

# Effect of E-Cadherin (CDH1) -160C/A polymorphism on prostate cancer risk: a meta-analysis

## Authors :

Yang Bo<sup>1\*</sup>, He Yi<sup>2\*</sup>, Wen Xiaofei<sup>3\*</sup>, Liu Hui<sup>1</sup>, Liao Guoqiang<sup>1</sup>, Liu Feng<sup>1</sup>, Wang Weifeng<sup>1</sup>, Hao Jidong<sup>1</sup>, Ouyang Jun<sup>4\*\*</sup>

1. Dept.Urology, Shanghai Zhoupu Hospital, Pudong New District.
2. Dept.Urology, Jiaxing No.1 Hospital, Zhejiang.
3. Dept.Urology, Shanghai East Hospital affiliated to Tongji University.
4. Dept.Urology, Suzhou No.1 Hospital affiliated to Suzhou University.

\*These authors contributed equally to this work

## \*\*Corresponding author

Ouyang Jun, Ph.D, Dept.Urology, Suzhou No.1 Hospital affiliated to Suzhou University.

Shizi Street.No 188,Suzhou,Jiangsu Province,China.215006

Tel:+86-051265223637-8130

E-mail: 443472918@qq.com

**Running head:** E-cadherin polymorphism and prostate cancer risk

**Acknowledgements:** This study was funded in part by academic pacesetter program of Shanghai Pudong New District Health System. (PDRd2011-08). Research project of Shanghai health bureau (2013-609). Natural Science Foundation of China (81070591).

**Competing interests** None

## Abstract

E-Cadherin (CDH1) genetic variations may be involved in invasion and metastasis of various cancers by altering gene transcriptional activity of epithelial cells. However, published studies on the association of CDH1 gene polymorphisms and prostate cancer (PCA) risk remain contradictory, owing to differences in living habits and genetic backgrounds. To derive a more better and comprehensive conclusion, the present meta-analysis was performed. Electronic searches of several databases were conducted for all publications on the association between the CDH1 -160 C/A polymorphism and prostate cancer before Oct 2014. The odds ratio (OR) and its 95% confidence interval (CI) were used for statistical analysis. A total of 7 eligible studies including 1294 cases and 1782 controls were involved in this meta-analysis. Overall, meta-analysis indicated that the -160A allele carriers (AA, CA, AA+CA and A allele) had an increased risk of PCA compared with the homozygotes (CC). In the subgroup analyses by ethnicity, a positive association was found in Asians with A allele, AA, CA, AA+CA genotype and Caucasian descendants with AA genotype, dominant and recessive models. On the contrary, a decreased prostate cancer risk was found in Africans with heterozygous, dominant and allele models. Taken together, this meta-analysis showed that the CDH1 -160A allele might be a risk factor for prostate cancer in Asians and Caucasians. However, this result should be verified by additional population-based studies with large sample sizes.

**Keywords:** E-cadherin (CDH1) polymorphism ; homozygotes ; heterozygous meta-analysis ; prostate cancer;

## Introduction

Prostate cancer is the most common cancer among men and the second leading cause of cancer death in men.<sup>1</sup> The mechanism of prostatic tumorigenesis is still not fully understood. Evidence from epidemiological and genetic studies provides more focus on the inherited susceptibility to cancer. It is likely that gene environment interactions are involved in tumorigenesis and development.<sup>2</sup> Among these genetic factors, the E-cadherin (CDH1) gene, consists of a large extracellular domain composed of smaller transmembrane and cytoplasmic domains and five repeat domains.<sup>3</sup> CDH1, located on chromosome 16q22.1, is one of the most important tumor suppressor genes encoding an adhesion glycoprotein.<sup>4-5</sup> Several polymorphisms and somatic mutations have been identified in CDH1.<sup>6</sup> It also plays important roles in such aspects of establishment and maintenance of cell polarity and tissue architecture and intracellular adhesion.<sup>7</sup> Therefore, abnormal expression of CDH1 is often occurred in a number of human epithelial cancers. Aberrant CDH1 functions have been reported to be associated with malignant transformation of prostatic epithelium as well as metastasis and poor prognosis of PCA.<sup>8-9</sup> A number of studies had investigated the roles of CDH1 gene polymorphisms in human prostate cancers risk, but the results were not consistent. Therefore, we performed a search of relevant literatures and carried out a meta-analysis to obtain a more accurate evaluation of the association between CDH1 genetic polymorphisms and prostate cancer.

