 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18. Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.64] 21. Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.14 [0.92, 1.41] 28. Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 21. Haiman CA(Lush) 2003 287 554 369 804 3.6% 1.14 [0.92, 1.41] 28. Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31. Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32. Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 (P < 0.00001); l <sup>2</sup> = 76% Test for overall effect: Z = 2.06 (P = 0.04)	21.Haiman CA(Japan) 2003	366	568	468	714	3.5%	0.95 [0.76, 1.20]	+
25. Mendizabal-Ruiz AP2011 14 126 299 576 2.1% 0.12 [0.06, 0.21] 26. Cheon KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27. Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33. Vasku V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Ch <sup>2</sup> = 95.22, df = 21 ( $P < 0.00001$ ); $P = 78\%$ Test for overall effect: $Z = 1.54$ ( $P = 0.12$ ) 25.2 Caucasians 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nikitas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18. Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Lishi) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28. Holla L 1988 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31. Tunny T J 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32. Ozer F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Ch <sup>2</sup> = 49.53, df = 12 ( $P < 0.00001$ ); $P = 76\%$ Test for overall effect: $Z = 2.06$ ( $P = 0.04$ )	24.Li ZH 2011	212	350	330	558	3.3%	1.06 [0.81, 1.39]	+
26. Cheon KT 2000 260 436 146 242 3.1% 0.97 [0.70, 1.34] 27. Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33. Vaskù V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] 7575 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 ( $P < 0.00001$ ); $I^2 = 78\%$ Test for overall effect: Z = 1.54 ( $P = 0.12$ ) 2.5.2 Caucasians 1-2. Vairaktaris E 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18. Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Latin) 2003 277 498 679 1304 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(Lush) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28. Holla L 1988 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2007 143 282 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31. Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32. Qzen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 ( $P < 0.0001$ ); $I^2 = 76\%$ Test for overall effect: Z = 2.06 ( $P = 0.04$ )	25.Mendizabal-Ruiz AP2011	14	126	299	576	2.1%	0.12 [0.06, 0.21]	
27. Ding XJ 2008 166 242 48 66 2.0% 0.82 [0.45, 1.50] 33. Vaski V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% Cl) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 ( $P < 0.00001$ ); $I2 = 78\%$ Test for overall effect: Z = 1.54 ( $P = 0.12$ ) 2.5.2 Caucasians 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmari BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18. Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Liatin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28. Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.2% 1.02 [0.63, 1.66] 32. Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% Cl) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 ( $P < 0.00001$ ); $I2 = 76\%$ Test for overall effect: Z = 2.06 ( $P = 0.04$ )	26.Cheon KT 2000	260	436	146	242	3.1%	0.97 [0.70, 1.34]	+
33. Vasků V 2004 75 154 189 406 2.9% 1.09 [0.75, 1.58] 34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% Cl) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.00001); I <sup>2</sup> = 78% Test for overall effect: $Z = 1.54$ (P = 0.12) 2.5.2 Caucasians 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(LuSA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28. Holla L 1998 61 80 166 404 2.2% 4.60 [2.55, 7.99] 29. Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.2% 1.02 [0.63, 1.66] 32. Ozor F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] 30.308 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 (P < 0.00001); I <sup>2</sup> = 76% Test for overall effect: $Z = 2.06 (P = 0.04)$	27.Ding XJ 2008	166	242	48	66	2.0%	0.82 [0.45, 1.50]	
