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ARTICLE

The *E-cadherin* (*CDH1*) −160 C/A polymorphism and prostate cancer risk: a meta-analysis

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Published data on the association between *E-cadherin* (*CDH1*) −160 C/A polymorphism and prostate cancer (PCA) risk are inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. A logistic regression approach proposed for molecular association studies was used to estimate a biological model of the gene effect. A total of 11 studies including 2637 cases and 2673 controls were involved in this meta-analysis. Logistic regression analysis indicated that the *CDH1* −160 C/A genotypes were associated with PCA risk. The genetic model test indicated that the genetic model was most likely to be dominant (CA + AA *vs* CC). Overall, meta-analysis indicated that the −160A allele carriers (CA + AA) had a 21% elevated risk of PCA, when compared with the homozygotes (CC) (odds ratio (OR) = 1.21; 95% confidence interval (CI): 0.97–1.51; $P = 0.090$, $P_{heterogeneity} = 0.001$). In the subgroup analyses by ethnicity, significantly elevated risks were associated with −160 variant genotypes (CA + AA) in both European and Asian populations (OR = 1.24; 95% CI: 1.08–1.43; $P = 0.003$, $P_{heterogeneity} = 0.220$ and OR = 1.54; 95% CI: 1.23–1.93; $P < 0.001$, $P_{heterogeneity} = 0.200$). However, no significant associations were found in Africans (OR = 0.59; 95% CI: 0.32–1.09; $P = 0.090$, $P_{heterogeneity} = 0.070$). Although some modest bias could not be eliminated, this meta-analysis suggests that the *CDH1* −160A allele is a low-penetrant risk factor for developing PCA, especially in Europeans and Asians.

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Introduction

Prostate cancer (PCA) is one of the most common malignant diseases among men in developed countries, which has become a major public health challenge. Traditionally considered as a disease of elderly men, an increasing proportion of PCA cases now occur in men of pre-retirement ages. New markers for identifying high-risk populations as well as novel strategies for early detection and preventive care are urgently needed.[1] The mechanism of prostatic tumorigenesis is still not fully understood. It has been suggested that low-penetrance susceptibility genes combining with environmental factors may be important in the development of cancer.[2,3] In recent years, several common low-penetrant genes have been identified as potential PCA susceptibility genes.[4] An important one is

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E-cadherin (*CDH1*), a gene encoding an adhesion glycoprotein, which mediates cell–cell adhesion and establishes and maintains cell polarity and tissue architecture.[5,6] The *CDH1* gene is located at 16q22.1, consisting of 16 exons spanning approximately 100 kb of the genomic DNA. Several polymorphisms and somatic mutations have been identified in *CDH1*.[7,8] A −160 C/A polymorphism in the promoter region has been reported to have an approximately 68% decreased transcriptional activity for the A allele compared with the C allele.[9] Furthermore, aberrant *CDH1* functions have been reported to be associated with malignant transformation of prostatic epithelium as well as metastasis and poor prognosis of PCA.[10,11] A number of studies have reported the function of *CDH1* −160 C/A polymorphism in PCA risk, but the results are inconclusive, partially because of the possible small effect of the polymorphism on PCA risk and the relatively small sample size in each of published studies. Therefore, we performed a meta-analysis of the published studies to derive a more precise estimation of the association.

Materials and methods

Publication search

Two electronic databases (PubMed and Embase) were searched (last search was updated on 10 January 2008, using the search terms: '*E-cadherin,*' 'polymorphism,' and 'prostate'). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full-text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Inclusion criteria

The inclusion criteria were as follows: (a) evaluation of the *CDH1* −160 C/A polymorphism and PCA risk, (b) case–control studies, and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors (Qiu L and Li R), according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author (Qian X) was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were collected from each study: first author's surname, publication date, ethnicity, definition of cases, characteristics of controls, age distribution, genotyping methods, total number of cases and controls, and numbers of cases and controls with the AA, CA, and CC genotypes, respectively. Different ethnicity descents were categorized as European, Asian, and African. When studies included patients of more than one ethnicity, genotype data were extracted separately according to the ethnicities for subgroup analyses. We did not define any minimum number of patients to include a study in our meta-analysis.

