Evidence from 40 Studies that 2 Common Single-Nucleotide Polymorphisms (SNPs) of RNASEL Gene Affect Prostate Cancer Susceptibility: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-Compliant Meta-Analysis

Jun Xia
Rulin Sun

Background: Numerous studies have evaluated the relationship between RNASEL gene polymorphisms (rs486907 G>A and rs627928 T>G) and the risk of cancer. However, many of the results have been controversial. To explore the role of RNASEL gene polymorphisms in prostate cancer, we carried out the present meta-analysis.

Material/Methods: The qualified articles were collected from PubMed, Web of Science, Scopus, CNKI, and WanFang databases to August 2018. A total 23 articles with 40 studies were incorporated into our analysis.

Results: Our data show that rs486907 was not associated with the risk of prostate cancer in any populations. Nevertheless, rs627928 was reported to promote the development of prostate cancer (T vs. G: OR=1.08, 95% CI=1.01–1.15; TT+TG vs. GG: OR=1.14, 95% CI=1.03–1.25) in allele and recessive models in overall populations. Stratified analyses showed that similar results were obtained in white populations.

Conclusions: We report the effect of rs627928 on the development of prostate cancer and confirm that rs486907 is not involved in the risk of prostate cancer in the current meta-analysis. However, research in larger populations is needed to validate our conclusions.

MeSH Keywords: Anus Neoplasms • Polymorphism, Single-Stranded Conformational • Ribonuclease, Pancreatic

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META-ANALYSIS

Background

Cancer is a major public health problem and results in significant morbidity and mortality worldwide [1]. Many studies show that the process of carcinogenesis is always accompanied by inflammation. Therefore, certain inflammatory cytokines promote or inhibit tumor development [2].

As prominent factors during the process, interferons exert their various roles by inducing the expression of many proteins [3]. For instance, endoribonuclease L (RNASEL), induced by interferons, is associated with the antiproliferative and antiviral effects of interferon [4]. RNASEL gene expression and mutation have been receiving increased research attention.

Single-nucleotide polymorphisms (SNPs) of some genes affect the function of these genes. Sequence analysis of RNASEL gene has identified the 2 most common corresponding SNPs: rs486907 G>A and rs627928 T>G [5,6]. These SNPs has been reported to affect the expression and activity of the protein derived from the RNASEL gene [7,8]. RNASEL has been demonstrated to play a role in carcinogenesis, such as in prostate cancer [9,10]. Thus, rs486907 and rs627928 are thought to be involved in prostate cancer susceptibility.

Recent studies have shown the association between risk of prostate cancer and these SNPs of RNASEL. Unfortunately, the conclusions in these studies were not consistent. To resolve these inconsistent results, several meta-analyses on rs486907 and rs627928 were conducted up to 2011. For the next 6 years, 14 original studies on this scientific problem were also carried out. However, the conclusions in these studies remain controversial. Therefore, we performed this updated meta-analysis, including new studies, and attempted to assess the role of these SNPs in tumor development [4–6,11–36].

Material and Methods

Search strategy

All relevant articles were collected from PubMed, Web of Science, Scopus, CNKI, and WanFang databases before August 2018. The search keywords were: “SNP” and “RNASEL or Ribonuclease L” and “cancer or tumor or neoplasm or carcinoma” and “polymorphism”. Additional relevant studies were found by manually screening the references in reviews and the identified articles. The quality of the studies included in our meta-analysis were evaluated using the Newcastle-Ottawa scale.

Inclusion and exclusion conditions

Study inclusion criteria were: (a) evaluation of the relationship between rs486907 and rs627928 and the risk of prostate cancer; (b) case-control design; (c) published in Chinese or English; and (d) enough data obtained in the studies, including the amounts of these genotypes (for rs486907 and rs627928) in cases and controls, which could be used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Exclusion criteria were: (a) abstracts from conferences and reviews; (b) case only studies; (c) duplicate studies; and (d) studies without detailed genotyping information.

