

ORIGINAL ARTICLE

ELAC2 polymorphisms and prostate cancer risk: a meta-analysis based on 18 case–control studiesB Xu^{1,3}, N Tong^{2,3}, J-m Li^{1,3}, Z-d Zhang² and H-f Wu¹¹Department of Urology, Nanjing BenQ Hospital, the Affiliated Hospital of Nanjing Medical University, Nanjing, China and²Department of Molecular and Genetic Toxicology, Cancer Center of Nanjing Medical University, Nanjing, China

Polymorphisms in the *elaC* homolog-2 (*ELAC2*)/*HPC2* gene have been hypothesized to alter the risk of prostate cancer. However, the results of the related published studies remained conflicting. We performed a meta-analysis of 18 studies evaluating the association between *ELAC2* Ser217Leu and Ala541Thr polymorphisms and prostate cancer risk. Overall, *ELAC2* Leu217 allele was associated with increased prostate cancer risk as compared with the Ser217 allele (odds ratio (OR) = 1.13, 95% confidence interval (CI): 1.03–1.24, $P=0.019$ for heterogeneity), as well as in the heterozygote comparison (OR = 1.21, 95% CI: 1.07–1.36, $P=0.034$ for heterogeneity) and the dominant genetic model (OR = 1.20, 95% CI: 1.07–1.35, $P=0.025$ for heterogeneity). Furthermore, the *ELAC2* Thr541 allele was associated with increased prostate cancer risk as compared with the Ala541 allele (OR = 1.22, 95% CI: 1.00–0.48, $P=0.131$ for heterogeneity). In the stratified analyses for Ser217Leu polymorphism, there was significantly increased prostate cancer risk in Asian and Caucasian populations, and studies using sporadic and familial prostate cancer cases. Similar result was found in the Asian population in the stratified analyses for Ala541Thr polymorphism. This meta-analysis showed evidence that *ELAC2* Ser217Leu and Ala541Thr polymorphisms were associated with prostate cancer risk, and might be low-penetrance susceptibility markers of prostate cancer.

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Introduction

Prostate cancer is the most common solid tumor diagnosed and the second leading cause of cancer-related death among American men, with an estimated 192 280 new cases and 27 360 deaths in the United States in 2008.¹ To date, the mechanisms that underlie the occurrence and progression of prostate cancer remain largely unknown. Risk factors such as diet, lifestyle and hormones have long been recognized as contributing to the risk of prostate cancer.^{2–4} In addition to age and race, family history of prostate cancer is the only other well-established prostate cancer risk factor.^{2,5–7}

The *elaC* homolog-2/hereditary prostate cancer (*ELAC2*/HPC2) gene at 17p11 is the first candidate gene identified for human prostate cancer on the basis of linkage analysis and positional cloning.⁸ *ELAC2* was thought to serve as a metal-dependent hydrolase and to be potentially involved in DNA inter-strand crosslink repair and mRNA editing.⁸ Moreover, the human *ELAC2* protein was shown to possess 3'-tRNase activity⁹ and to

interact with γ -tubulin,¹⁰ a component of the mitotic apparatus, suggesting a possible role for *ELAC2* in the regulation of cell-cycle progression.

Mutations in *ELAC2* are rare. Sequence analyses of *ELAC2* identified two common missense changes, which may function as low-penetrance modifiers of prostate cancer risk. The first variant, Ser217Leu, is located in hydrophilic segment of the protein sequence, and substitution of the hydrophobic leucine residue may alter the protein structure. A second variant, Ala541Thr, is adjacent to a histidine motif and may impair protein function.^{8,11} Previously, Camp *et al.*¹² and Severi *et al.*¹³ performed two meta-analyses of the association of these two variants in *ELAC2* and prostate cancer risk, but presented inconsistent results. Moreover, the number of studies focusing on these two polymorphisms in prostate cancer susceptibility is growing in recent years, but the results are often conflicting.

Hence, to derive a more precise estimation of the association of the Ser217Leu and Ala541Thr variants in *ELAC2* and prostate cancer risk, we performed a meta-analysis of all eligible case–control studies.

Methods*Publication search*

PubMed was searched using the search terms 'ELAC2' or 'HPC2' 'polymorphism' and 'prostate cancer'. And the

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latest search update was 9 December 2009. All published English language papers with available full text matching the eligible criteria were retrieved. Additional studies were identified by a hand search of the references of original studies. Of the studies with overlapping data published by the same investigators, only the most recent or complete study was included in this meta-analysis.

