

The RNASEL –1385G/A polymorphism is associated with risk of prostate cancer in Africans

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Abstract: The RNASEL –1385G/A (rs486907) variant has been reported to be associated with increased risk of prostate cancer. However, these associations are not consistent among studies. To address this issue, we performed a meta-analysis to evaluate the association between RNASEL –1385G/A polymorphism and prostate cancer risk. The PubMed, Embase, and Web of Science databases were searched for relevant papers published in the past 20 years from 1997 to 2017. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of associations. Based on our search for manuscripts reporting prostate cancer susceptibility related to the rs486907 polymorphism, 16 case-control studies from 13 different publications were retrieved. No significantly positive associations were found for the polymorphism and prostate cancer susceptibility in the total population. When stratified by ethnicity, the results demonstrated that the –1385G/A polymorphism was associated with a decreased cancer risk in Africans (GG vs AA: OR =0.371, 95% CI=0.176–0.783; GG/GA vs AA: OR =0.368, 95% CI =0.175–0.776). We also found that the rs486907 polymorphism was associated with a decreased cancer risk in hospital-based controls (GG vs AA: OR =0.697, 95% CI =0.488–0.996; GG + GA vs AA: OR =0.701, 95% CI =0.502–0.978). Our meta-analysis suggests that polymorphism in the RNASEL gene is a protective factor against prostate cancer in Africans. Further studies using larger sample sizes should be conducted to elucidate the role of gene polymorphism in prostate cancer risk.

Keywords: RNASEL, prostate cancer, polymorphism, meta-analysis

Introduction

RNase L, encoded by the *RNASEL* gene, is a ubiquitously expressed endoribonuclease.¹ It is activated by dimerization, which occurs upon 2'–5'A binding, and results in cleavage of all RNAs in the cell. This can lead to activation of MDA5, an RNA helicase involved in the production of interferons.² Beyond its antiviral activity, RNASEL contributes toward innate immunity and cell metabolism including inflammation, cell proliferation and differentiation, migration, apoptosis, and tumorigenesis.^{3–5}

Several variations in RNASEL have been identified, of which the mutation at codon 462 is functionally distinct: the Arg-to-Gln variant has a threefold reduced enzyme activity, which could enhance virus susceptibility, impair the cellular stress response, diminish control of cellular RNA levels, or induce apoptosis.⁶

Over the years, the rs486907 G/A polymorphism in the *RNASEL* gene has been studied to assess its association with risk of prostate cancer.^{7,10–13} However, the results are inconsistent, which might be caused by the limitation of individual studies. To shed light on the associations between the *RNASEL* gene polymorphism and prostate cancer risk, we performed this meta-analysis of 16 case-control studies retrieved from 13 published papers.^{7–19}

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Methods

Search strategy

We searched the PubMed, Embase, and Web of Science databases for papers published in the past 20 years from 1997 through to 2017, using the keywords “*RNASEL*”, “cancer or carcinoma or tumor”, and “polymorphism or variant”. A search conducted with these terms yielded a total of 81 publications, of which 14 were finally selected. We also screened the referenced literature of the selected publications manually.

Inclusion and exclusion criteria

Studies were required to fulfill the following inclusion criteria: they should 1) assess the correlation between prostate cancer risk and the *RNASEL* –1385G/A polymorphism, 2) be case–control studies, and 3) consider sufficient numbers of genotypes for cases and controls. Studies were excluded if they 1) included no control population, 2) did not report genotype frequency data, and 3) were publications using the same dataset.

Data extraction

Two authors independently extracted all data from the selected publications. These data included the first author’s last name, year of publication, country of origin, ethnicity of the study population, total number of samples in case and control groups, numbers of each genotype in both case and control groups, *P*-value of Hardy–Weinberg equilibrium (HWE) of the control group, and genotyping method. Ethnicity was categorized as individuals of European descent and African or Asian, and control subgroups were population-based and hospital-based (HB).