## Methods

### Publication selection

Electronic databases (PubMed, Embase, the Cochrane Controlled Trials Register, the Science Citation Index, and the Chinese Biomedical Database) were searched independently by two authors for all publications regarding the association between the E-Cadherin polymorphism and prostate cancer before

Oct 2014. The keywords were as follows: CDH1/ E-Cadherin/ polymorphism/ prostate cancer. A comprehensive search of reference lists of all review articles and original studies retrieved by this method was performed to identify additional reports.. The results were limited to papers with full-text and published in the English language.

#### Inclusion and exclusion criteria

Studies estimating the association between CDH1 genetic polymorphisms and prostate cancer risk had to meet all of the following criteria: 1) published in English 2) they were original epidemiological studies on the correlation between CDH1 genetic polymorphisms and prostate cancer susceptibility; 3) case-control studies; 4) sufficient information provided to estimate odds ratios (ORs) with 95% confidence intervals (CIs). However, duplicated studies, case-only studies, case reports, unpublished data letters, comments, and reviews must be excluded.

#### Data extraction

Two investigators independently extracted the data and reached a consensus on all the items according to the inclusion criteria listed above. For each study, the following characteristics were collected: author's first name, year of publication, country of origin, ethnicity, definition of cases, genotyping method, sources of control and case groups, total number of cases and controls, as well as number of cases and controls with AA, CA and CC genotypes.

#### Statistical methods

For the control group of each study, the observed genotype frequencies of the CDH1 polymorphism were assessed for Hardy–Weinberg equilibrium using the Pearson chi-squared test;  $P < 0.05$  was considered to be statistically significant. Based on both fixed effects and random-effects models, a pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of

association between CDH1 –160 C/A polymorphisms and prostate cancer risk, depending on the heterogeneity of the analysis. The pooled ORs were also assessed for –160 C/A by homozygous (AA vs CC), heterozygous (CA vs CC), recessive (AA vs CC+ CA) and dominant models (AA +CA vs CC) as well as allele comparison (A vs.C).

Heterogeneity was evaluated using the Q test and  $I^2$  score. If the result of the heterogeneity test was  $P>0.1$ , ORs were pooled according to the fixed-effects (Mantel–Haenszel) model. Otherwise, ORs were pooled according to the random-effects (DerSimonian and Laird) model. Sensitivity analysis was performed by omitting one study at a time and recalculating the pooled OR for the remaining studies to assess the stability of the results.

Publication bias was assessed using Egger's test and Begg's test. All statistical tests were performed using STATA version 10.0 software (Stata Corporation, College Station, TX, USA). The results were considered statistically significant if the P-value was  $<0.05$ .

## Results

### Study Selection

The electronic search strategy identified 31 potentially relevant articles, which were evaluated further in detail, including their titles, abstracts, full text, or a combination of these. Twenty-four articles were excluded (Figure 1). Nine studies were not focused on prostate cancer and seven were not focused on the CDH1 polymorphism. Six studies were laboratory studies, and one study was a systematic review. One study<sup>10</sup> was eliminated because it did not follow Hardy–Weinberg equilibrium, indicating that these groups might not represent the general population very well. Finally, seven studies<sup>11-17</sup> on CDH1 genotypes and prostate cancer risk including a total of 1294 prostate cancer cases and 1782 controls were identified.