Inclusion and exclusion criteria

For inclusion in the meta-analysis, the identified articles had to provide: (1) information on the evaluation of Ser217Leu or Ala541Thr polymorphisms in *ELAC2* and prostate cancer risk, (2) information on using a case-control design and (3) information on containing information about available genotype frequency that can help infer the results in the papers. The major reasons for exclusion of studies were: (1) no control population; (2) no usable data reported and (3) duplicates.

Data extraction

All of the data were extracted independently by two reviewers according to the pre-specified inclusion criteria, and reached a consensus on all the items. For each study, the following characteristics were collected: the first author's last name, year of publication, country of origin, ethnicity, numbers of genotyped cases and controls, source of case groups (familial or sporadic prostate cancer cases), genotyping methods and quality control. Different ethnic descents were categorized as Caucasian, Asian, African or Mixed, which included more than one ethnic descent. For studies including subjects of familial or sporadic prostate cancer cases, data were extracted separately for each group whenever possible.

Statistical analysis

The strength of the association between the Ser217Leu and Ala541Thr polymorphisms and prostate risk was

measured by odds ratios (ORs) with 95% confidence intervals (CIs). The statistical significance of the summary OR was determined with the Z-test. For Ser217Leu polymorphism, we first explored the association between allele Leu217 and prostate cancer risk, as well as heterozygote comparison (SL vs SS) and homozygote comparison (LL vs SS) and the dominant genetic model (SL/LL vs SS). For the Ala541Thr polymorphism, we evaluated the same effects. Stratified analyses were also performed by ethnicities and sources of cases.

Heterogeneity assumption was checked by a χ^2 -based Q-test. A P-value more than 0.05 for the Q-test indicated lack of heterogeneity among the studies, and so the summary OR estimate of each study was calculated by the fixed-effects model (the Mantel-Haenszel method). Otherwise, the random-effects model (DerSimonian and Laird method) was used.^{14,15} To explore the reasons of heterogeneity, subgroup analyses were performed by grouping studies that showed similar characteristics, such as ethnicity and source of cases. Inter-study variance (I^2) was used to quantify the degree of heterogeneity between studies, and percentage of I^2 was used to describe the extent of explained heterogeneity of the characteristics. Potential publication bias was determined using Egger's linear regression test by visual inspection of a funnel plot. All statistical analyses were performed with the Stata software (version 8.2; StataCorp LP, College Station, TX, USA), using two-sided P-values.

Results

There were 18 studies retrieved on the basis of the search criteria for prostate cancer susceptibility related to *ELAC2* Ser217Leu and Ala541Thr polymorphisms^{8,11,13,16-31} The study characteristics are summarized in Table 1. Rokman *et al.*³¹ studied both *ELAC2* Ser217Leu and Ala541Thr polymorphisms, but there was no available genotype frequency of the Ser217Leu polymorphism in the article, so this study was included when analyzing the association between the Ala541Leu

Table 1 Main characteristics of selected studies

First author	Year	Country	Ethnicity	Case	Control	Genotyping method
Suarez	2001	US	Caucasian	257	355	PCR-RFLP
Suzuki	2002	Japan	Asian	81	106	PCR-RFLP
Stanford	2003	Mixed	Mixed	551	521	PCR-RFLP
Noonan-Wheeler	2006	US	Caucasian	150	170	Prosequencing
Robbins	2008	US	African	243	296	Prosequencing
Shea	2002	Tobago	African	119	223	PCR-RFLP
Xu	2001	US	Caucasian	362	182	PCR-RFLP
Yokomizo	2004	Japan	Asian	285	233	PCR-RFLP
Meitz	2002	UK	Caucasian	382	435	PCR-RFLP
Vesprini	2001	Mixed	Mixed	431	1505	PCR-RFLP
Wang	2001	US	Caucasian	444	502	Prosequencing
Takahashi	2003	Japan	Asian	98	255	PCR-SSCP
Severi	2003	Australia	Caucasian	825	732	PCR-RFLP
Fujiwara	2002	Japan	Asian	350	356	PCR-RFLP
Adler	2003	Canada	Caucasian	199	525	PCR-RFLP
Tavigian	2001	Canada	Caucasian	429	148	Taqman
Rebbeck	2000	US	Caucasian	270	250	PCR-RFLP
Rokman	2001	Finland	Caucasian	574	568	PCR-RFLP

Abbreviation: RFLP, restriction fragment length polymorphism.

polymorphism and prostate cancer. Therefore, there are 17 studies with 5476 cases and 6794 controls concerning the Ser217Leu polymorphism and 14 studies with 5120 cases and 6209 controls concerning the Ala541Leu polymorphism. For the Ser217Leu polymorphism, there were 9 studies of Caucasian descendents, 4 studies of Asian descendents, 2 of African descendents and 2 of Mixed descendents. For Ala541Thr polymorphism, there were 7 studies of Caucasian descendents, 4 studies of Asian descendents, 1 of African descendents and 2 of Mixed descendents.