Statistical analysis

Based on genotype frequencies for cases and controls, crude odds ratio (OR) with 95% confidence interval (CI) was used to measure the strength of associations between the rs486907 polymorphism and prostate cancer risk. The statistical significance of the OR was determined with the *Z* test. The heterogeneity assumption among studies was evaluated using a χ^2 -based *Q* test. A *P*-value of >0.10 for the *Q* test indicated a lack of heterogeneity among studies. If significant heterogeneity was detected, the DerSimonian–Laird random-effects model or the Mantel–Haenszel fixed-effects model was chosen for analysis.^{20,21} We investigated the relationship between the rs486907 genetic variant of the *RNASEL* gene and cancer risk by testing for the allelic contrast (G vs A), homozygote comparison (GG vs AA),

heterozygote comparison (GG vs GA), and dominant genetic model (GG + GA vs AA). A sensitivity analysis was performed by omitting studies, one after the other, to assess the stability of results. The departure of frequencies of the *RNASEL* polymorphism from expectations under HWE was assessed by the Pearson’s χ^2 test, and the values of $P < 0.05$ were considered significant.²² Publication bias was investigated using Egger’s linear regression method and Begg’s funnel plots, where $P < 0.05$ was considered significant.²³ All statistical tests for meta-analyses were performed using Stata software version 10.0 (StataCorp LP, College Station, TX, USA).

Results

Study characteristics

Using various combinations of key terms, a total of 81 publication titles were identified from the PubMed, Embase, and Web of Science databases. As shown in Figure 1, 40 publications were excluded from the analysis after screening the abstracts. The full texts of the remaining papers were then evaluated, and 27 additional publications were excluded for the following reasons: duplications (10), meta-analyses or systematic reviews (1), publications dealing with other polymorphisms (16), and one publication having no case–control group. Finally, 13 publications including 16 case–control studies were chosen for our meta-analysis. The distribution of genotypes in all the control groups was in agreement with HWE. The genotyping methods used in the different studies that were a part of our meta-analysis included restrictive fragment length polymorphism polymerase chain reaction, TaqMan,

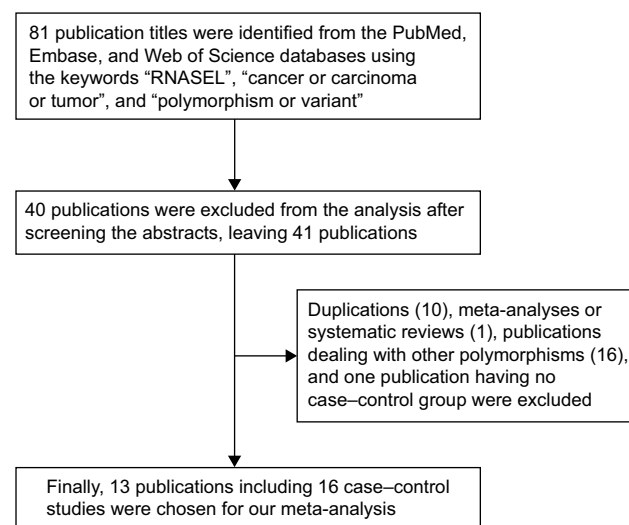


Figure 1 A flowchart illustrating the search strategy used to identify association studies for gene polymorphisms and prostate cancer risk.

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

Studies	Year	Country	Ethnicity	Cancer type	Case/ control	SOC	Genotype assay	Case			Control			
								GG	GA	AA	GG	GA	AA	HWE
Alvarez-Cubero et al ⁷	2016	Spain	European	Prostate cancer	141/145	HB	RFLP-PCR	63	53	25	52	68	25	0.091
Cybulski et al ⁸	2007	Poland	European	Prostate cancer	737/511	HB	RFLP-PCR	245	376	116	177	252	82	0.625
Robbins et al ¹²	2008	USA	African	Prostate cancer	243/296	HB	iPLEX assay	183	55	5	225	66	5	0.951
Shook et al ¹⁹	2007	USA	European	Prostate cancer	430/503	HB	TaqMan assay	187	183	60	221	225	57	0.981
Shook et al ¹⁹	2007	USA	European	Prostate cancer	150/239	HB	TaqMan assay	72	62	16	136	96	7	0.039
Shook et al ¹⁹	2007	USA	African	Prostate cancer	68/145	HB	TaqMan assay	45	13	10	111	31	3	0.633
Daugherty et al ⁹	2008	USA	African	Prostate cancer	98/380	HB	TaqMan assay	73	23	2	277	98	5	0.261
Daugherty et al ⁹	2008	USA	European	Prostate cancer	1,116/1,344	HB	TaqMan assay	463	505	148	554	602	188	0.237
Nam et al ¹⁰	2010	Canada	Mixed	Prostate cancer	996/1,092	PB	MS	477	409	110	521	459	112	0.463
Nakazato et al ¹⁴	2003	Japan	Asian	Prostate cancer	101/105	HB	PCR	69	32	0	71	26	8	0.021
Wiklund et al ¹³	2004	Sweden	European	Prostate cancer	1,622/796	PB	TaqMan assay	597	778	247	297	384	115	0.627
Rökmán et al ²⁶	2002	Finland	European	Prostate cancer	233/176	HB	Sequenom platform	88	106	39	69	84	23	0.745
Shea et al ¹⁸	2008	USA	European	Prostate cancer	230/452	PB	RFLP-PCR	187	41	2	362	88	2	0.168
Wang et al ¹⁷	2002	USA	European	Prostate cancer	918/493	PB	Sequenom platform	389	427	102	193	233	67	0.802
Beuten et al ¹¹	2010	USA	European	Prostate cancer	156/224	HB	PCR	75	64	17	126	91	7	0.048
Maier et al ¹⁶	2005	German	European	Prostate cancer	363/207	PB	PCR	133	171	59	73	97	37	0.628