## Study Characteristics

Table 1 showed the characteristics of the studies included in this meta-analysis. A total of seven publications met the inclusion criteria.<sup>11-17</sup> All of them are case-control studies. Almost all of the cases were histologically confirmed. The controls were mainly healthy populations except for some having benign prostatic hyperplasia. There were three studies of Asians, two studies of Caucasians, and two studies of Africans. Genotyping methods used in the studies included polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), TaqMan-assay, and dynamic allele-specific hybridization (DASH). The distribution of genotypes among the controls was consistent with the Hardy–Weinberg equilibrium ( $P > 0.05$ ) in all studies.

## Quantitative data synthesis

The results for associations between -160C/A polymorphism and prostate cancer risk and for heterogeneity testing are shown in Table 2. The combined results of all studies showed that significantly increased risk was found between -160C/A polymorphism and prostate cancer (OR 1.84, 95%CI 1.31–2.60 for AA versus CC,  $P = 0.001$ ; OR 1.18, 95% CI 1.01–1.38 for CA versus CC,  $P = 0.04$ ; OR 1.25, 95%CI 1.07–1.45 for the dominant model AA+CA versus CC,  $P = 0.005$ ; OR 1.77, 95%CI 1.27–2.48 for the recessive model AA versus CC + CA,  $P = 0.001$ , Figure 2). Further, we detected an association between the -160C/A polymorphism and prostate cancer when examining the comparison of A versus C (OR 1.23, 95%CI 1.04–1.46 for A versus C,  $P = 0.02$ , Fig 2)

Ethnicity subgroup analysis revealed that -160C/A polymorphism was related with increased risk of prostate cancer in Asian when examining the comparison of A versus C (OR 1.55, 95%CI 1.23–1.95,  $P = 0.001$ ), AA versus CC (OR 1.95, 95%CI 1.05–3.64,  $P = 0.04$ ), CA versus CC (OR 1.50, 95%CI 1.19–1.90,  $P = 0.001$ ) and AA+CA versus CC (OR 1.54, 95% CI 1.23–1.93,  $P = 0.001$ ,

Figure3). However, no significant difference was found in the recessive model (AA versus CC+CA, OR 1.75, 95%CI 0.94–3.25, P=0.08)

In the Caucasian group, there was a significant increased risk between -160C/A polymorphism and prostate cancer risk when examining the comparison of AA versus CC (OR 2.33, 95%CI 1.45–3.73, P=0.001), AA+CA versus CC (OR 1.33, 95% CI 1.03–1.71, P=0.03) and AA versus CC+CA (OR 2.15, 95%CI 1.37–3.39, P=0.001, Figure3). However, no significant difference was found in the other genotype distributions (A versus C: OR 1.22, 95%CI 0.87–1.72, P=0.25; CA versus CC: OR 1.19, 95%CI 0.91–1.55, P=0.21 )

In the African group, results indicated that -160C/A polymorphism was related with decreased prostate cancer risk when examining the comparison of A versus C (OR 0.65, 95%CI 0.44–0.97, P=0.03), CA versus CC (OR 0.64, 95%CI 0.44–0.94, P=0.02) and AA+CA versus CC (OR 0.66, 95%CI 0.46–0.94, P=0.02, Figure3). However, no significant association was found in any genetic models (AA versus CC, OR 0.74, 95%CI 0.30–1.84, P=0.52; AA versus CC+CA, OR 0.88, 95%CI 0.36–2.19, P=0.79).

### Tests of heterogeneity

Statistically significant heterogeneity was found between the trials using the Q statistic and  $I^2$  score (A versus C, P=0.006,  $I^2$ =67%; CA versus CC, P=0.003,  $I^2$ =70%; the dominant model AA+CA versus CC, P=0.001,  $I^2$ =73%). The random-effects model was employed in these studies. There was no significant heterogeneity between the following comparisons: AA versus CC (P=0.34,  $I^2$ =12%) and recessive model AA versus CC+CA (P=0.62,  $I^2$ =0%, Table 2), and the fixed-effects model was employed in these studies.

### Sensitivity analysis

Sensitivity analysis was conducted to assess the stability of the results by sequential removal of each eligible study. The significance of the pooled ORs was not influenced by any single study, indicating that our results were

statistically robust(data not shown).