All the studies used frequency-matched controls to the cases by the age, sex or ethnicity. PCR-restriction fragment length polymorphism assay was adopted in 13 of the 18 studies, and 11 studies mentioned quality control on genotyping, such as randomly repeated assays or validation using directed sequencing. In addition, Rokman *et al.*³¹ studied both sporadic and familial prostate cancer risk, but they did not show the data on familial prostate cancer risk, so this study was defined as a study of sporadic prostate cancer risk only. Therefore, 12 studies investigated sporadic prostate cancer risk, four studies^{8,25,26,28} investigated familial prostate cancer risk and two studies^{22,29} investigated both sporadic and familial prostate cancer risk. The distribution of genotypes in the controls was consistent with the Hardy-Weinberg equilibrium in all studies except for two studies.^{26,27}

The ELAC2 Ser217Leu polymorphism

We observed a wide variation of Leu217 allele frequencies across different ethnicities. The frequency of the Leu217 allele was 1.94% among Asian controls, which was significantly lower than that in Caucasian controls (29.01%, $P < 0.001$).

In the overall analysis, the ELAC2 Leu217 allele was associated with increased prostate cancer risk as compared with the Ser217 allele (OR = 1.13, 95% CI: 1.03–1.24, $P = 0.019$ for heterogeneity), as well as in heterozygote comparison (OR = 1.21, 95% CI: 1.07–1.36, $P = 0.034$ for heterogeneity) and in the dominant genetic model (OR = 1.20, 95% CI: 1.07–1.35, $P = 0.025$ for heterogeneity), but not in homozygote comparison

(OR = 1.11, 95% CI: 0.93, $P = 0.284$ for heterogeneity; Table 2 and Figure 1), and the positive association maintained in some subgroup analyses. Specifically, in the comparison of Leu217 and Ser217, there was significantly increased risk of prostate cancer in Caucasian population (OR = 1.12, 95% CI: 1.00–1.25, $P = 0.045$ for heterogeneity), Asian population (OR = 2.09, 95% CI: 1.07–4.05, $P = 0.134$ for heterogeneity) and among studies with sporadic prostate cancer (OR = 1.14, 95% CI: 1.01–1.28, $P = 0.007$ for heterogeneity) or familial prostate cancer (OR = 1.14, 95% CI: 1.01–1.28, $P = 0.525$ for heterogeneity; Table 2 and Figure 2). The same results were observed also in heterozygote comparison and the dominant genetic model.

There was significant heterogeneity for the Leu217 versus Ser217 comparison ($P = 0.019$ for heterogeneity), heterozygote comparison ($P = 0.034$ for heterogeneity) and dominant model comparison ($P = 0.025$ for heterogeneity), but not for homozygote comparison ($P = 0.284$ for heterogeneity). Consequently, we assessed the source of heterogeneity for the Leu217 versus Ser217 comparison by ethnicity, source of cases and sample size (subjects >200 in both case and control group). As a result, sample size ($\chi^2 = 6.22$, $df = 1$, $P = 0.013$) but not ethnicity ($\chi^2 = 6.97$, $df = 3$, $P = 0.073$) or source of cases ($\chi^2 = 0.43$, $df = 1$, $P = 0.513$) was found to account for the substantial heterogeneity. In addition, meta-regression analysis indicated that ethnicity could explain 46.3% of the I^2 , whereas source of cases could explain 43.3% of the I^2 .

The ELAC2 Ala541Thr polymorphism

As shown in Table 3 and Figure 3, a statistically significant difference was observed in the comparison of the variant Thr541 allele frequency in control populations between the Asians and Caucasians (0.27 vs 3.64%; $P < 0.001$). Overall, the ELAC2 Thr541 allele was associated with increased prostate cancer risk as compared with the Ala541 allele (OR = 1.22, 95% CI: 1.00–1.48, $P = 0.131$ for heterogeneity). Moreover, significantly elevated risk was observed among the Asian populations (OR = 4.44, 95% CI: 1.84–10.69, $P = 0.941$ for heterogeneity) in comparison of Thr541 and Ala541, as well as in

Table 2 Stratified analyses of the ELAC2 Ser217Leu polymorphism on prostate cancer risk