Abbreviations: SOC, source of control; HB, hospital-based; PB, population-based; RFLP-PCR, restriction fragment length polymorphism polymerase chain reaction; MS, mass spectrometry; PCR, polymerase chain reaction; HWE, Hardy–Weinberg equilibrium.

Sequenom platform, and mass spectrometry-based genotyping analysis. Characteristics of the case–control studies included in this meta-analysis are shown in Table 1.

Quantitative synthesis

Results of the overall meta-analysis are shown in Table 2. There was no positive association between this polymorphism and prostate cancer susceptibility (Figure 2). When stratified by ethnicity, we observed that the polymorphism was associated with a decreased prostate cancer risk in African-descent patients (GG/GA vs AA: OR =0.366, 95% CI=0.174–0.770, $P_{\text{heterogeneity}}=0.095$; GG vs AA: OR =0.370, 95% CI=0.176–0.783, $P_{\text{heterogeneity}}=0.098$; Figure 3). Analysis of the subgroups based on the source of control indicated that the polymorphism was associated with a decreased

prostate cancer risk in HB controls (GG vs AA: OR =0.697, 95% CI =0.488–0.996, $P_{\text{heterogeneity}}=0.000$; GG + GA vs AA: OR =0.701, 95% CI =0.502–0.978, $P_{\text{heterogeneity}}=0.001$; Figure 4).

Bias diagnosis and sensitivity analysis

Egger's and Begg's tests were performed to assess publication bias. No proof of publication bias was found, except overall GG vs GA and GG/GA vs AA. A sensitivity analysis was performed to assess the influence of each study on the pooled OR by sequential removal of individual studies. Neither Begg's funnel plot nor Egger's test detected any obvious evidence of publication bias in the subgroup analyses for all genetic models. Figure 5 shows the funnel plot for GG vs AA of prostate cancer in Africans.

Table 2 Results of meta-analysis for the RNASEL –I385G/A polymorphism and prostate cancer risks

Study groups	N*	G vs A		GG vs GA		GG vs AA		GG/GA vs AA	
		OR (95% CI)	P-value ^a	OR (95% CI)	P-value ^a	OR (95% CI)	P-value ^a	OR (95% CI)	P-value ^a
Total	16	0.964 (0.893–1.042) [‡]	0.029	1.009 (0.938–1.085)	0.973	0.854 (0.69–1.057) [‡]	0.001	0.855 (0.703–1.040) [‡]	0.002
Ethnicity									
Asian	1	1.40 (0.192–1.69)	0.116	1.14 (0.96–1.36)	0.057	1.265 (0.902–1.51) [‡]	<0.001	1.280 (0.098–1.65) [‡]	0.001
European	11	1.13 (0.60–1.97)	0.070	1.01 (0.73–1.51)	0.154	0.98 (0.69–1.37) [‡]	0.070	1.11 (0.76–1.52) [‡]	0.029
African	3	0.787 (0.49–1.247) [‡]	0.038	1.020 (0.760–1.368)	0.907	0.371 (0.176–0.783)	0.098	0.368 (0.175–0.776)	0.098
Mixed	1	1.40 (0.192–1.69)	0.116	1.14 (0.96–1.36)	0.057	1.265 (0.902–1.51) [‡]	<0.001	1.280 (0.098–1.65) [‡]	0.001
SOC									
Hospital-based	11	0.908 (0.803–1.028) [‡]	0.013	0.985 (0.891–1.090)	0.866	0.697 (0.488–0.996) [‡]	0.000	0.701 (0.502–0.978) [‡]	0.001
Population-based	5	1.40 (0.192–1.69)	0.116	1.14 (0.96–1.36)	0.017	1.265 (0.902–1.51) [‡]	<0.001	1.280 (0.098–1.65) [‡]	0.001

Notes: ^aP-value of Q test for heterogeneity test. ^{*}Studies of comparison. [‡]Random model was used.