### Publication bias

Begg's test and Egger's test were used to assess for publication bias. Egger's weighted regression did not indicate publication bias (A versus C,  $P=0.855$ ; AA versus CC,  $P=0.942$ ; CA versus CC,  $P=0.832$ ; dominant model AA + CA versus CC,  $P=0.686$ ; recessive model AA versus CC + CA,  $P=0.629$ ). This was confirmed by Begg's rank correlation (A versus C,  $P=1.000$ ; AA versus CC,  $P=1.000$ ; CA versus CC,  $P=0.443$ ; dominant model AA + CA versus CC,  $P=0.443$ ; recessive model AA versus CC + CA,  $P=1.000$ , Table 3).

### Discussion

Many studies have attempted to reveal the genetic basis of prostate cancer. Despite suggestive evidence of gene association, reports have been difficult to replicate, indicating that prostate cancer is more genetically heterogeneous than initially believed. The polymorphisms of CDH1 may play a critical role in the tumorigenesis, development and prognosis of sever kinds of cancer, such as urothelial cancer, colorectal cancer, gastric cancer, prostate cancer, breast cancer and esophageal cancer.<sup>18-23</sup> Because PCA is one of the most common malignant diseases among men and a number of studies have reported a function of the CDH1 -160 C>A polymorphism in PCA risk with inconclusive results, we performed this meta-analysis to estimate the association specifically. At the same time, because the same polymorphism seemed to have different functions in cancer susceptibility among different ethnic populations and because the frequencies of single-nucleotide polymorphisms might be different among different ethnic groups, subgroup analyses on the basis of ethnicity were conducted.

We concluded that rs16260 A allele was obviously associated with increased cancer risk based on 1294 cases and 1782 controls in overall pooled results from 7 studies. A stratified analysis by cancer type indicated that rs16260 AA



genotype increased risk of prostate cancer. Subsequently stratified analysis by country indicated borderline increased cancer risk was found in Asian and Caucasian population. In contrast, results appeared in African population revealed that -160C/A polymorphism was related with decreased risk of prostate cancer. This may be related with different genetic background and the environment exposure<sup>24</sup> or the different frequency of rs16260 A allele variant in this study. In addition, it is also possible that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.<sup>25</sup> Considering the limited studies and population numbers of Africans included in the meta-analysis, our results should be interpreted with caution.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses.<sup>26</sup> Significant between-study heterogeneity existed in overall comparisons. After subgroup analyses by ethnicity, the heterogeneity was effectively decreased or removed in Europeans and Asians. The reason might be that differences of genetic backgrounds and the environment existed among different ethnicities.

Some limitations of this meta-analysis should be acknowledged. First, the influence of the genetic variant may be masked by the presence of other as yet unidentified genes involved in carcinogenesis, which restricted our evaluation of potential gene–gene interactions. Secondly, while publication bias was not detected in three polymorphisms of CDH1, publication bias which we did not detect might also exist in other polymorphisms owing to small amount of studies. Thirdly, controls were not uniformly defined. Although the healthy populations were the main source of the controls, some of them might be patients. Fourthly, in the subgroup analysis, the number of cases and controls was relatively small in different cancers, races and source of controls, not having sufficient statistical power to achieve the real association. At last, our results were based on unadjusted evaluation, so a more precise analysis

should be conducted with adjustment for other variables, eg, environmental factors. Larger and better designed studies are needed to evaluate further the association between the CDH1 polymorphism and prostate cancer risk, including considering the possibility of gene–gene or SNP–SNP interactions and the possibility of linkage disequilibrium between polymorphisms.

In conclusion, it is worthwhile searching for polymorphic variants influencing the risk of prostate cancer. This meta-analysis provides evidence of an association between CHD1 –160 C>A polymorphism and prostate cancer risk, supporting the hypothesis that the CHD1 –160 C>A A allele may act as a risk factor for prostate cancer in Asians but not in Caucasians. However, our results should be interpreted with caution because of some limitations. Given that the results of this meta-analysis are preliminary and may be biased by the relatively small number of subjects, additional population-based studies including large sample sizes should be conducted to verify the association of CDH1 polymorphism in prostate cancer.