Variables	n ^a	Cases/controls	Leu allele vs Ser allele		SL vs SS		LL vs SS		SL/LL vs SS	
			OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b
Total	17	5476/6794	1.13 (1.03–1.24) ^c	0.019	1.21 (1.07–1.36) ^c	0.034	1.11 (0.93–1.31)	0.284	1.20 (1.07–1.35) ^c	0.025
<i>Ethnicities</i>										
Caucasian	9	3318/3299	1.12 (1.00–1.25) ^c	0.045	1.18 (1.03–1.36)	0.097	1.15 (0.90–1.46)	0.110	1.18 (1.03–1.37)	0.054
Asian	4	814/950	2.09 (1.07–4.05)	0.134	2.37 (1.26–4.44)	0.206	1.10 (0.17–7.00)	0.690	2.24 (1.17–4.28)	0.171
African	2	362/519	1.02 (0.81–1.28)	0.619	1.17 (0.87–1.58)	0.290	0.65 (0.31–1.34)	0.542	1.11 (0.84–1.46)	0.387
Mixed	2	982/2026	1.10 (0.97–1.26)	0.286	1.09 (0.92–1.29)	0.407	1.22 (0.92–1.62)	0.363	1.11 (0.95–1.31)	0.316
<i>Sources of cases</i>										
Sporadic	13	4043/5683	1.14 (1.01–1.28) ^c	0.007	1.25 (1.07–1.47) ^c	0.008	1.06 (0.88–1.28)	0.345	1.23 (1.05–1.44) ^c	0.005
Familial	6	1433/1589	1.14 (1.01–1.28)	0.525	1.16 (0.99–1.36)	0.708	1.26 (0.90–1.77)	0.304	1.18 (1.01–1.38)	0.727

Abbreviations: CI, confidence interval; ELAC2, elaC homolog-2; OR, odds ratio.

^aNumber of comparisons.

^bP-value of Q-test for heterogeneity test.

^cA random-effects model was used when P-value for heterogeneity test was <0.05; otherwise, a fixed-effects model was used.