Abbreviations: SOC, source of control; OR, odds ratio; CI, confidence interval.

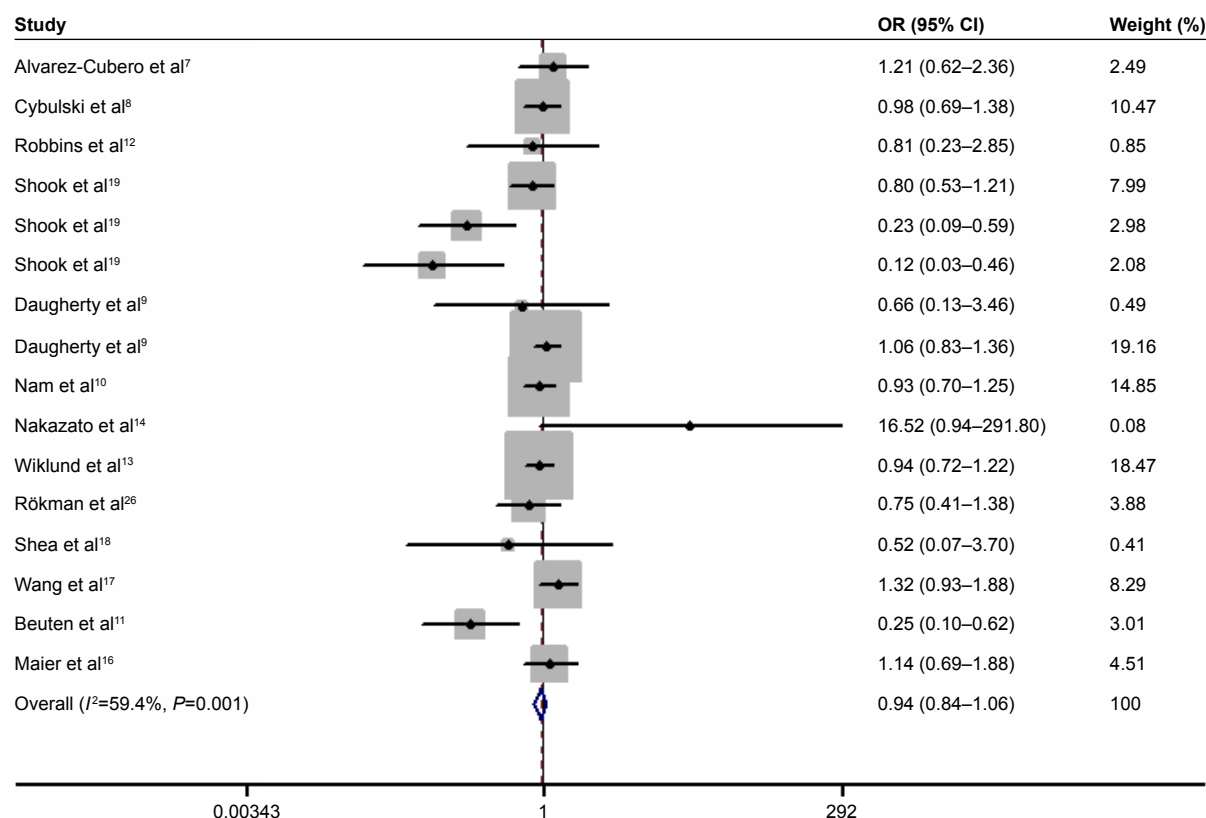


Figure 2 Forest plot of the rs486907 polymorphism and prostate cancer risk: GG vs AA for total.
Abbreviations: OR, odds ratio; CI, confidence interval.

Discussion

Under normal conditions, RNASEL has tumor-suppressive and antiproliferative functions, although the common rs486907 variant of *RNASEL* gene has been associated with risk of a number of cancers.^{21–24} Up to now, many molecular epidemiological studies were performed to assess the associations of this polymorphism with prostate cancer risk.