Data extraction

The data in eligible studies were extracted by 2 investigators. The following elements from each study were collected: the (first) author name, edition year, district, people and populations, the quality of each study, control source, tumor types, the numbers of controls and cases, the genotype distribution for rs486907 and rs627928, the minor allele frequency (MAF) in each study, and the result of Hardy-Weinberg equilibrium (HWE) test.

Statistical analysis

The chi-square test was used to assess deviation from HWE in controls. The evaluation of the relationship between these SNPs of RNASEL gene and prostate cancer susceptibility was performed using ORs and 95% CIs. Pooled ORs were assessed using the Z test in the following 5 genetic models: allele, recessive, dominant, homozygous, and heterozygous models.

The heterogeneity among the studies included for meta-analysis were checked by Q-test based on chi-square test by using the I² index value. If P<0.10 and I² >50%, the significant heterogeneity could not be ignored. Hence, the pooled OR was obtained through the random-effects model. If not, the fixed-effects model was used. Stratification was conducted based on ethnicity and cancer type.

The impact of each study on the pooled ORs were checked by sensitivity analysis. Risk of publication bias among studies was evaluated by Begg’s test and Egger’s test. STATA software (Version 11.0, STATA Corp., College Station, TX, USA) was used for all statistical analyses. All statistics were two-sided and the differences were defined as significant at P < 0.05.

Ethics review

Because this meta-analysis was based on previous studies, ethics approval was not required.
the fixed-effects model was used (Table 2). Our results indicated that rs627928, in allele and recessive models, was related to high risk of prostate cancer (Table 2, Figure 2C).

In subgroup analysis, rs486907 was not involved in prostate cancer susceptibility in Caucasian populations (covering 19 studies) across all genetic models (Table 2). Furthermore, no obvious association between rs486907 and the risk of onset for prostate cancer was found in African American populations (covering 3 studies) or in non-Hispanic Caucasian populations (covering 3 studies) (Table 2, Figure 2B).

For rs627928, heterogeneity among studies was observed in 5 genetic models in non-Caucasian populations. Consequently, the ORs and 95% CIs were derived from the random-effects model, and the fixed-effects model was used for the other populations (Table 2).

As expected, our results indicated that rs627928 promotes the development of prostate cancer in African American populations (covering 2 studies) and Caucasian populations (covering 10 studies) in allele, recessive, and homozygous genetic models (Table 2, Figure 2D). However, in non-Caucasian populations, no significant correlation was found between rs627928 and prostate cancer susceptibility (Table 2).

Sensitivity analysis and publication bias

To assess whether the results of any single study affected the final conclusion in our meta-analysis, we carried out sensitivity analysis to evaluate the influence for both rs486907 and rs627928. We found that our results were not affected by exclusion of individual studies (Figure 3).

In addition, the publication bias for both rs486907 and rs627928 was evaluated by Begg’s test and Egger’s test showing there was no clear evidence of publication bias or trending bias in our analysis (Table 3).

Trial sequential analysis

To avoid random errors and ensure stability of our results for both rs486907 and rs627928, trial sequential analysis (TSA) was carried out in different genetic models or various populations. However, none of the cumulative Z-curves crossed the trial sequential monitoring boundary or the required information size line (Figure 4).

Discussion

Cancers seriously affect patients and impose large economic burdens on society [1]. In recent years, more and more research groups have focused on genetic susceptibility to cancer.
Table 1. Characteristics of the studies included in this meta-analysis.