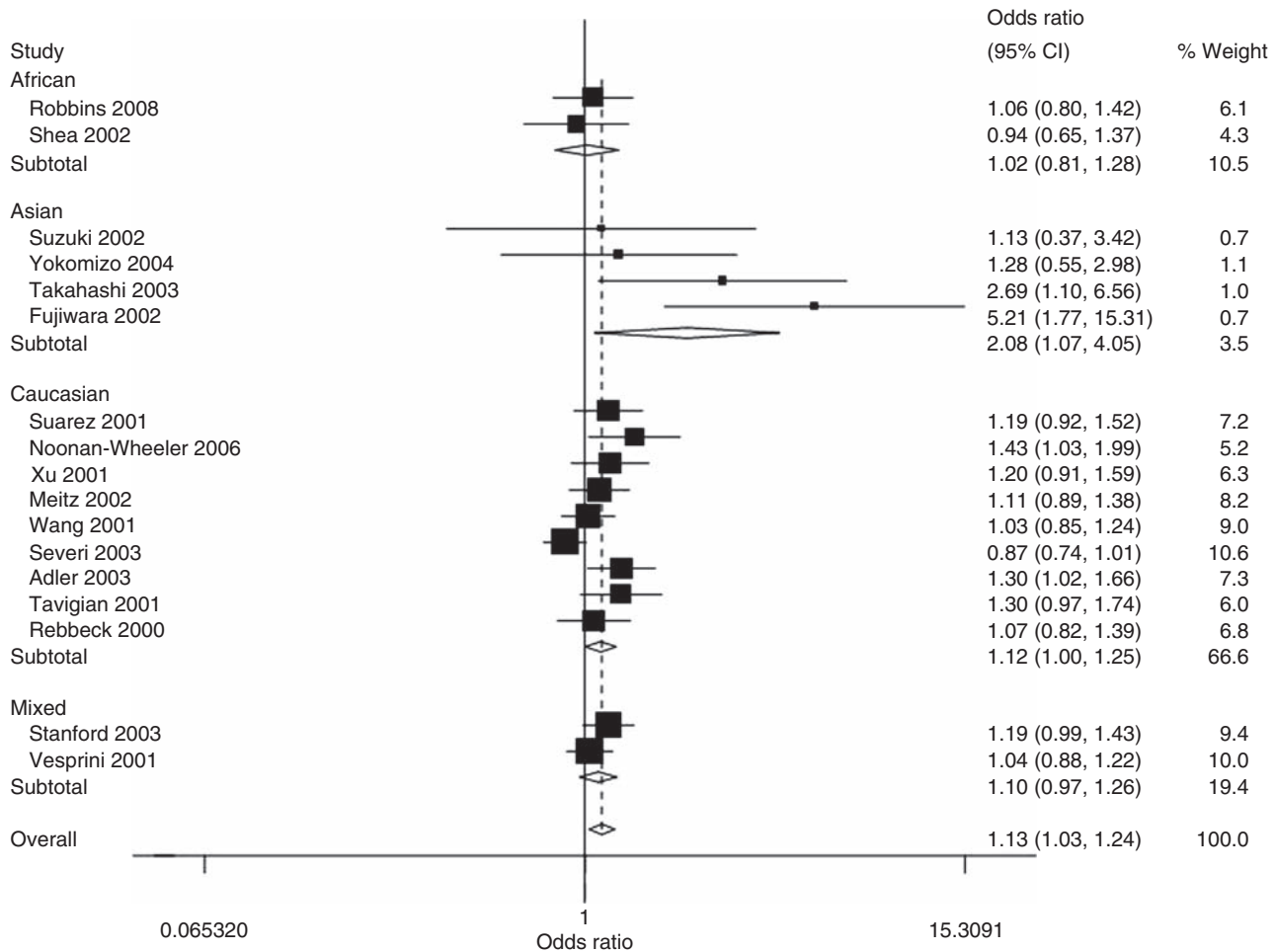


Figure 1 Forest plot of cancer risk associated with the *ELAC2* Ser217Leu polymorphism (Leu allele vs Ser allele). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. CI, confidence interval; *ELAC2*, *elaC* homolog-2; OR, odds ratio.

heterozygote comparison (OR = 4.27, 95% CI: 1.75–10.40, $P = 0.928$ for heterogeneity) and the dominant genetic model (OR = 4.42, 95% CI: 1.82–10.74, $P = 0.937$ for heterogeneity), but not among other populations in any genetic effect models. In addition, there was no significantly increased risk of prostate cancer among studies with sporadic prostate cancer and familial prostate cancer.

There was no significant heterogeneity for the Thr541 versus Ala541 comparison ($P = 0.131$ for heterogeneity), homozygote comparison ($P = 0.920$ for heterogeneity) and the dominant model comparison ($P = 0.076$ for heterogeneity), but for heterozygote comparison ($P = 0.043$ for heterogeneity). Similarly, we assessed the source of heterogeneity for the Thr541 versus Ala541 comparison by ethnicity, source of cases and sample size (subjects >200 in both case and control group). As a result, ethnicity ($\chi^2 = 10.54$, $df = 3$, $P = 0.014$) but not source of cases ($\chi^2 = 1.09$, $df = 1$, $P = 0.297$) or sample size ($\chi^2 = 0.78$, $df = 1$, $P = 0.378$) was found to account for the substantial heterogeneity. In addition, meta-regression analysis indicated that ethnicity could explain 31.5% of the I^2 , whereas source of cases could explain 22.0% of the I^2 .

Sensitivity analyses

ELAC2 Ser217Leu. Sensitivity analyses indicated that one independent study by Severi *et al.*¹³ was the main origin of the heterogeneity. The heterogeneity was effectively removed after exclusion of this study (Leu217 vs Ser217: $P = 0.204$ for heterogeneity). Although two studies^{26,27} did not follow the Hardy–Weinberg equilibrium, the summary ORs were not effectively altered with or without including these two studies. Moreover, no other single study influenced the summary OR qualitatively as indicated by sensitivity analyses.

ELAC2 Ala541Thr. Similarly, sensitivity analyses indicated that no other single study influenced the summary OR qualitatively.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plots seemed asymmetrical in allele comparison for both polymorphisms, suggesting the presence of publication