In a large American series, Casey et al observed statistically significant ORs for prostate cancer patients carrying the RNASEL variant G-allele (GG vs AA: OR = 2.12, 95% CI = 1.19–3.78; GA vs AA: OR = 1.46, 95% CI = 0.65–1.19).⁶ In 2002, Rökman et al analyzed 233 unselected patients with prostate cancer and 176 unaffected sibling controls from Finland, and found that the Gln/Gln variant was more

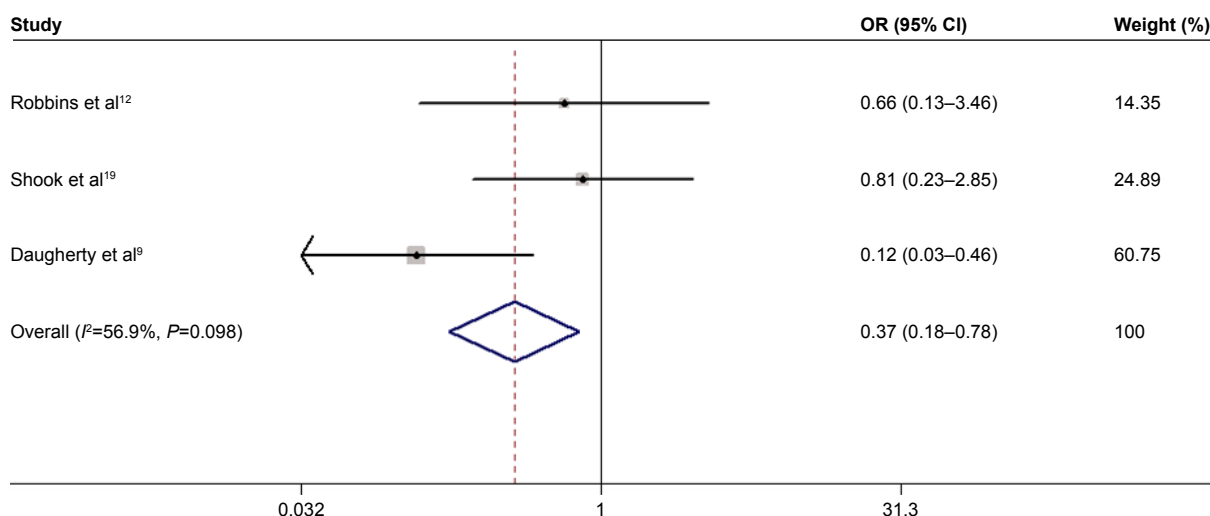


Figure 3 Forest plot of the rs486907 polymorphism and prostate cancer risk: GG + GA vs AA for Africans.
Abbreviations: OR, odds ratio; CI, confidence interval.