34. Wang HW 2000 26 68 44 76 1.8% 0.45 [0.23, 0.88] 35. Zhang OZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 ( $P < 0.00001$ ); $P = 78\%$ Test for overall effect: $Z = 1.54$ ( $P = 0.12$ ) 2.5.2 Caucasians 1-2.Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18.Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20.Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.14 [0.92, 1.41] 21.Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28.Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 9.9.Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30.Rocken C 2007 143 282 177 378 3.1% 0.99 [0.71, 1.37] 30.Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31.Turny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32.Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 ( $P < 0.00001$ ); $P = 76\%$ Test for overall effect: $Z = 2.06 (P = 0.04)$	33.Vasků V 2004	75	154	189	406	2.9%	1.09 [0.75, 1.58]	+
35. Zhang QZ 2005 63 94 70 108 2.1% 1.10 [0.62, 1.98] Subtotal (95% CI) 6976 9846 62.1% 0.89 [0.76, 1.03] Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.00001); I <sup>2</sup> = 78% Test for overall effect: Z = 1.54 (P = 0.12) 2.5.2 Caucasians 1-2.Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18.Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20.Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21.Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28.Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 29.Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30.Rocken C 2007 143 282 177 378 3.2% 1.07 [0.86, 1.59] 31.Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32.Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 (P < 0.00001); I <sup>2</sup> = 76% Test for overall effect: Z = 2.06 (P = 0.04)	34.Wang HW 2000	26	68	44	76	1.8%	0.45 [0.23, 0.88]	
Subtotal (95% CI)6976984662.1%0.89 [0.76, 1.03]Total events40775755Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.00001); l <sup>2</sup> = 78%Test for overall effect: Z = 1.54 (P = 0.12)2.5.2 Caucasians1-2. Vairaktaris E 2007130320843063.1%1.81 [1.29, 2.53]1-5. Nikiteas N 200757184562042.7%1.19 [0.77, 1.84]1-6. Kupcinskas J 20111132282344763.2%1.02 [0.74, 1.39]1-9. Usmani BA 20004511649711062.8%0.78 [0.52, 1.15]18. Lukic S 201165901322562.3%2.44 [1.45, 4.12]20. Toma M 20091002161333003.0%1.08 [0.76, 1.54]21. Haiman CA(Latin) 200327349867913043.6%1.12 [0.91, 1.37]21. Haiman CA(USA) 20032875843698043.6%1.14 [0.92, 1.41]28. Holla L 199861801664042.2%4.60 [2.65, 7.99]29. Rocken C 20051052261773783.2%1.17 [0.86, 1.59]31. Tunny TJ 199657110821602.5%1.02 [0.63, 1.66]32. Ozen F 2013501042394242.7%0.72 [0.47, 1.10]Subtotal (95% CI)3038650037.9%1.23 [1.01, 1.49]Total events14863025Heterogeneily: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.5	35.Zhang QZ 2005	63	94	70	108	2.1%	1.10 [0.62, 1.98]	
Total events 4077 5755 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 ( $P < 0.00001$ ); $I^2 = 78\%$ Test for overall effect: $Z = 1.54$ ( $P = 0.12$ ) 2.5.2 Caucasians 1-2.Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18.Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20.Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21.Haiman CA(LSA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28.Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29.Rocken C 2005 105 226 177 378 3.2% 1.17 [0.86, 1.59] 31.Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32.Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 ( $P < 0.00001$ ); $I^2 = 76\%$ Test for overall effect: $Z = 2.06$ ( $P = 0.04$ )	Subtotal (95% CI)		6976	100	9846	62.1%	0.89 [0.76, 1.03]	•
Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 95.22, df = 21 (P < 0.00001); I <sup>2</sup> = 78% Test for overall effect: Z = 1.54 (P = 0.12) 2.5.2 Caucasians 1-2.Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18.Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20.Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21.Haiman CA(LUSA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28.Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29.Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30.Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31.Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32.Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 (P < 0.00001); I <sup>2</sup> = 76% Test for overall effect: Z = 2.06 (P = 0.04)	Total events	4077		5755				