| Author                  | Year | Region | Ethnicity       | Source | Tumor          | Case        | Control       | MAF       | HWE     | Score |
|-------------------------|------|--------|-----------------|--------|----------------|-------------|--------------|-----------|---------|-------|
| Alvarez-Cubero MJ       | 2015 | Spain  | Caucasian       | HB     | Prostate cancer | 80          | 120          | 37 237    | 61 114  | 41 216 | 0.409 |
| Winchester DA           | 2015 | USA    | Non-Hispanic    | PB     | Prostate cancer | 352         | 407          | 105 864   | 330 372 | 129 831 | 0.454 |
| San Francisco IF        | 2014 | Chile  | Hispanic Caucasian | HB     | Prostate cancer | 43          | 31           | 9 83      | 11 6    | 4 210  | 0.342 |
| Arredondo M             | 2012 | Spain  | Caucasian       | HB     | Prostate cancer | 17          | 40           | 10 67     | 28 57   | 20 105 | 0.346 |
| Sakuma T                | 2011 | USA    | Caucasian       | PB     | Prostate cancer | 43          | 55           | 12 110    | 11 21   | 8 40  | 0.157 |
| Meyer MS                | 2010 | USA    | Caucasian       | PB     | Prostate cancer | 529         | 547          | 159 1235  | 505 546 | 159 210 | 0.357 |
| Agalliu I               | 2010 | USA    | Caucasian       | PB     | Prostate cancer | 467         | 414          | 84 965    | 572 556 | 109 1237 | 0.313 |
| Beuten J                | 2010 | USA    | Hispanic Caucasian | PB     | Prostate cancer | 75          | 64           | 17 156    | 126 91  | 7 224  | 0.048 |
| Wang MH                 | 2009 | USA    | Caucasian       | PB     | Prostate cancer | 100         | 121          | 27 248    | 88 132  | 33 253 | 0.391 |
| Robbins CM              | 2008 | USA    | African American | HB     | Prostate cancer | 183         | 55           | 5 243     | 225 66  | 5 296 | 0.110 |
| Shea PR                 | 2008 | USA    | Caucasian       | PB     | Prostate cancer | 187         | 41           | 2 230     | 362 88  | 2 452 | 0.168 |
| Daugherty SE            | 2007 | USA    | Non-Hispanic Caucasian | PB     | Prostate cancer | 463         | 505          | 148 1116  | 554 602 | 188 1344 | 0.364 |
| Daugherty SE            | 2007 | USA    | African American | PB     | Prostate cancer | 73          | 23           | 2 98      | 277 98  | 5 380 | 0.261 |
| Nam RK                  | 2005 | Canada | Caucasian       | PB     | Prostate cancer | 477         | 409          | 110 996   | 521 459 | 112 1092 | 0.313 |
| Wiklund F               | 2004 | Sweden | Caucasian       | PB     | Prostate cancer | 597         | 778          | 247 1622  | 297 384 | 115 796 | 0.386 |
| Nakazato H              | 2003 | Japan  | Asian           | HB     | Prostate cancer | 69          | 32           | 0 101     | 71 26   | 8 105 | 0.020 |
| Rokman A                | 2002 | Finland| Caucasian       | PB     | Prostate cancer | 60          | 83           | 24 167    | 69 84   | 23 176 | 0.745 |
| Fischer N               | 2008 | Germany| Caucasian       | HB     | Prostate cancer | 51          | 29           | 7 87      | 42 24   | 4 70  | 0.816 |
| Maier C                 | 2005 | Germany| Caucasian       | HB     | Prostate cancer | 133         | 171          | 59 363    | 73 97   | 37 207 | 0.629 |
| Wang L                  | 2002 | USA    | Caucasian       | PB     | Prostate cancer | 389         | 427          | 102 918   | 193 233 | 67 493 | 0.802 |
| Cybulski C              | 2007 | Poland | Caucasian       | HB     | Prostate cancer | 245         | 376          | 116 737   | 177 252 | 82 511 | 0.625 |
As a tumor-suppressor gene, RNASEL gene polymorphisms (including rs486907 and rs627928) have been demonstrated to be involved in carcinogenesis [32,34,38,39]. Many epidemiological studies have recently attempted to identify associations between rs486907 and rs627928 and the risk of prostate cancer. Unfortunately, the conclusions among these studies articles are inconsistent. Six years ago, 5 meta-analyses