Statistical methods

Odd ratios with 95% CI were used to assess the strength of association between the *CDH1* −160 C/A polymorphism and PCA risk, according to the method of Woolf.[12] A logistic regression approach proposed for molecular association studies was used to estimate a biological model of the gene effect.[13] Heterogeneity assumption was checked by the χ^2-based *Q*-test.[14] A *P*-value greater than 0.10 for the *Q*-test indicates a lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (the Mantel–Haenszel method). Otherwise, the random-effects model (the DerSimonian and Laird method) was used.[15] The significance of the pooled OR was determined by the *Z*-test, and $P<0.05$ was considered as statistically significant. To evaluate the ethnicity-specific effect, subgroup analyses were performed by ethnic group. One-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR.[16] An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the *t*-test, suggested by Egger ($P<0.05$ was considered representative of statistically significant publication bias).[17] All the statistical tests were performed with Review Manager version 4.2 (The Cochrane Collaboration, Oxford, England) and STATA version 9.2 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

A total of nine publications met the inclusion criteria.[18–26] The study of Verhage *et al*[18] was first published data set with an inflated estimate of OR, and sensitivity analyses indicated that it was the main origin of the heterogeneity in the Europeans, so it was not included in the meta-analysis. In two of these studies, the ORs were presented

Table 1 Main characteristics of all studies included in the meta-analysis

Author	*Ethnicity*	*Definition of cases*	*Characteristics of controls (matched for)*	*Age distribution cases/controls (years)*	*Methods*	*Cases/controls*
Hajdinjak and Toplak[19]	European	Histologically confirmed	Healthy ($n=168$), BPH ($n=30$)	<70 (88), >70 (95)/ No report	TaqMan	183/198
Jonsson *et al*[20]	European	Pathologically confirmed	Healthy (age, gender, and residence)	67 (48–80)/65 (48–80)	TaqMan	1038/669
Lindstro *et al*[21]	European	Family positive cases	Healthy (age, gender, and residence)	65.5 (43–81)/67.8 (45–80)	DASH	199/506
Pookot *et al*[22]	European	Histologically confirmed	Healthy	No report	RFLP	86/120
Pookot *et al*[22]	African	Histologically confirmed	Healthy	No report	RFLP	49/117
Bonilla *et al*[23]	African	No report	Healthy (age and ethnicity)	65.1 ± 0.9/67.2 ± 1.1	RFLP	119/112
Bonilla Bonilla[23]	European	Clinically localized PCA	Healthy (age and ethnicity)	61.0 ± 0.6/63.9 ± 1.0	RFLP	219/102
Bonilla Bonilla[23]	African	Diagnosed by a pathologist	Healthy (age and ethnicity)	67.1 ± 1.2/65.4 ± 1.0	RFLP	89/123
Tsukino *et al*[24]	Asian	Histologically diagnosed	Healthy (age)	Mean 72.4/72.2	RFLP	219/219
Kamoto *et al*[25]	Asian	Histologically diagnosed	Healthy ($n=139$), BPH ($n=209$)	72.2 ± 7.9/74.7 ± 6.9	RFLP	236/348
Goto *et al*[26]	Asian	Histologically diagnosed	BPH	72.7 ± 7.5/74.5 ± 8.6	RFLP	200/159

PSA, prostate-specific antigen; DRE, digital rectal exams; RFLP, restriction fragment length polymorphism; DASH, dynamic allele-specific hybridization; SPC, sporadic prostate cancer; BPH, benign prostatic hyperplasia; HPC, hereditary prostate cancer.

separately according to the different ethnic groups: Pookot *et al*[22] sorted the data in white American men (European descent) and black American men (African descent) respectively, and Bonilla *et al*[23] presented the data according to African-Americans (African descent), Jamaicans (African descent), and European-Americans (European descent). Therefore, each group in one study was considered separately for pooling subgroup analyses. In Lindstrom's study, case subjects utilized by Jonsson *et al*[21] were not included. Hence, a total of 11 groups including 2637 cases and 2673 controls were used in the pooled analyses. Table 1 lists the studies identified and their main characteristics. Of the 11 groups, sample sizes ranged from 166 to 1707. There were five studies of Europeans, three studies of Asians and three studies of Africans. Almost all of the cases were histologically confirmed. The controls were mainly healthy populations except for some having benign prostatic hyperplasia. No significant differences were found in the age distributions between the cases and controls. Genotyping methods used in the studies included polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), TaqMan-assay, and dynamic allele-specific hybridization.