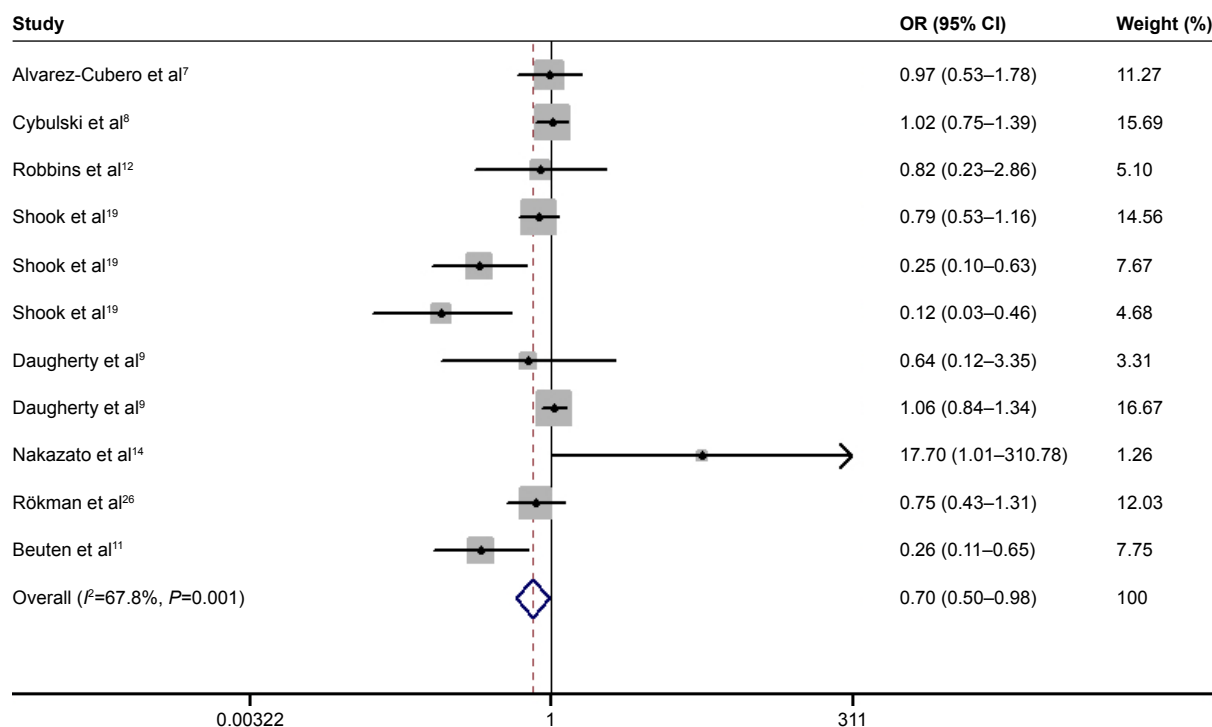


Figure 4 Forest plot of the rs486907 polymorphism and prostate cancer risk in hospital-based controls: GG + GA vs AA.

Note: Weights are from random-effects analysis.

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

frequent in 66 patients with hereditary prostate cancer than in 176 controls, but was not more frequent in unselected 167 patients with prostate cancer compared with controls.²⁶ By contrast, Wang et al found that homozygosity for the Arg variant was less frequent in 493 controls compared with 433 familial prostate cancer patients from the USA.¹⁷ Following these studies, two more papers on the association involving larger sample sizes were published,^{24,25} which indicated that the rs486907 polymorphism in the RNASEL gene is not associated with an increased risk of developing prostate

cancer. In order to verify this association, our meta-analysis combined data from 7,602 patients with prostate cancer and 7,108 controls, and revealed that the rs486907 polymorphism was not associated with prostate cancer risk. When stratified by ethnicity, we found that the rs486907 variant was associated with a decreased cancer risk in Africans (GG vs AA: OR =0.370, 95% CI =0.176–0.783; GG/GA vs AA: OR =0.366, 95% CI =0.174–0.770). Therefore, the variant G-allele might be a protective factor against prostate cancer in African-descent individuals.

Although we expended considerable efforts in identifying as many associations between the *RNASEL* gene polymorphism and cancer risk as possible, our study still suffers from some inherent limitations. First, the different genotyping strategies may contribute to bias in the analysis. Second, factors associated with gene–gene and gene–environment interactions were poorly represented. It is possible that specific environmental and lifestyle factors such as age, sun exposure, smoking, drinking, and family history could alter the associations between the gene polymorphism and prostate cancer risk. Therefore, it is necessary to determine the roles of specific environmental factors and lifestyles. Third, we were unable to analyze how the different developmental stages of prostate cancer are associated with the *RNASEL* polymorphism.

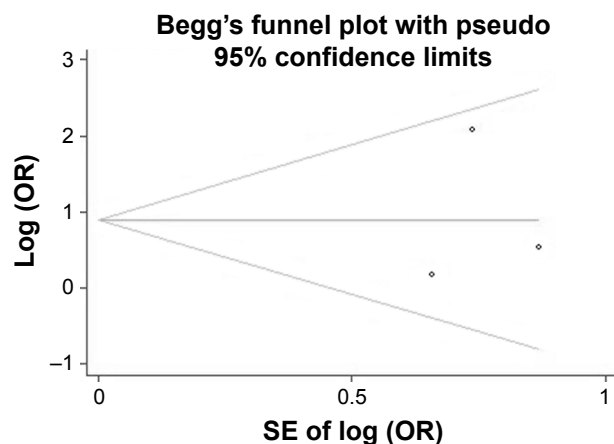


Figure 5 Begg's funnel plot for publication bias test of prostate cancer (GG vs AA).

Abbreviations: OR, odds ratio; SE, standard error.

In conclusion, our present meta-analysis suggests that the rs486907 polymorphism in the *RNASEL* gene may not be associated with prostate cancer risk. However, the variant G allele might be a protective factor against prostate cancer in African-descent individuals. Further studies based on larger sample sizes and considering additional gene–environment interactions should be conducted in the future.

Disclosure

The authors report no conflicts of interest in this work.

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