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# Different Effects of the RNASEL R462Q Mutation on the Risk of Developing Prostate and Cervical Cancer in Latin American Subjects: A Meta-Analysis

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## Abstract

**Background:** Prostate and cervical tissues are highly susceptible to carcinogenesis. Furthermore, some reports suggest that alterations in RNASEL have been associated with augmented risk of developing cancer, specifically the arginine to glutamine mutation at position 462 (R462Q). However, with conflicting results of the R462Q mutation on cancer risk, our goal was to determine what effect this mutation had on prostate and cervical cancers in Latin Americans.

**Methods:** PubMed, EBSCO, SCOUPS, Wiley and OVID databases, and study bibliographies were systematically searched for case-control studies that examined for the R462Q mutation until June 2015. Odds ratios (ORs) and 95%CI were calculated from the genotype data. The pooled ORs were obtained by the Peto method for the heterozygous, the homozygous, the dominant, the recessive, and the allelic genetic models. Heterogeneity was assessed by the Q-test and I2-test. Publication bias was assessed by the Begg and Mazumdar's test and the Egger's test. The sensitivity was determined by reevaluation of the pooled OR after removal of one study.

**Results:** From the 153 retrieved studies, four studies met the inclusion criteria (n=808 subjects). The pooled results did not indicate any association between R462Q and overall cancer risk for any of the genetic model assessed. However, when stratified by type of cancer, the homozygous and the recessive genetic models demonstrated a significant association between prostate cancer (OR=2.26, 95%CI=1.15-4.44, p<0.05 and OR=2.18, 95%CI=1.12-4.23, p<0.05, respectively) and cervical cancer (OR=0.32, 95%CI=0.13-0.74, p<0.01 and OR=0.35, 95%CI=0.16-0.77, p<0.01, respectively). Furthermore, the risk associated with this mutation for prostate cancer and cervical cancer was different (p<0.01).

**Conclusion:** Here we denote, for Latin Americans, the different effects the RNASEL R462Q mutation has for prostate (increased risk) and cervical (decreased risk) cancers.

**Keywords:** Arg462Gln, Ribonuclease L, Genetic biomarkers, Prediction, Viral-induced cancer, Polymorphism, Hispanic ethnicity

## Introduction

Prostate and cervical cancers are one of the most common causes of cancer-related deaths worldwide, with 2.7 and 2.4 deaths per 100,000 per year in men and women, respectively [1, 2]. However, the prevalence and mortality rates for these cancers has demonstrated a marked geographic variation [2]. For Latin Americans, the incidence was 15,400 and 76,000 for prostate and cervical cancers, respectively [2,3]. The majority of the population in Latin American countries shares many ethnic and genetic characteristics that are different from other European, Asian, and North American countries [4-6]. However, with few reports focusing on Latin American countries, there is a current need to determine the importance of certain factors that elevate the risk of developing cancer.

During the past years, numerous studies have shown that prostate and cervical cancers are viral-induced related cancers [7-9]. Therefore, examining components of the anti-viral pathway may aid in understanding how certain proteins factor in carcinogenesis. One gene of interest, expressed in both prostate and cervical tissue, is the ribonuclease L (RNASEL), an enzyme in the interferon-induced antiviral 2-5A pathway [10-12]. Mutations in the RNASEL gene lead to reduced enzymatic activity and abrogate its tumor suppressor role [13,14]. One of the most studied RNASEL variant is the 1385G→A polymorphism, which results in the amino-acid substitution from arginine to glutamine at position 462 (R462Q), whose potential impact on prostate and cervical cancer risk remains controversial [15,16].