| Author                  | Year | Region | Ethnicity | Source          | Tumor       | Case AA | Case Aa | Case All | Control AA | Control Aa | Control All | MAF Case | MAF Control | HWE Score | Score |
|-------------------------|------|--------|-----------|-----------------|-------------|---------|---------|----------|------------|------------|-------------|----------|-------------|-----------|-------|
| Kruger S                | 2005 | Germany| Caucasian | HB              | Prostate Cancer | 91      | 126    | 34 251   | 163        | 212        | 64          | 439.386  | 0.387       | 0.713     | 6     |
| Shook SJ                | 2007 | USA    | Non-Hispanic | Caucasian | Prostate Cancer | 187     | 183    | 60 430   | 221        | 225        | 57          | 503.352  | 0.337       | 0.981     | 7     |
| Shook SJ                | 2007 | USA    | Hispanic | Caucasian        | Prostate Cancer | 72      | 62     | 16 150   | 136        | 96         | 7           | 239.313  | 0.230       | 0.039     | 7     |
| Shook SJ                | 2007 | USA    | African American | PB | Prostate Cancer  | 45      | 13     | 10 68    | 111        | 31         | 3           | 145.243  | 0.128       | 0.633     | 7     |

**rs627928 T>G**

| Author                  | Year | Region | Ethnicity | Source          | Tumor       | Case AA | Case Aa | Case All | Control AA | Control Aa | Control All | MAF Case | MAF Control | HWE Score | Score |
|-------------------------|------|--------|-----------|-----------------|-------------|---------|---------|----------|------------|------------|-------------|----------|-------------|-----------|-------|
| Alvarez-Cubero MJ       | 2015 | Spain  | Caucasian | HB              | Prostate Cancer | 35      | 124    | 78 237   | 34         | 113        | 69          | 216.409  | 0.419       | 0.273     | 7     |
| San Francisco IF        | 2014 | Chile  | Caucasian | HB              | Prostate Cancer | 34      | 31     | 18 83    | 7          | 9          | 5           | 21.596   | 0.548       | 0.536     | 6     |
| Meyer MS                | 2010 | USA    | Caucasian | PB              | Prostate Cancer | 277     | 560    | 378 1215 | 282        | 536        | 376 1194   | 0.458    | 0.461       | <0.001    | 7     |
| Beuten J                | 2010 | USA    | Hispanic | Caucasian        | Prostate Cancer | 41      | 45     | 70 156   | 59         | 48         | 120         | 227.407  | 0.366       | <0.001    | 6     |
| Robbins CM              | 2008 | USA    | African American | HB | Prostate Cancer  | 103     | 102    | 38 243   | 143        | 129        | 24          | 296.634  | 0.701       | 0.495     | 7     |
| Shea PR                 | 2008 | USA    | Caucasian | PB              | Prostate Cancer | 107     | 97     | 26 230   | 217        | 201        | 40          | 458.676  | 0.693       | 0.496     | 6     |
| Noonan-Wheeler FC       | 2006 | USA    | Caucasian | HB              | Prostate Cancer | 22      | 73     | 55 150   | 33         | 93         | 44          | 170.390  | 0.468       | 0.198     | 7     |
| Wiklund F               | 2004 | Sweden | Caucasian | PB              | Prostate Cancer | 273     | 768    | 522 1563 | 162        | 372        | 257         | 791.420  | 0.440       | 0.199     | 6     |
| Nakazato H              | 2003 | Japan  | Asian     | HB              | Prostate Cancer | 18      | 32     | 51 101   | 3          | 43         | 59          | 105.337  | 0.233       | 0.138     | 7     |
| Rokman A                | 2002 | Finland| Caucasian | PB              | Prostate Cancer | 21      | 94     | 52 167   | 29         | 91         | 56          | 176.407  | 0.423       | 0.434     | 6     |
| Maier C                 | 2005 | Germany| Caucasian | HB              | Prostate Cancer | 62      | 176    | 125 363  | 41         | 97         | 69          | 207.413  | 0.432       | 0.514     | 7     |
| Cybulski C              | 2007 | Poland | Caucasian | HB              | Prostate Cancer | 111     | 372    | 254 737  | 84         | 259        | 168         | 511.403  | 0.418       | 0.344     | 6     |
| Shook SJ                | 2007 | USA    | Non-Hispanic | Caucasian | Prostate Cancer | 100     | 190    | 140 430  | 91         | 254        | 139         | 484.453  | 0.450       | 0.187     | 7     |
| Shook SJ                | 2007 | USA    | Hispanic | Caucasian        | Prostate Cancer | 41      | 66     | 43 150   | 69         | 125        | 48          | 242.493  | 0.543       | 0.525     | 7     |
| Shook SJ                | 2007 | USA    | African American | PB | Prostate Cancer  | 31      | 28     | 9 68    | 71         | 60         | 15          | 146.662  | 0.692       | 0.661     | 7     |
Table 2. Meta-analysis of RNASEL gene polymorphism and the risk of prostate cancer.

