# Assessment of Association between Common Variants at 17q12 and Prostate Cancer Risk—Evidence from Serbian Population and Meta-Analysis

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**Abstract**

This study aimed to evaluate possible association between genotypes and alleles of two 17q12 polymorphisms (rs3760511 and rs7501939) and prostate cancer (PCa) risk and progression. Two hundred seventy-one patients with PCa, 261 patients with benign prostatic hyperplasia (BPH), and 171 controls were included in the study. Single nucleotide polymorphisms (SNPs) were genotyped by using PCR followed by restriction fragment length (PCR-RFLP) analysis. We conducted meta-analysis of published studies regarding association of these SNPs with PCa risk. Evidence of positive association between the AC genotype of the SNP rs3760511 and BPH risk for the best-fitting overdominant model of association (BPH vs. controls comparison, $p = 0.026$; odds ratio [OR] = 1.58; 95% confidence interval [95%CI] 1.05–2.36) were obtained. The association between T allele of rs7501939 and PCa risk was determined in PCa versus controls comparison ($p = 0.0032$; OR = 0.66, 95%CI 0.50–0.87) with the best-fitting model of inheritance being log-additive. This variant was also found to be associated with the risk of BPH ($p = 0.0023$; OR = 0.65, 95%CI 0.49–0.86). We found no association between parameters of PCa progression and the analyzed SNPs. Meta-analysis showed strong association between these variants and PCa risk. Our study shows association between SNPs at locus 17q12 and the risk of prostatic diseases in Serbian population. At the same time, results of meta-analysis suggest the association of these SNPs with PCa risk. Clin Trans Sci 2014; Volume 7: 307–313

**Keywords:** prostate cancer, association study, single nucleotide polymorphism (SNP), 17q12, meta-analysis

## Introduction

Prostate cancer (PCa) is one of the most common cancers among men in the majority of Western countries.[1] Almost 899,000 PCa cases and 258,000 PCa deaths are estimated to have occurred in 2008 worldwide, with 72% of the cases and 53% of the deaths in developed countries.[2] The only firmly established risk factors for PCa are age, family history, and ethnicity.[3] Considerable differences exist in age-adjusted incidence and mortality between countries in eastern Asia and northwestern Europe.[4] Concerning Serbian population, PCa shows increasing trend of newly diagnosed cases, from 662 in 1999 to 1,673 in 2009.[5,6] With the increasing incidence of PCa, identifying common genetic variants that confer risk and/or progression of the disease is of great importance.

Genome-wide association (GWA) analyses have identified variants in seven most important chromosomal regions associated with the risk of PCa. These variants occur in five independent regions at 8q24, in one region at 17q12, and another at 17q24.3.[7]

Single nucleotide polymorphisms (SNPs) rs7501939 and rs3760511 are located in the first intron of the HNF1β (hepatocyte nuclear factor 1 homeobox β) or TCF2 gene (transcription factor 2) at 17q12. The HNF1β gene encodes a transcription factor and it was initially identified as a MODY gene (maturity onset diabetes of the young), which is mutated in individuals with MODY type 5.[8,9] The expression profile of this gene shows a tissue-specific pattern. Some mutations in HNF1β have been associated with the development of renal cysts, diabetes syndromes, insulin-dependent diabetes mellitus, and cancer.[9–11]

Gudmundsson et al.[7] showed association between C alleles of both rs3760511 and rs7501939 with the increased PCa risk in populations of Iceland, The Netherlands, and the United States, but not among Hispanics. Studies conducted in Swedish population[12] and among European Americans (non-Hispanic) showed similar results for rs7501939.[13,14] In correlation with these results are findings from studies conducted among European Americans[15,16] and Koreans[17] that reported association of rs7501939 allele T with decreased PCa risk. Lack of evidence for this association was observed in African American population.[14,18–20] When considering association between rs3760511 and PCa risk, similar results were found in Swedish and Korean populations,[12,17] as well as among European Americans (non-Hispanic),[14,16] but not in African American population.[14] There are no reports of association between these two polymorphisms and the prognostic parameters of PCa progression. A study conducted in the population of Ashkenazi Jewish ancestry has shown no evidence of correlation of rs7501939 with the biochemical recurrence of PCa, clinical metastases, and PCa-related death.[21]

Due to possible interpopulation differences, it is of great importance to test previously identified disease susceptibility SNPs in multiple populations. In this study, we examined the possible association of two SNPs at 17q12 with PCa risk in Serbian population for the first time. In addition, we evaluated the possible linkage of these SNPs with standard prognostic parameters of PCa progression, as well as with the risk of disease progression.

## Material and Methods

### Subjects

Two 17q12 polymorphisms were genotyped in 271 patients with PCa (mean age: 69.77; range: 45–96 years) and 261 patients with

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benign prostatic hyperplasia (BPH; mean age: 68.87; range: 33–85 years) who were treated at Clinical Centers "dr Dragiša Mišović" and "Zvezdara," Belgrade, Serbia, in the period from 2008 to 2012.