The R462Q mutation, which is located in the kinase-like domain, is able to bind 2-5A but with diminished capability to form its active conformation [17]. The QQ genotype has shown to reduce its enzymatic activity by 3-fold and unable to induce apoptosis [17,18]. For prostate cancer, the R462Q mutation has an ethnic component. For patients from Germany and Sweden, there is no association [19,20]; however, there was a significant association for patients of Finnish or African descent for increase prostate cancer risk [21,22]. For cervical cancer, there are few reports to determine if there is an

ethnic component. A recent report suggested that 13% of all prostate cancer cases are associated with the R462Q mutation [18], on the other hand, with cervical cancer, the data on its prevalence is lacking. The effect of the R462Q mutation on cervical cancer has been posited to be "protective" [16], whereas with prostate cancer the effect in mainly associated with cancer development [23]. In Latinos, no direct comparison of the effect of the R462Q mutation on prostate and cervical cancer has been established; therefore, we conducted a meta-analysis to deduce and compare the impact of the R462Q mutation on prostate and cervical cancer risk in Latin Americans.

## Methods and Materials

### Publication search

PubMed, OVID, Wiley, SCOPUS and EBSCO databases were searched for all case-control studies that investigated the association between RNASEL (R462Q) and cancer. The following keywords and related index terms were used: "RNASEL", "mutation or polymorphism", "cancer or carcinogenesis" and terms specific for prostate and cervical cancers for any studies published up to June 10, 2015. Only studies published in English, Spanish, and Portuguese were reviewed. The titles and abstract were examined, and studies that were not eligible for this meta-analysis were eliminated. The complied publications´ references were hand searched. Three authors determined if each study was to be included. All studies had to meet the following criteria: case-controls studies that focused on examining the association of the mutation in human subjects with prostate or cervical cancer. Afterwards, only studies focusing on Latin American countries or their descendants were considered. Non-human studies, reviews, prospective studies, or studies with insufficient information were excluded.

### Data extraction

Two of the authors extracted all data independently. If there was a disagreement, another author assessed the study in question. If a single sample was believed to be use in multiple reports, the reports were assessed to determine which one was the most representative and that data was used, or the corresponding author was contacted to resolve the issue. The data collected were first author's name, year of publication, geographical location, type of cancer, genotyping method, source of control, distribution of genotypes among the cases and controls, as well as the total number of subjects.

### Statistical analysis

The Hardy-Weinberg Equilibrium (HWE) was determined by the Ψ2-test for the controls for each study. The crude odds ratio (OR) and the 95% confidence interval (95%CI) were calculated for each study and used to assess the level of association between the mutation and cancer susceptibility. The pooled ORs were assessed for the following genetic models: homozygous (QQ versus RR), heterozygous (RQ versus RR), dominant (QQ + RQ versus RR), recessive (QQ versus RQ + RR), and allelic (Q versus R). The analyses were stratified by type of cancer. To determine the pooled OR, the Peto method was used [24]. Heterogeneity was determined using the Ψ2-based Q-test and its degree was assessed by the I2 value (inconsistency index). The stability and sensitivity of the results were assessed by removing one study and re-calculating the pooled OR. Publication bias was evaluated by the Begg and Mazumdar adjusted rank correlation asymmetry test (Kendall's tau) and the Egger regression asymmetry test [25,26]. The Ψ2-test was used to determine differences between groups. Statistical analyses were performed using either Review Manager (RevMan) v5.3. (Copenhagen, DK) and StatDirect Statistical Software version 3.0.147 (Cheshire, UK). P-values <0.05 (two-sided) were considered statistically significant.

## Results

### Characteristics of the studies

One-hundred fifty-three studies were retrieved from searching the multiple databases and from reviewing the study's bibliographies. Ninety-seven studies were exclude because they did not focused on cancer and RNASEL, focused on animals or cell lines, or were not a research article. The remaining 56 studies were evaluated extensively. Six studies did not focus on the R462Q mutation, two lacked sufficient information, and twelve were not case-control studies, therefore they were excluded. From the remaining 36 studies, only four utilized subjects from Latin America or their descendants (Figure 1).