| Variables | Genetic comparison | Number of studies | I² | Pq | 95% CI | Pz | Model |
|-----------|-------------------|-------------------|----|----|--------|----|-------|
| **rs486907** |                   |                   |    |    |        |    |       |
| All       | G vs. A           | 22                | 0.00% | 0.507 | 0.97 (0.94–1.01) | 0.212 | Fixed |
|           | GG+GA vs. AA      | 22                | 10.80% | 0.315 | 0.96 (0.88–1.04) | 0.352 | Fixed |
|           | GG vs. GA+AA      | 22                | 0.00% | 0.973 | 0.97 (0.92–1.03) | 0.278 | Fixed |
|           | GG vs. AA         | 22                | 13.50% | 0.280 | 0.95 (0.87–1.04) | 0.301 | Fixed |
|           | GA vs. GG         | 22                | 0.00% | 0.999 | 1.03 (0.97–1.09) | 0.345 | Fixed |
| **Ethnicity** |                 |                   |    |    |        |    |       |
| African American | G vs. A       | 3                 | 69.50% | 0.038 | 1.27 (0.80–2.01) | 0.308 | Random |
|           | GG+GA vs. AA      | 3                 | 56.90% | 0.098 | 2.55 (0.74–8.72) | 0.137 | Random |
|           | GG vs. GA+AA      | 3                 | 9.90%  | 0.330 | 1.10 (0.83–1.45) | 0.520 | Fixed |
|           | GG vs. AA         | 3                 | 56.90% | 0.098 | 2.53 (0.73–8.72) | 0.141 | Random |
|           | GA vs. GG         | 3                 | 0.00%  | 0.907 | 1.02 (0.76–1.37) | 0.897 | Fixed |
| Caucasian  | G vs. A           | 19               | 0.00%  | 0.905 | 0.97 (0.93–1.01) | 0.132 | Fixed |
|           | GG+GA vs. AA      | 19               | 0.00%  | 0.793 | 0.95 (0.87–1.03) | 0.217 | Fixed |
|           | GG vs. GA+AA      | 19               | 0.00%  | 0.986 | 0.96 (0.91–1.02) | 0.216 | Fixed |
|           | GG vs. AA         | 19               | 0.00%  | 0.748 | 0.94 (0.86–1.03) | 0.175 | Fixed |
|           | GA vs. GG         | 19               | 0.00%  | 0.996 | 1.03 (0.97–1.09) | 0.348 | Fixed |
| Non-Hispanic Caucasian | G vs. A   | 3                 | 0.00%  | 0.397 | 0.97 (0.89–1.05) | 0.467 | Fixed |
|           | GG+GA vs. AA      | 3                 | 57.30% | 0.096 | 0.94 (0.72–1.21) | 0.628 | Random |
|           | GG vs. GA+AA      | 3                 | 0.00%  | 0.931 | 0.98 (0.88–1.10) | 0.777 | Fixed |
|           | GG vs. AA         | 3                 | 44.60% | 0.164 | 0.92 (0.78–1.10) | 0.354 | Fixed |
|           | GA vs. GG         | 3                 | 0.00%  | 0.934 | 1.00 (0.89–1.12) | 0.962 | Fixed |
| **rs627928** |                   |                   |    |    |        |    |       |
| All       | T vs. G           | 13               | 18.90% | 0.252 | 1.08 (1.01–1.15) | 0.016 | Fixed |
|           | TT+TG vs. GG      | 13               | 13.40% | 0.310 | 1.14 (1.03–1.25) | 0.014 | Fixed |
|           | TT vs. TG+GG      | 13               | 38.00% | 0.080 | 1.07 (0.92–1.25) | 0.367 | Random |
|           | TT vs. GG         | 13               | 40.80% | 0.062 | 1.21 (1.00–1.47) | 0.054 | Random |
|           | TG vs. TT         | 13               | 42.10% | 0.054 | 0.99 (0.84–1.17) | 0.940 | Random |
| **Ethnicity** |                 |                   |    |    |        |    |       |
| Non-Caucasian | T vs. G        | 3                 | 80.30% | 0.006 | 1.00 (0.62–1.61) | 0.990 | Random |
|           | TT+TG vs. GG      | 3                 | 67.20% | 0.047 | 1.30 (0.68–2.48) | 0.419 | Random |
|           | TT vs. TG+GG      | 3                 | 82.70% | 0.003 | 0.73 (0.30–1.75) | 0.480 | Random |
|           | TT vs. GG         | 3                 | 86.60% | 0.001 | 0.84 (0.20–3.44) | 0.805 | Random |
|           | TG vs. TT         | 3                 | 80.40% | 0.006 | 1.49 (0.63–3.57) | 0.366 | Random |
Table 2 continued. Meta-analysis of RNASEL gene polymorphism and the risk of prostate cancer.