Determining the best genetic model

Logistic regression analysis was used to examine the association between the *CDH1* −160 C/A polymorphism and PCA risk. To assess the main effect of *CDH1* genotypes, the logistic regression test was used to compare the two models with and without the *CDH1* genotype. These two models were significantly different ($P<0.001$), indicating that the *CDH1* −160 C/A genotypes were associated with PCA risk. The genetic model test indicated that the genetic model was most likely to be dominant (CA + AA *vs* CC).[13]

Meta-analysis results

Overall meta-analysis indicated that the −160A allele carriers (CA + AA) had a 21% elevated risk of PCA, when compared with the homozygotes (CC) (OR = 1.21; 95% CI: 0.97–1.51; $P=0.090$, $P_{\text{heterogeneity}}=0.001$). In the subgroup analyses by ethnicity, significantly elevated risks were associated with −160 variant genotypes in both European and Asian populations (OR = 1.24; 95% CI: 1.08–1.43; $P=0.003$, $P_{\text{heterogeneity}}=0.220$ and OR = 1.54; 95% CI: 1.23–1.93; $P=0.001$, $P_{\text{heterogeneity}}=0.200$) (Figure 1). However, no significant associations were found in Africans (OR = 0.59; 95% CI: 0.32–1.09; $P=0.090$, $P_{\text{heterogeneity}}=0.070$). The test of heterogeneity for simply a comparison of those three combined ethnicity samples suggested a significant heterogeneity among them ($P<0.001$). Although the genotype distribution in the studies of Jonsson *et al* and Pookot *et al* did not follow Hardy–Weinberg equilibrium,[19,21] the corresponding pooled ORs were not materially altered with or without including these two studies. Similarly, no other single study influenced the pooled OR qualitatively as indicated by sensitivity analyses (data not shown).