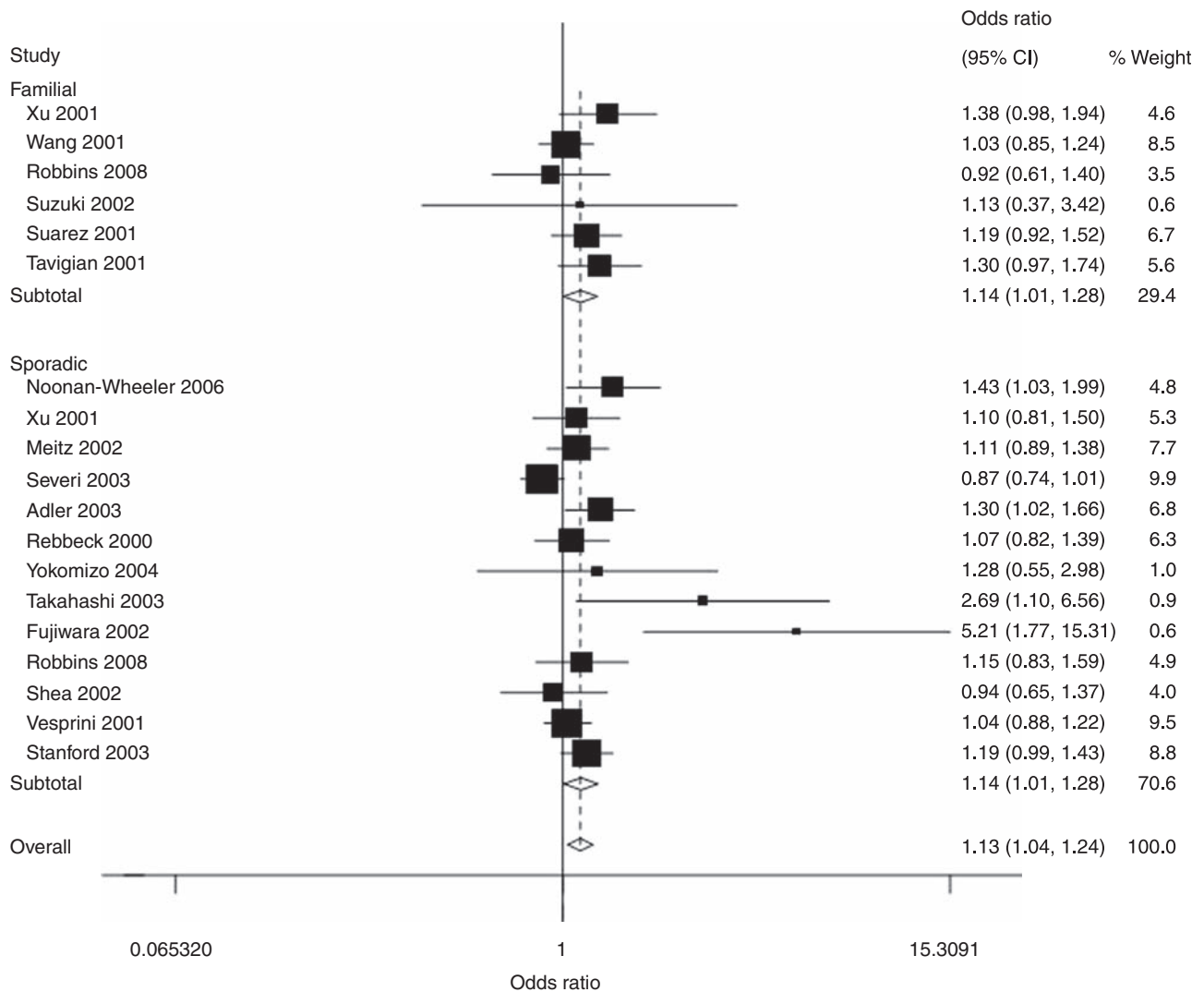


Figure 2 A forest plot of cancer risk associated with the *ELAC2* Ser217Leu polymorphism (Leu allele vs Ser allele) stratified by source of cases. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. CI, confidence interval; *ELAC2*, *elaC* homolog-2; OR, odds ratio.

Table 3 Stratified analyses of the *ELAC2* Ala541Thr polymorphism on prostate cancer risk

Variables	n ^a	Cases/controls	Thr allele vs Ala allele		AT vs AA		TT vs AA		AT/TT vs AA	
			OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b
Total	14	5120/6209	1.22 (1.00–1.48)	0.131	1.23 (0.97–1.55) ^c	0.043	1.64 (0.59–4.57)	0.920	1.23 (0.99–1.53)	0.076
<i>Ethnicities</i>										
Caucasian	7	3084/3333	1.19 (0.98–1.44)	0.084	1.20 (0.91–1.57)	0.063	1.67 (0.44–6.39)	0.667	1.19 (0.94–1.52)	0.139
Asian	4	805/553	4.44 (1.84–10.69)	0.941	4.27 (1.75–10.40)	0.928	2.62 (0.11–64.67)	—	4.42 (1.82–10.74)	0.937
African	1	243/296	1.22 (0.17–8.69)	—	1.22 (0.17–8.72)	—	—	—	1.22 (0.17–8.72)	—
Mixed	2	988/2027	0.96 (0.71–1.30)	0.859	0.98 (0.72–1.35)	0.848	1.37 (0.22–8.41)	0.763	0.95 (0.70–1.30)	0.899
<i>Sources of cases</i>										
Sporadic	11	4134/5246	1.14 (0.93–1.38)	0.276	1.12 (0.91–1.37)	0.294	1.64 (0.51–5.31)	0.992	1.13 (0.92–1.38)	0.275
Familial	5	986/1441	1.46 (0.93–2.28)	0.210	1.51 (0.75–3.05) ^c	0.035	2.31 (0.30–17.59)	0.263	1.50 (0.84–2.68)	0.094

Abbreviations: CI, confidence interval; *ELAC2*, *elaC* homolog-2; OR, odds ratio.