| Variables | Genetic comparison | Number of studies | I² | P<sub>q</sub> | 95% CI | P<sub>z</sub> | Model |
|-----------|-------------------|-------------------|----|-------------|--------|-------------|-------|
| African American | T vs. G | 2 | 0.00% | 0.516 | 1.30 (1.04–1.62) | 0.020 | Fixed |
| TT+TG vs. GG | 2 | 0.00% | 0.388 | 1.86 (1.18–2.94) | 0.008 | Fixed |
| TT vs. GG | 2 | 0.00% | 0.732 | 1.23 (0.92–1.65) | 0.164 | Fixed |
| Caucasian | T vs. G | 10 | 0.00% | 0.942 | 0.92 (0.67–1.25) | 0.588 | Fixed |
| TT+TG vs. GG | 10 | 0.00% | 0.626 | 1.12 (1.01–1.24) | 0.032 | Fixed |
| TT vs. TG+GG | 10 | 0.00% | 0.539 | 1.09 (0.97–1.22) | 0.169 | Fixed |
| TT vs. GG | 10 | 0.00% | 0.815 | 1.18 (1.03–1.36) | 0.018 | Fixed |

Figure 2. Forest plots for the meta-analysis between the 2 SNPs of RNASEL and prostate cancer risk. (A) Allelic model (G vs. A) for rs486907 in overall populations. (B) Allelic model (G vs. A) for rs486907 in Caucasian populations. (C) Allelic model (T vs. G) for rs627928 in overall populations. (D) Allelic model (T vs. G) for rs627928 in Caucasian populations.
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Figure 3. Sensitivity analysis for rs486907 and rs627928. (A) Allelic model (G vs. A) for rs486907 in overall populations. (B) Allelic model (G vs. A) for rs486907 in Caucasian populations. (C) Allelic model (T vs. G) for rs627928 in overall populations. (D) Allelic model (T vs. G) for rs627928 in Caucasian populations.

were carried out to elucidate this relationship [40–44]. Li demonstrated that rs627928 leads to high risk of prostate cancer [40]. Zhang proved that rs486907 can enhance cancer susceptibility in African American populations, but did not affect the risk of cancer in overall populations [41]. Wei found that rs627928 might be a low-risk factor for prostate cancer [42]. Yu indicated that rs627928 leads to high risk of prostate cancer in African populations [43]. In an update analysis, Mi et al. [44] proved that rs486907 promotes carcinogenesis in prostate cancer in African populations, and rs627928 increases the onset risk of cancer.

During the next few years, several new studies on these SNPs have been published. However, the results of these various studies remain inconsistent [12,13,15]. Thus, we carried out the present analysis (covering more studies) to clarify the relationship of the 2 SNPs and prostate cancer susceptibility [4,11–15]. Our results demonstrated that rs627928 is involved in the development of prostate cancer risk, and the conclusion was similar to those of previous meta-analyses. In addition, our analysis proved that rs486907 is not involved in the risk of prostate cancer in overall or in Caucasian populations. Therefore, our conclusion confirms the conclusions of these previous meta-analyses.