Test for overall effect: $Z = 1.54$ (P = 0.12) 2.5.2 Caucasians 1-2.Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5.Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6.Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9.Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18.Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20.Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21.Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21.Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28.Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29.Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30.Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31.Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32.Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 (P < 0.00001); I <sup>2</sup> = 76% Test for overall effect: Z = 2.06 (P = 0.04)	Heterogeneity: Tau <sup>2</sup> = 0.09; Ch	i <sup>2</sup> = 95.22	df = 21	(P < 0.00	0001); l <sup>2</sup>	= 78%		
2.5.2 Caucasians 1-2. Vairaktaris E 2007 130 320 84 306 3.1% 1.81 [1.29, 2.53] 1-5. Nikiteas N 2007 57 184 56 204 2.7% 1.19 [0.77, 1.84] 1-6. Kupcinskas J 2011 113 228 234 476 3.2% 1.02 [0.74, 1.39] 1-9. Usmani BA 2000 45 116 497 1106 2.8% 0.78 [0.52, 1.15] 18. Lukic S 2011 65 90 132 256 2.3% 2.44 [1.45, 4.12] 20. Toma M 2009 100 216 133 300 3.0% 1.08 [0.76, 1.54] 21. Haiman CA(Latin) 2003 273 498 679 1304 3.6% 1.12 [0.91, 1.37] 21. Haiman CA(USA) 2003 287 584 369 804 3.6% 1.14 [0.92, 1.41] 28. Holla L 1998 61 80 166 404 2.2% 4.60 [2.65, 7.99] 29. Rocken C 2005 105 226 177 378 3.1% 0.99 [0.71, 1.37] 30. Rocken C 2007 143 282 177 378 3.2% 1.17 [0.86, 1.59] 31. Tunny TJ 1996 57 110 82 160 2.5% 1.02 [0.63, 1.66] 32. Ozen F 2013 50 104 239 424 2.7% 0.72 [0.47, 1.10] Subtotal (95% CI) 3038 6500 37.9% 1.23 [1.01, 1.49] Total events 1486 3025 Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 49.53, df = 12 (P < 0.00001); I <sup>2</sup> = 76% Test for overall effect: Z = 2.06 (P = 0.04)	Test for overall effect: Z = 1.54	(P = 0.12)	)	•				
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1-2. Vairaktaris E 2007       130       320       84       306       3.1%       1.81 [1.29, 2.53]         1-5. Nikiteas N 2007       57       184       56       204       2.7%       1.19 [0.77, 1.84]         1-6. Kupcinskas J 2011       113       228       234       476       3.2%       1.02 [0.74, 1.39]         1-9. Usmani BA 2000       45       116       497       1106       2.8%       0.78 [0.52, 1.15]         18. Lukic S 2011       65       90       132       256       2.3%       2.44 [1.45, 4.12]         20. Toma M 2009       100       216       133       300       3.0%       1.08 [0.76, 1.54]         21. Haiman CA(Latin) 2003       273       498       679       1304       3.6%       1.12 [0.91, 1.37]         21. Haiman CA(USA) 2003       287       584       369       804       3.6%       1.14 [0.92, 1.41]         28. Holla L 1998       61       80       166       404       2.2%       4.60 [2.65, 7.99]         29. Rocken C 2005       105       226       177       378       3.1%       0.99 [0.71, 1.37]         30. Rocken C 2007       143       282       177       378       3.2%       1.17 [0.86, 1.59]         31.	2.5.2 Caucasians							
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$\frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{100000} \frac{1}{10000000000000000000000000000000000$	Heterogeneity: Tau? = 0.10: Ch	i <sup>2</sup> = 158 0	5 df - 2	4 (P - 0.0	00011	2 = 78%		
Test for overall effect $T = 0.03$ ( $P = 0.7$ ) 0.01 0.1 1 10 100	Test for overall effect: $7 = 0.03$	(P = 0.07)	o, ui – 5	4 (1 - 0.0	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	- 10 /0		0.01 0.1 1 10 100
Test for subarroun differences: $(Di^2 = 6.59)$ df = 1 (P = 0.01) I <sup>2</sup> = 84.8% Favours [experimental] Favours [control]	Test for subgroup differences:	$Chi^2 = 6.50$	df = 1	(P = 0.01)	$  ^2 = 8$	4 8%	F	avours [experimental] Favours [control]

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 reninangiotensin 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 metaanalysis 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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