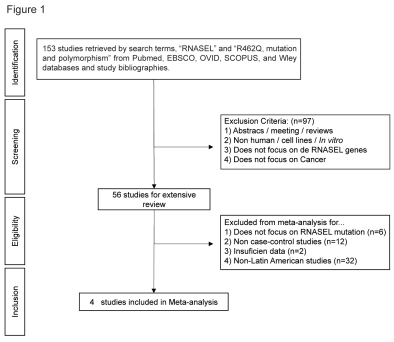


**Figure 1:** Meta-analysis selection diagram

Therefore, our sample consisted of 808 subjects (controls=420 and cases=388). Detailed characteristics of these studies are listed in Table 1.

| First Author | Year | Country | Cancer | Genotyping Methods | Source of controls | Groups | R462Q Genotypes | | | Total | HWE a | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | RR | RQ | QQ | | | |
| Barbison | 2011 | Argentina | Cervical | Pyrosequencing | HB | Controls | 44 | 57 | 22 | 123 | 0.64 | [22] |
| | | | | | | Cases | 44 | 48 | 6 | 98 | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Beuten | 2010 | USA | Prostate | Taqman Assay | HB | Controls | 126 | 91 | 7 | 224 | 0.05 | [24] |
| | | | | | | Cases | 75 | 64 | 17 | 156 | | |
| San Francisco | 2014 | Chile | Prostate | Taqman Assay | PB | Controls | 11 | 6 | 4 | 21 | 0.11 | [12] |
| | | | | | | Cases | 43 | 31 | 9 | 83 | | |
| Zabala | 2009 | Venezuela | Prostate | PCR-ASA | HB | Controls | 34 | 16 | 2 | 52 | 0.95 | [23] |
| | | | | | | Cases | 37 | 10 | 4 | 51 | | |

Abbreviation: HB: Hospital Base; PB: Population Based; PCR-ASA: Polymerase-Chain Reaction Allelic Specific Amplification; HWE: Hardy-Weinberg Equilibrium. [a] The Hardy-Weinberg Equilibrium was calculated by the 2-test, values greater than 0.05 are consider to agree

**Table 1:** Characteristics of each study included in the meta-analysis.

| Genetic Model | Cancer | Heterogeneity | | Association analysis[b] | | | | Publication Bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | Q-test [a] | I2-test | OR | 95% CI | P[c] | P[d] | Begg[e] | Egger[f] |
| RQ vs. RR | Cervical | | | 0.84 | 0.48 – 1.48 | 0.55 | 0.50 | | |
| | Prostate | | | 1.06 | 0.74 – 1.53 | 0.74 | | | |
| | Overall | 0.46 | 0.0% | 0.99 | 0.73 – 1.35 | 0.97 | | τ=-0.33, p=0.33 | p=0.59 |
| QQ vs. RR | Cervical | | | 0.32 | 0.13 – 0.74 | <0.01 | <0.01 | | |
| | Prostate | | | 2.26 | 1.15 – 4.44 | 0.02 | | | |
| | Overall | <0.01 | 82% | 1.06 | 0.63 – 1.80 | 0.82 | | τ=-0, p=0.75 | p=0.90 |
| QQ+RQ vs RR | Cervical | | | 0.68 | 0.40 – 1.18 | 0.17 | 0.09 | | |
| | Prostate | | | 1.19 | 0.85 – 1.68 | 0.31 | | | |
| | Overall | 0.18 | 39% | 1.02 | 0.76 – 1.36 | 0.91 | | τ=-0, p=0.75 | p=0.98 |
| QQ vs. RQ+RR | Cervical | | | 0.35 | 0.16 – 0.77 | <0.01 | <0.01 | | |
| | Prostate | | | 2.18 | 1.12 – 4.23 | 0.02 | | | |
| | Overall | <0.01 | 82% | 1.03 | 0.62 – 1.71 | 0.92 | | τ=-0, p=0.75 | p=0.47 |
| Q vs R | Cervical | | | 0.64 | 0.43 – 0.94 | 0.02 | <0.04 | | |
| | Prostate | | | 1.28 | 0.97 – 1.68 | 0.08 | | | |
| | Overall | 0.01 | 74% | 1.02 | 0.81 – 1.27 | 0.89 | | τ=0.33, p=0.33 | p=0.59 |