## References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;**60**: 277-300.
2. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;**343**: 78-85.
3. Ringwald M, Schuh R, Vestweber D, Eistetter H, Lottspeich F, Engel J, Dolz R, Jahnig F, Epplen J, Mayer S, et al. The structure of cell adhesion molecule uvomorulin. Insights into the molecular mechanism of Ca<sup>2+</sup>-dependent cell adhesion. *EMBO J* 1987;**6**: 3647-53.
4. Kangelaris KN, Gruber SB. Clinical implications of founder and recurrent CDH1 mutations in hereditary diffuse gastric cancer. *JAMA* 2007;**297**: 2410-1.
5. Tamgue O, Chai CS, Hao L, Zambe JC, Huang WW, Zhang B, Lei M, Wei YM. Triptolide inhibits histone methyltransferase EZH2 and modulates the expression of its target genes in prostate cancer cells. *Asian Pac J Cancer Prev* 2013;**14**: 5663-9.
6. Nakamura A, Shimazaki T, Kaneko K, Shibata M, Matsumura T, Nagai M, Makino R, Mitamura K. Characterization of DNA polymorphisms in the E-cadherin gene (CDH1) promoter region. *Mutat Res* 2002;**502**: 19-24.
7. Pecina-Slaus N. Tumor suppressor gene E-cadherin and its role in normal and malignant cells. *Cancer Cell Int* 2003;**3**: 17.
8. Dunsmuir WD, Gillett CE, Meyer LC, Young MP, Corbishley C, Eeles RA, Kirby RS. Molecular markers for predicting prostate cancer stage and survival. *BJU Int* 2000;**86**: 869-78.
9. Umbas R, Isaacs WB, Bringuier PP, Schaafsma HE, Karthaus HF, Oosterhof GO, Debruyne FM, Schalken JA. Decreased E-cadherin expression is associated with poor prognosis in patients with prostate cancer. *Cancer Res* 1994;**54**: 3929-33.
10. Jonsson BA, Adami HO, Hagglund M, Bergh A, Goransson I, Stattin P, Wiklund F, Gronberg H. -160C/A polymorphism in the E-cadherin gene promoter and risk of hereditary, familial and sporadic prostate cancer. *Int J Cancer* 2004;**109**: 348-52.
11. Lindstrom S, Wiklund F, Jonsson BA, Adami HO, Balter K, Brookes AJ, Xu J, Zheng SL, Isaacs WB, Adolfsson J, Gronberg H. Comprehensive genetic evaluation of common E-cadherin sequence variants and prostate cancer risk: strong confirmation of functional promoter SNP. *Hum Genet* 2005;**118**: 339-47.
12. Hajdinjak T, Toplak N. E-cadherin polymorphism--160 C/A and prostate cancer. *Int J Cancer* 2004;**109**: 480-1.
13. Bonilla C, Mason T, Long L, Ahaghotu C, Chen W, Zhao A, Coulibaly A, Bennett F, Aiken W, Tullock T, Coard K, Freeman V, et al. E-cadherin polymorphisms and haplotypes influence risk for prostate cancer. *Prostate*

2006;**66**: 546-56.

14. Tsukino H, Kuroda Y, Imai H, Nakao H, Qiu D, Komiya Y, Inatomi H, Hamasaki T, Kohshi K, Osada Y, Katoh T. Lack of evidence for the association of E-cadherin gene polymorphism with increased risk or progression of prostate cancer. *Urol Int* 2004;**72**: 203-7.

15. Goto T, Nakano M, Ito S, Ehara H, Yamamoto N, Deguchi T. Significance of an E-cadherin gene promoter polymorphism for risk and disease severity of prostate cancer in a Japanese population. *Urology* 2007;**70**: 127-30.