RNASEL rs486907, also named Arg462Gln, is found in in approximately 13% of prostate cancer patients [45]. Winchester et al. found that men with the minor allele of rs486907 appeared to have slightly lower serum prostate-specific antigen (PSA) concentrations than men with the major allele [46]. These changes in individuals with rs486907 help explain our results. However, rs627928, also known as Asp541Glu, seems to have nothing to do with this phenomenon [7].
For a comprehensive understanding, we have predicted the impact of the 2 RNASEL SNPs at protein level using PolyPhen 2. The data from PolyPhen 2 showed that rs486907 was predicted to possibly damage the function of RNASEL, with a score of 0.864. However, rs627928 was predicted to be benign, with a score of 0.000. The data suggest that rs486907 possibly affects the function of RNASEL protein. Therefore, the SNP could further reduce the incidence of prostate cancer. However, our results indicated that rs627928, but not rs486907, is involved in the risk of prostate cancer.

During the study selection process, the data extracted from 23 articles including 40 studies were used for this meta-analysis. These preselected studies are listed in Table 1. However, the distributions of the control genotypes in 5 studies deviated from HWE. Therefore, only 22 studies (including 11 135 cases and 10 817 controls) for rs486907 and 13 studies (including 4522 cases and 3823 controls) for rs627928 have been included in our study for the final meta-analysis. In addition to HWE testing, we also assessed the RNASEL 2 polymorphisms MAF reported for the worldwide populations and compared the frequency to the overall estimates reported [47]. Data from the PubMed SNP database (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=486907) show that the MAFs for rs486907 (the frequency of allele A) were 0.385, 0.291, 0.193, 0.066, and 0.316 in European, Chinese, Japanese, Sub-Saharan African, and Caucasian populations, respectively. In overall populations, the highest MAF was <0.5. The MAF in each study included in our article was less than 0.5. Hence, no significant difference among them was detected. Data from the PubMed SNP database (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=627928) showed that the MAFs for rs627928 (the frequency of allele G) were 0.593, 0.821, 0.634, 0.252, and 0.474 in European, Chinese, Japanese, Sub-Saharan African, and Caucasian populations, respectively. In overall populations, the highest MAF was <0.5. The MAF in each study included in our article was less than 0.5. Hence, no significant difference among them was detected.

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### Table 3. Publication bias analysis of the meta-analysis.

| Variables | Genetic comparison | Begg’s test | Egger’s test |
|-----------|-------------------|-------------|--------------|
|           |                   | P value     | t            | P value | 95% CI       |
| rs486907  |                   |             |              |         |              |
| All       | G vs. A           | 0.693       | 0.28         | 0.783   | –0.84, 1.10 |
|           | GG+GA vs. AA      | 0.652       | 0.75         | 0.464   | –0.61, 1.29 |
|           | GG vs. GA+AA      | 0.910       | 0.11         | 0.910   | –0.67, 0.75 |
|           | GG vs. AA         | 0.652       | 0.66         | 0.515   | –0.66, 1.27 |
|           | GA vs. GG         | 0.735       | 0.18         | 0.863   | –0.50, 0.59 |
| Caucasian | G vs. A           | 0.234       | –1.16        | 0.260   | –1.33, 0.38 |
|           | GG+GA vs. AA      | 0.441       | –0.75        | 0.466   | –1.26, 0.60 |
|           | GG vs. GA+AA      | 0.484       | –0.77        | 0.453   | –0.98, 0.46 |
|           | GG vs. AA         | 0.576       | –0.78        | 0.445   | –1.30, 0.59 |
|           | GA vs. GG         | 0.726       | 0.22         | 0.830   | –0.59, 0.72 |
| rs627928  |                   |             |              |         |              |
| All       | T vs. G           | 0.855       | –0.41        | 0.691   | –2.11, 1.45 |
|           | TT+TG vs. GG      | 0.300       | 1.21         | 0.252   | –0.67, 2.29 |
|           | TT vs. TG+GG      | 0.360       | –1.46        | 0.173   | –3.10, 0.63 |
|           | TT vs. GG         | 0.951       | –0.48        | 0.642   | –2.36, 1.52 |
|           | TG vs. TT         | 0.360       | 1.56         | 0.147   | –0.56, 3.27 |
| Caucasian | T vs. G           | 1.000       | 0.28         | 0.789   | –1.28, 1.63 |
|           | TT+TG vs. GG      | 0.210       | 1.20         | 0.266   | –0.74, 2.34 |
|           | TT vs. TG+GG      | 0.858       | –0.19        | 0.857   | –2.11, 1.79 |
|           | TT vs. GG         | 0.721       | 0.49         | 0.636   | –1.17, 1.81 |
|           | TG vs. TT         | 0.721       | 0.39         | 0.705   | –1.85, 2.60 |