^aNumber of comparisons.

^bP-value of Q-test for heterogeneity test.

^cA random-effects model was used when P-value for heterogeneity test was <0.05; otherwise, a fixed-effects model was used.

bias (Supplementary Figure). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. As expected, the results have shown an

obvious evidence of publication bias (Leu allele vs Ser allele, $t = 3.21$, $P = 0.006$; Thr allele vs Ala allele, $t = 3.06$, $P = 0.011$).

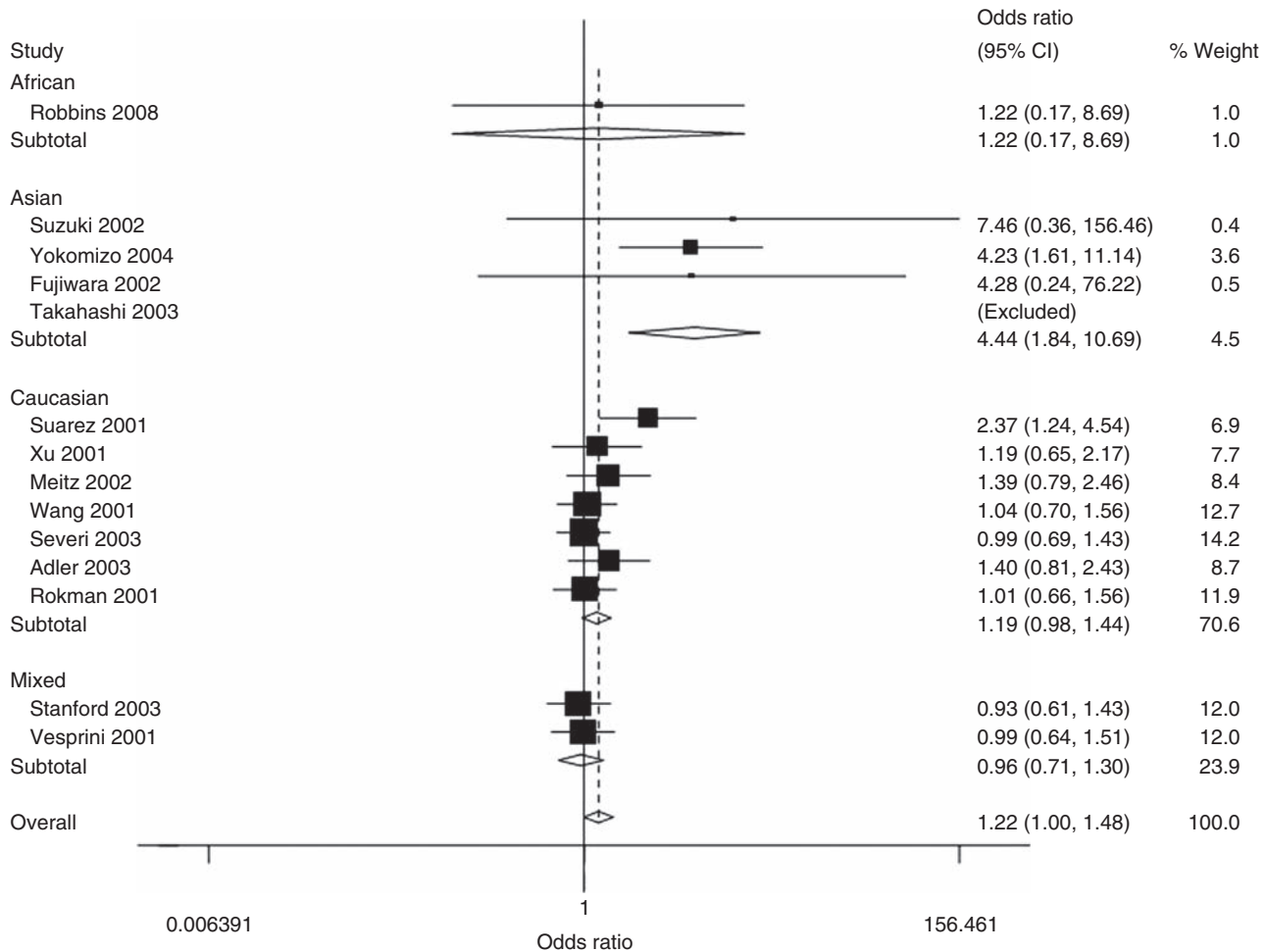


Figure 3 A forest plot of cancer risk associated with the *ELAC2* Ala541Thr polymorphism (Thr allele vs Ala allele). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. CI, confidence interval; *ELAC2*, *elaC* homolog-2; OR, odds ratio.