16. Pookot D, Li LC, Tabatabai ZL, Tanaka Y, Greene KL, Dahiya R. The E-cadherin -160 C/A polymorphism and prostate cancer risk in white and black American men. *J Urol* 2006;**176**: 793-6.

17. Kamoto T, Isogawa Y, Shimizu Y, Minamiguchi S, Kinoshita H, Kakehi Y, Mitsumori K, Yamamoto S, Habuchi T, Kato T, Ogawa O. Association of a genetic polymorphism of the E-cadherin gene with prostate cancer in a Japanese population. *Jpn J Clin Oncol* 2005;**35**: 158-61.

18. Lei H, Sjoberg-Margolin S, Salahshor S, Werelius B, Jandakova E, Hemminki K, Lindblom A, Vorechovsky I. CDH1 mutations are present in both ductal and lobular breast cancer, but promoter allelic variants show no detectable breast cancer risk. *Int J Cancer* 2002;**98**: 199-204.

19. Tsukino H, Kuroda Y, Nakao H, Imai H, Inatomi H, Kohshi K, Osada Y, Katoh T. E-cadherin gene polymorphism and risk of urothelial cancer. *Cancer Lett* 2003;**195**: 53-8.

20. Medina-Franco H, Ramos-De la Medina A, Vizcaino G, Medina-Franco JL. Single nucleotide polymorphisms in the promoter region of the E-cadherin gene in gastric cancer: case-control study in a young Mexican population. *Ann Surg Oncol* 2007;**14**: 2246-9.

21. Wu MS, Huang SP, Chang YT, Lin MT, Shun CT, Chang MC, Wang HP, Chen CJ, Lin JT. Association of the -160 C --> a promoter polymorphism of E-cadherin gene with gastric carcinoma risk. *Cancer* 2002;**94**: 1443-8.

22. Zhang XF, Wang YM, Ge H, Cao YY, Chen ZF, Wen DG, Guo W, Wang N, Li Y, Zhang JH. Association of CDH1 single nucleotide polymorphisms with susceptibility to esophageal squamous cell carcinomas and gastric cardia carcinomas. *Dis Esophagus* 2008;**21**: 21-9.

23. Li Y, Tang Y, Zhou R, Sun D, Duan Y, Wang N, Chen Z, Shen N. Genetic polymorphism in the 3'-untranslated region of the E-cadherin gene is associated with risk of different cancers. *Mol Carcinog* 2011;**50**: 857-62.

24. Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. *Genet Med* 2002;**4**: 45-61.

25. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst* 2004;**96**: 434-42.

26. Munafo MR, Flint J. Meta-analysis of genetic association studies. *Trends Genet* 2004;**20**: 439-44.

## Figure Legends

Figure 1. Flow chart of study selection based on inclusion and exclusion criteria.

Figure 2. Forest plot showing the association of the CDH1 -160C>A A allele with risk of prostate cancer compared with the C allele. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The diamond represents the summary OR and 95% CI.

Abbreviations: CI, confidence interval; OR, odds ratio.

Figure 3. Forest plot describing the association of the CDH1 -160C>A genetic models (AA versus cc, CA versus cc, AA + CA versus CC, AA versus CC + CA) with the risk of prostate cancer. Abbreviations: CI, confidence interval; OR, odds ratio.

Table1 Characteristics of Studies Included in the Meta-analysis

Reference	Ethnicity	Definition of cases	Methods	Controls	Genotype						Case/Control	HWE
					Case			Control				
					AA	CA	CC	AA	CA	CC		
Kamoto	Asian	Histologically diagnosed	RFLP	Health BPH	11	71	154	11	85	252	236/348	0.25
Tsukino	Asian	Histologically diagnosed	RFLP	Health	9	77	133	6	66	147	219/219	0.66
Goto	Asian	Histologically diagnosed	RFLP	BPH	6	79	115	1	39	119	200/159	0.25
Bonilla	African	Diagnosed by a pathologist	RFLP	Health	6	50	152	6	67	162	208/235	0.77
Pookot	African	Histologically diagnosed	RFLP	Health	2	9	38	8	46	63	49/117	0.92
Lindstrom	Caucasian	Family positive cases	DASH	Health	24	88	87	29	209	268	199/506	0.15
Hajdinjak	Caucasian	Histologically diagnosed	TanMan	Health	21	72	90	12	81	105	183/198	0.48

Abbreviation: HWE, hardy–Weinberg equilibrium.