For a comprehensive understanding, we have predicted the impact of the 2 RNASEL SNPs at protein level using PolyPhen 2. The data from PolyPhen 2 showed that rs486907 was predicted to possibly damage the function of RNASEL, with a score of 0.864. However, rs627928 was predicted to be benign, with a score of 0.000. The data suggest that rs486907 possibly affects the function of RNASEL protein. Therefore, the SNP could further reduce the incidence of prostate cancer. However, our results indicated that rs627928, but not rs486907, is involved in the risk of prostate cancer.

During the study selection process, the data extracted from 23 articles including 40 studies were used for this meta-analysis. These preselected studies are listed in Table 1. However, the distributions of the control genotypes in 5 studies deviated from HWE. Therefore, only 22 studies (including 11 135 cases and 10 817 controls) for rs486907 and 13 studies (including 4522 cases and 3823 controls) for rs627928 have been included in our study for the final meta-analysis. In addition to HWE testing, we also assessed the RNASEL 2 polymorphisms MAF reported for the worldwide populations and compared the frequency to the overall estimates reported [47]. Data from the PubMed SNP database (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=486907) show that the MAFs for rs486907 (the frequency of allele A) were 0.385, 0.291, 0.193, 0.066, and 0.316 in European, Chinese, Japanese, Sub-Saharan African, and Caucasian populations, respectively. In overall populations, the highest MAF was <0.5. The MAF in each study included in our article was less than 0.5. Hence, no significant difference among them was detected. Data from the PubMed SNP database (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=627928) showed that the MAFs for rs627928 (the frequency of allele G) were 0.593, 0.821, 0.634, 0.252, and 0.474 in European, Chinese, Japanese, Sub-Saharan African, and Caucasian populations, respectively. In overall populations, the highest MAF was <0.5. The MAF in each study included in our article was less than 0.5. Hence, no significant difference among them was detected.
and Caucasian populations, respectively. In certain populations, the highest MAF was <0.5, but the highest MAF was >0.5 in the other populations. In this meta-analysis, several studies had a MAF <0.5 and the other studies had a MAF >0.5, but there was no obvious difference between them.

We found no obvious heterogeneity in the process of analysis, nor did we find any significant publication bias or trend bias. Sensitivity analysis indicated that our conclusion was robust under these conditions, in which individual studies were omitted. However, the TSA data suggested that the false-positive results should not be excluded completely in this study due to its relatively small sample size. Therefore, the results of TSA show that larger studies, specially focusing on Asians and Africans, should be carried out to assess the association between RNASEL gene polymorphism and the risk of prostate cancer.

Although it has some weaknesses, this meta-analysis also makes important contributions. To the best of our knowledge, this is the first meta-analysis to assess the association between these 2 important SNPs and susceptibility to prostate cancer. Our results show that rs627928, but not rs486907, promotes the development of prostate cancer.

Conclusions

Our meta-analysis found no association between rs486907 and risk of prostate cancer, and confirmed that rs627928 promotes the progression of prostate cancer. These results indicate that rs627928 has potential as a predictor of prostate cancer. However, larger studies are needed to validate our conclusions.

Conflicts of interest.

None.

Figure 4. TSA of the 2 SNPs of RNASEL and prostate cancer risk. (A) Allelic model (G vs. A) for rs486907 in overall populations. (B) Allelic model (G vs. A) for rs486907 in Caucasian populations. (C) Allelic model (T vs. G) for rs627928 in overall populations. (D) Allelic model (T vs. G) for rs627928 in Caucasian populations.
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