Discussion

The rapid growth of human genetics creates countless opportunities for studies of disease association. Given the number of potentially identifiable genetic markers and the multitude of clinical outcomes to which these may be linked, the testing and validation of statistical hypotheses in genetic epidemiology is a task of unprecedented scale. Meta-analysis provides a quantitative approach for combining the results of various studies with the same topic, and for estimating and explaining their diversity.³²

The present meta-analysis, including 18 published case-control studies, explored the association between two polymorphisms in the *ELAC2* gene region and prostate cancer risk. We found that both *ELAC2* Ser217Leu and Ala541Thr polymorphisms were associated with significant increase in prostate cancer risk. Given the potential roles of *ELAC2* in DNA inter-strand crosslink repair, mRNA editing and cell-cycle progression, the *ELAC2* polymorphisms may modulate the risk of prostate cancer. Tavgigian *et al.*⁸ and Vesprini *et al.*¹¹ found that the Ser217Leu variant is located in the hydrophilic segment of the *ELAC2* protein sequence, and substitution of the hydrophobic leucine residue may alter the protein structure, and the Ala541Thr

variant is adjacent to a histidine motif and may impair protein function. Thus, it is reasonable that the Leu217 allele and the Thr541 allele may decrease protein expression leading to impaired *ELAC2* function. In our meta-analysis, we found that subjects carrying the Leu217 or Thr541 allele were associated with higher risk of prostate cancer than those with the wild-type allele, which confirmed the hypothesis described above.

We found evidence for the association between the Ser217Leu polymorphism and prostate cancer risk among Caucasians (Leu217 vs Ser217) and Asians (Leu217 vs Ser217) but not among Africans (all genetic models). Moreover, the Ala541Thr polymorphism was associated with increased prostate cancer risk among Asians but not among Caucasians and Africans in all genetic models. It may be a possible reflection of the differences in genetic backgrounds and gene-environment interactions in the etiology. Other factors such as time-lag bias and publication bias may also have a role. In time-lag bias,³³ studies with 'negative' results take longer time to be published, whereas enthusiastic results are published much more quickly. In publication bias,^{34,35} small studies with 'negative' results are never published, whereas equally small studies with similar quality but 'positive' results would appear in the literature. We examined these possibilities and found

that 'positive' studies were reported more in Leu217 and Thr541 allele carriers' studies (especially in the Asian studies). Furthermore, there is only one published study using African population. Therefore, the observed ethnic differences may be due to chance as studies with small sample size may have insufficient statistical power to detect a slight effect. So, further investigations are warranted to validate the ethnic difference in the effect of these polymorphisms on prostate cancer risk especially in African population.

In this study we also found an association between the Ser217Leu polymorphism and prostate cancer risk among studies using sporadic or familial prostate cancer cases, whereas no significant difference was found in the stratified analysis for the Ala541Thr polymorphism. Different roles of these two polymorphisms in the formation process of sporadic and familial prostate cancer might contribute to this discrepancy.

There are some limitations of this meta-analysis to be acknowledged. First, only published studies were included in the meta-analysis; therefore, publication bias might have occurred and our results may have a substantial risk of being affected by such bias. Second, these results should be interpreted with caution because the control populations were not uniform as in most meta-analyses. Non-differential misclassification bias is possible because the majority of the studies did not consider that some controls might have developed prostate cancer in subsequent years. Third, in some sporadic studies, a small proportion of cases with family history were included,^{18,25,27} because it is not feasible to separate the familial cases from the sporadic cases on the basis of available information. Fourth, our result was based on unadjusted estimates, while a more precise analysis should be conducted adjusted by other factors like age, sex, and smoking and drinking status. Lack of the information for data analysis may cause serious confounding bias. Fifth, lack of the original data of the reviewed studies limited our further evaluation of potential interactions such as gene-gene, gene-environment and different polymorphic loci of the same gene, which may also modulate cancer risk. We minimized the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search for published studies and by using explicit methods for study selection, data extraction and data analysis. Therefore, our meta-analysis also had some advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, the studies included in our meta-analysis were satisfactory and strictly met our inclusion and criterion.

Conclusions

This meta-analysis showed evidence that the *ELAC2* Ser217Leu and Ala541Thr polymorphisms might be associated with prostate cancer risk, which supported the hypothesis that these two polymorphisms may be low-penetrance susceptibility markers of prostate cancer. Further prospective researches with larger numbers of worldwide participants are expected to examine associa-

tions between *ELAC2* Ser217Leu and Ala541Thr polymorphisms, and prostate cancer risk to make a comprehensive and true conclusion, and other possible confounding risk factors like age, sex, life style and race should also be controlled when important genetic risks for prostate cancer are assessed.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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