[a]p-value was calculated by Cochran $\psi^2$-based Q test using RevMan v5.3

[b]Significant associations are bold

[c]Test of overall effect

[d]Comparison between pooled ORs for prostate and cervical cancer, p-value was determined by the $\psi^2$-test

[e]Begg-Mazumdar test was used to calculate publication bias. Results are given as Kendall's tau and p-value (any less than 0.1 was consider significant for publication bias)

[f]Egger's test was used to calculate publication bias. Results are given as a p-value (any less than 0.1 was consider significant for publication bias).

**Table 2:** Meta-analysis results for RNASEL R462Q mutation among Latin Americans Cancer subjects.

Three of the studies (one cervical [27] and two prostate cancers [12] were in agreement with Hardy-Weinberg Equilibrium, with one study's p-value equal to 0.05 [28].

## Association of the RNASEL R462Q mutation and developing prostate and cervical cancers

Overall, this meta-analysis does not suggest an association between the R462Q mutation and the risk for developing cancer among Latin Americans (Figure 2 and Table 2).

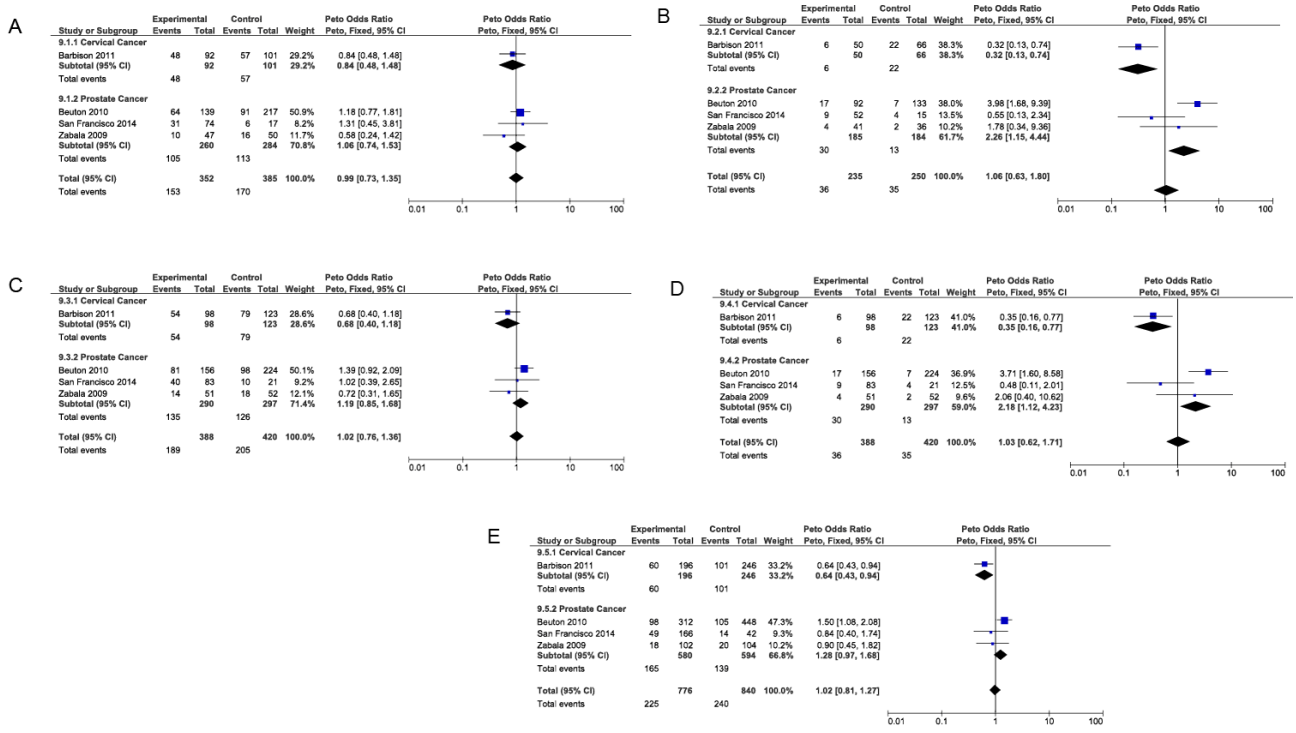


**Figure 2:** Forest plot of prostate and cervical cancer risk associated with the RNASEL R462Q polymorphism for the heterozygous (A), homozygous (B), dominant (C), recessive (D), and allelic (E) genetic models. The squares and horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI.

However, when stratified by type of cancer, different effects were determined. For cervical cancer, the homozygous, the recessive, and the allelic genetic models all showed a decreased risk of developing cancer (OR=0.32, 95%CI: 0.13-0.74, p<0.01, OR=0.35, 95%CI: 0.16-0.77, p<0.01, OR=0.64, 95%CI: 0.43-0.94, p<0.05, respectively). While, for prostate cancers, an increased risk for the homozygous and the recessive genetic models were determined (OR=2.26, 95%CI: 1.15-4.44, p<0.05 and OR=2.18, 95%CI: 1.12-4.23, p<0.05, respectively). Furthermore, for the