Table 2. Meta-analysis of the association between CDH1 -160 C>A polymorphism and prostate cancer risk						
Comparison	Odds ratio	95% CI	P-value	Heterogeneity		Effects model
				$I^2$	P-value	
A versus C	1.23	1.04-1.46	0.02	67%	0.006	Random
Africans	0.65	0.44-0.97	0.03	66%	0.08	
Asians	1.55	1.23-1.95	0.001	15%	0.31	
Caucasians	1.22	0.87-1.72	0.25	0%	0.80	
AA versus CC	1.84	1.31-2.60	0.001	12%	0.34	Fixed
Africans	0.74	0.30-1.84	0.52	0%	0.35	
Asians	1.95	1.05-3.64	0.04	0%	0.50	
Caucasians	2.33	1.45-3.73	0.001	0%	0.65	
CA versus CC	1.18	1.01-1.38	0.04	70%	0.003	Random
Africans	0.64	0.44-0.94	0.02	72%	0.06	
Asians	1.50	1.19-1.90	0.001	29%	0.25	
Caucasians	1.19	0.91-1.55	0.21	0%	0.42	
AA+CA versus CC	1.25	1.07-1.45	0.005	73%	0.001	Random
Africans	0.66	0.46-0.94	0.02	75%	0.05	
Asians	1.54	1.23-1.93	0.001	38%	0.20	
Caucasians	1.33	1.03-1.71	0.03	0%	0.41	
AA versus CC+CA	1.77	1.27-2.48	0.001	0%	0.62	Fixed
Africans	0.88	0.36-2.19	0.79	0%	0.50	
Asians	1.75	0.94-3.25	0.08	0%	0.58	
Caucasians	2.15	1.37-3.39	0.001	0%	0.81	

Abbreviation: CI, confidence interval

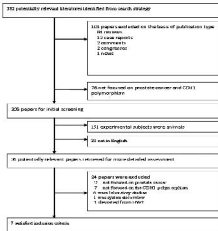
Table3.Publication bias test for CDH1 -160C>A polymorphism

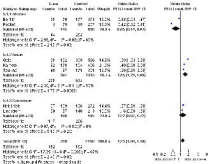
Comparison			Egger's test			Begger's test P value
			Coefficient	P value	95%CI	
A	versus	C	0.332	0.855	-6.594, 5.608	1.000
AA	versus	CC	0.425	0.942	-4.721, 4.225	1.000
CA	versus	CC	-0.573	0.832	-4.273, 3.138	0.443
AA+CA	versus	CC	-0.211	0.686	-5.286, 4.257	0.443
AA	versus	CC+AC	0.813	0.629	-4.672, 5.142	1.000

Abbreviation:CI,confidence interval

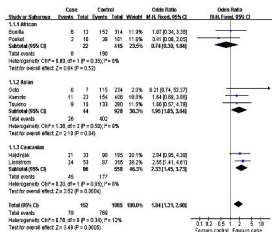


**Figure 1 The flowchart of study selection.**

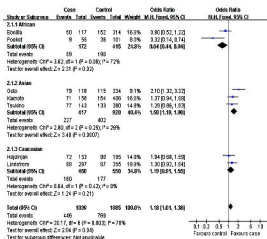




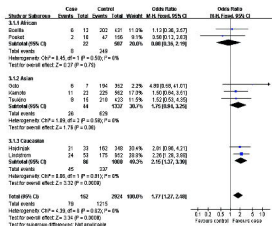
## AA vs CC



## CA vs CC



## Recessive model



## Dominant model