Publication bias

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. The shapes of the funnel

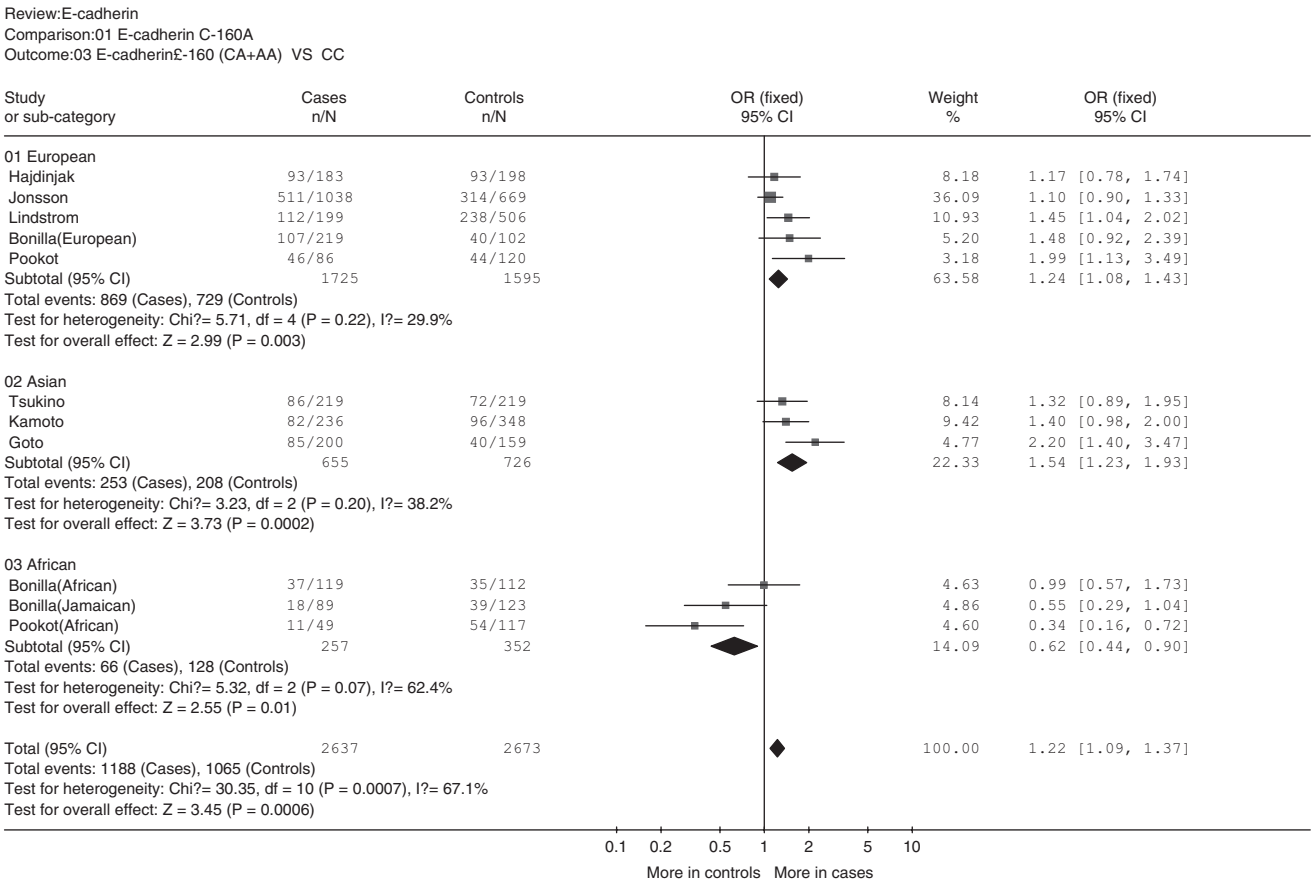

Figure 1 Forest plot of PCA risk associated with CDH1 −160 C/A polymorphism for CA + AA *vs* CC.

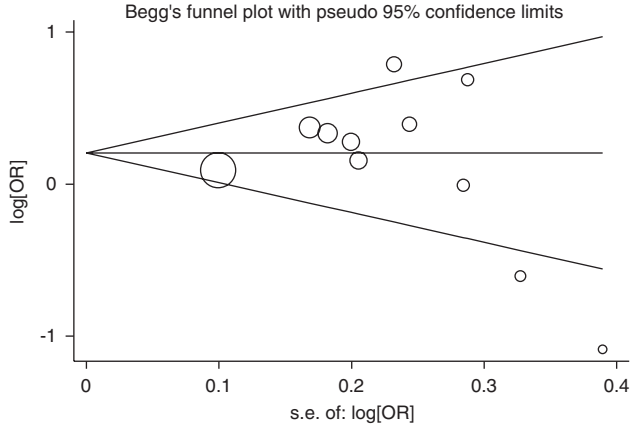

Figure 2 Begg's funnel plot for publication bias test.

plots did not reveal any evidence of obvious asymmetry (Figure 2). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias ($P = 0.700$).

Discussion

It is well recognized that there is individual susceptibility to the same kind of cancer even with the same environmental exposure. Host factors, including polymorphisms of genes involved in carcinogenesis may have accounted for this difference. Therefore, genetic susceptibility to cancer has been a research focus in scientific community. Recently, genetic variants of the *CDH1* gene in the etiology of several cancers have drawn increasing attention. Growing number of studies have suggested that −160A in the promoter region of the *CDH1* gene was emerging as a low-penetrance tumor susceptibility allele in the development of several kinds of cancer, such as PCA, urothelial cancer, and gastric cancer.[27,28] 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.

Our results indicated that the −160A allele carriers had a nearly 21% increased risk. The risk appeared to be more evident in the Europeans and Asians but not in Africans who even had a possible protective effect from the same genotypes, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in.[29] The HapMap LD patterns in CEU and CHB/JPT might be similar but was different in YRI. In Africans, the influence of the −160A allele might be masked by the presence of other as-yet unidentified causal genes involved in PCA development. In addition, it is also likely 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.[30] 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.[31] 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. Another very important factor contributing to the heterogeneity was that the genotype distribution of controls in the studies of Jonsson *et al* and Pookot *et al* did not follow Hardy–Weinberg equilibrium, indicating that these groups might not represent the general population very well.

Some limitations of this meta-analysis should be acknowledged. First, the associations were investigated in all kinds of cases (hereditary PCA, familial PCA, or sporadic PCA), and there may be PCA-specific genetic effects among these cases but we could not obtain enough information to further estimate these effects. Additionally, controls were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some had benign prostatic hyperplasia. Therefore, nondifferential misclassification bias was possible because these studies may have included the control groups who have different risks of developing PCA. Second, in the subgroup analyses, the number of Africans was relatively small, not having enough statistical power to explore the real association. Third, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other covariates including age, ethnicity, family history, environmental factors, and lifestyle.[32]

Despite these limitations, this meta-analysis suggests that the *CDH1* −160A allele is a low-penetrant risk factor for developing PCA, especially in Europeans and Asians. However, it is necessary to conduct large trials using standardized unbiased methods, homogeneous PCA patients and well-matched controls, with the assessors blinded to the data. Moreover, gene–gene and gene–environment interactions should also be considered in the analysis. Such studies taking these factors into account may eventually lead to our better, comprehensive understanding of the association between the *CDH1* −160 C/A polymorphism and PCA risk.

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