homozygous and allelic genetic model, the increased risk for prostate cancer and decreased risk for cervical cancer were different (p<0.01). Overall, these results suggest that in male subjects with the recessive homozygote genotype will have an increased risk of developing prostate cancer, whereas for females this genotype is associated with a decreased risk.

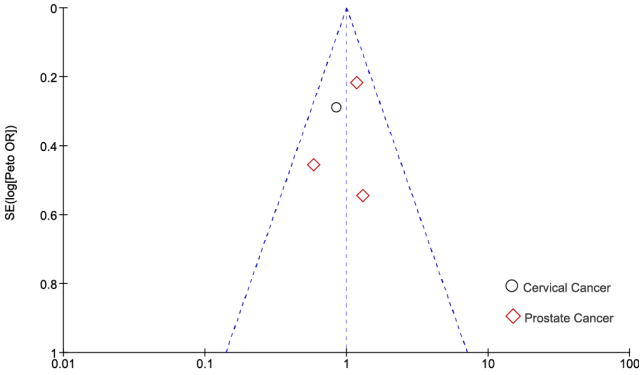


**Figure 3**: Begg's funnel plot for publication bias test (heterozygous model: RQ vs RR). Each point represents a separate study.

### Test for sensitivity and publication bias

Publication bias was assessed by examining Begg's funnel plot, calculating the Begg-Mazumdar´s test Kendall's tau and Egger's test. The funnel plot does not indicate any major asymmetry (Figure 3).

Furthermore, Kendall's tau and Egger's test also does not indicate any significant bias (Table 2).

To assess the sensitivity, one study was removed at a time and the effect on the pooled OR was reevaluated. No significant changes in the pooled OR for all cancers were observed. For prostate cancer alone, due to the small sample size, the homozygous, the recessive, and the allelic genetic models were sensitivity to the Beuten study (Table 3).

| | Removed Study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Beuten | | | San Francisco | | | Zabala | | |
| Genetic Model | OR | 95% CI | P-value | OR | 95% CI | P-Value | OR | 95% CI | P-value |
| RQ vs RR | 0.81 | 0.41 – 1.61 | 0.56 | 1.03 | 0.70 – 1.52 | 0.86 | 1.20 | 0.81 – 1.79 | 0.37 |
| QQ vs RR | 0.92 | 0.31 – 2.72 | 0.87 | 3.36 | 1.57 – 7.20 | <0.01 | 2.37 | 1.13 – 4.97 | 0.02 |
| QQ+RQ vs RR | 0.84 | 0.45 – 1.56 | 0.58 | 1.22 | 0.85 – 1.76 | 0.29 | 1.32 | 0.91 – 1.93 | 0.14 |
| QQ vs RQ+RR | 0.90 | 0.30 – 2.66 | 0.85 | 3.28 | 1.55 – 6.93 | <0.01 | 2.20 | 1.07 – 4.55 | 0.03 |
| Q vs R | 0.87 | 0.52 – 1.44 | 0.59 | 1.37 | 1.02 – 1.84 | 0.04 | 1.36 | 1.01 – 1.84 | 0.04 |

Table 3: Re-evaluation of pooled Odds Ratio of Prostate cancer studies.

## Discussion

Prostate and cervical cancers are two among the leading forms of cancers for Latin American men and women, respectively. Because these tissues are susceptible to viral infections and viral infections increase the risk of developing cancer, we examined a key regulator of the anti-viral response and pro-apoptotic pathway, namely RNASEL. One mutation, R462Q, has shown diminish protein activity, but its effect on augmenting cancer risk remains inconclusive. This meta-analysis examines the association between the R462Q mutation and risk of developing prostate and cervical cancers.

Four previous meta-analyses have examined the association between the R462Q mutation and prostate cancer, all leading to a similar conclusion that the mutation does not increase the risk of developing prostate cancer in the total population [29-32]. However, these analyses are using mixed samples and only three included the Beuten study. When stratified by ethnicity, the Latin American population was not individually analyzed. Here, we only used studies that focused on Latin American subjects or their descendants. We show that the homozygous mutant genotype is associated with a 2-fold increased risk of developing prostate cancer. Mi et al. (2010) demonstrated that the homozygous and the recessive genetic models had an increased risk in the total population (OR=1.20-fold, 95%CI: 0.96-1.50 and OR=1.18, 95%CI: 0.96-1.46, respectively) but was not significant [32]. However, the risk increased to 2.50-fold (95%CI: 1.28-4.87) for the homozygous genetic model and 2.54-fold (95%CI: 1.30-4.95) for the recessive genetic model when examining Africans only (four studies), which is similar to our results. The heterozygous and the dominant genetic models also did not show any increased risk of developing prostate cancer. This meta-analysis supports our results of how one ethnic group can have an increased risk of developing cancer, which is masked by inclusion of the other ethnicities.

Our review of literature only identified two studies that examined the R462Q mutation in cervical cancer: Barbison et al. [27], which focused on women from Argentina, and Madsen et al. [16], which focused on women from Denmark. Using the Madsen et al. data, we determined that the mutation decreased the risk for developing cervical cancer with ORs ranging between 0.35 to 0.65 depending on the genetic model used (data not shown); unfortunately, these data were not significant. For Argentines, Barbison et al. had a similar result, but for the homozygous mutant genotype, it was significant. This would posit the QQ genotype is "protective" as suggest by Madsen et al.; however, due to the lack of numerous studies, this potential effect of the R462Q mutation should be examined cautiously. More studies are required to support this conclusion among many different ethnicities.

Our study has at least four limitations. First, the ORs that were calculated by the genotype distributions and were unadjusted estimates. Adjusting the OR for age, prostate-specific antigen, etc., can influence the OR by a few tenths, possibly affecting the significances of our results. Second, we had limited number of studies to use. However, we selected to use the Peto method, which should minimize this effect. Third, the selection of the controls between studies were slightly different. We chose to include studies in which the controls had prostate-specific antigens levels were less than 4 ng/mL and a normal digit rectal examine. Lastly, we did not distinguish between severities of the case, by Gleason score, localized versus advanced stage, etc. It is possible that the homozygous mutation genotype is more associated with different forms of either prostate or cervical cancer.

## Conclusion

Here, we compile evidence to support the notion of the dual nature of the RNASEL R462Q mutation in the Latin Americans. We determined that the RNASEL R462Q mutation increases the risk of developing prostate cancer among Latin American men. Interestingly, this mutation is conceivably favorable for Latin American women decreasing the risk of developing cervical cancer.

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