All patients were diagnosed with PCa confirmed by histopathologic examination of specimens obtained by transrectal ultrasound (TRUS) guided biopsies, transurethral resection of the prostate and radical prostatectomy (RP). Grading was established according to Gleason score (GS) differentiation system (range 2–10).[22] Serum prostate-specific antigen (PSA) levels were determined by using Hybritech monoclonal immunoassay (Beckman Hybritech assay; Beckman Coulter, Inc., Fullerton, CA, USA), with the cutoff value of 4.0 ng/mL.[23] Patients with BPH were given a digital rectal examination (DRE) (compatible with BPH) and serum PSA analysis. One hundred and seventy-one healthy volunteers with normal PSA and normal DRE who had no previous history of PCa nor BPH served as the control group. The analysis was approved by the Ethics Committees of Clinical Center "dr Dragiša Mišović" and Clinical Center "Zvezdara," Belgrade, Serbia.

Risk of PCa progression was determined by using two classification systems: one proposed by D'Amico et al.[24] and the other by Medeiros et al.[25] According to D'Amico criteria, PCa patients were divided into three groups: low risk (PSA ≤ 10 ng/mL, clinical stage ≤ T2a, and GS ≤ 6), medium risk (PSA from 10 to 20 ng/mL, or clinical stage T2b-c, or GS 7), and high-risk group (PSA ≥ 20 ng/mL, or clinical stage ≥ T3, or GS ≥ 8).[24] Patients with metastases were added to high-risk group. Following instructions of Medeiros et al., patients were stratified into two groups: high risk of cancer progression (GS ≥ 7, or advanced clinical stage—T3 and T4, or presence of bone metastases), and low risk of cancer progression (low grade, early stage, and absence of bone metastases).[25]

Peripheral blood samples were collected in vacutainer tubes containing Na-citrate, and maintained at 4°C. All samples were obtained with the informed consent of the participants before their inclusion in the study.

### DNA extraction

Genomic DNA was extracted from 200 μL of peripheral blood obtained from PCa and BPH patients and buccal swabs provided by control subjects by using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturers' instructions.

### Amplification of the regions surrounding selected SNPs

The primer sets used for amplification of the regions surrounding selected SNPs are published by Zheng et al.[12] Each PCR was carried out in a 15-μL reaction mixture containing 0.3 μM (for rs3760511) or 0.2 μM (for rs7501939) of both primers (Eurofins MWG Operon, Huntsville, AL, USA), 200 μM of each deoxyribonucleoside triphosphate (dNTP, Fermentas, Hanover, MD, USA), 1.5 μL of 10X PCR buffer A (containing 15 mM $MgCl_2$, Kapa Biosystems, Woburn, MA, USA), 2 μL of genomic DNA (about 20 ng of DNA), 0.04 U/μL of Taq DNA polymerase (Kapa Biosystems), and nuclease-free water (Serva, Westbury, NY, USA). PCR reactions were run for 30 cycles: 95°C for 60 seconds, 52°C for 60 seconds (for rs7501939), or 56°C for 60 seconds (for rs3760511), and 72°C for 60 seconds; and final extension 10 minutes at 72°C. The amplified fragments were separated by 1.5% agarose gel electrophoresis and stained with ethidium bromide.

### Genotyping

Selected SNPs were genotyped by using PCR-RFLP analysis. Ten microliters of PCR products were digested at 37°C overnight with 1U of specific enzyme per single reaction (15 μL reaction mixture). Enzyme characteristics and lengths of digested PCR products are shown in Supporting Information *Table S1*. Digested products were separated by 3% agarose gel electrophoresis and stained with ethidium bromide.

For each SNP, 15 samples were randomly chosen to be retyped by bidirectional sequencing in order to assess the validity of proper SNP analysis by PCR-RFLP method. Amplified fragments were purified by using QIAquick PCR Purification Kit, following manufacturers' instructions (QIAquick PCR Purification Kit, Qiagen). Purified PCR products were sequenced with BigDyeTerm v1.1 CycleSeq Kit (Applied Biosystems, Foster City, CA, USA). Afterward, DNA sequencing reaction products were purified by using EDTA/ethanol purification method and analyzed by capillary gel electrophoresis on ABI PRISM 3100 Genetic Analyzer (Applied Biosystems).

### Statistical analysis

Descriptive statistics and exploratory analysis were used for data explanation. Deviations from Hardy–Weinberg equilibrium (HWE) were evaluated by using exact test implemented in SNPStats software (Catalan Institute of Oncology, Barcelona, Spain).[26] For each SNP, multiple logistic regression models were used to assess potential association with PCa risk and progression (dominant, recessive, codominant, overdominant, and log-additive). The best-fitting models were determined by using Akaike information criterion (AIC). The odds ratio (OR) and its 95% confidence interval (CI) were calculated as assessment measure of association between polymorphisms, genotypes, and PCa risk. A 5% level of significance was used in the analysis. Analyses of data were performed by using the statistical software SNPStats (Catalan Institute of Oncology) and PLINK v1.07.[26,27]

### Meta-analysis

Studies suitable for meta-analysis were selected in June 2013 by searching PubMed database using keywords "prostate cancer," "17q12," "rs3760511," "rs7501939," and "association study." We used statistical software PLINK, Meta-Analyst v. β 3.13 (Tufts Medical Center, Boston, MA, USA) and Open Meta-analyst[28] for meta-analysis and heterogeneity tests. Estimates of ORs and their 95% CIs were calculated for each SNP using fixed-effect or random-effect model based on the results of heterogeneity tests. Random-effect model was selected for meta-analysis when heterogeneity tests yielded significant results. For the fixed-effect model, the inverse variance method of weighting was used, while for pooling results under the random-effect model the method proposed by Der Simonian and Laird was applied.[29] For assessing heterogeneity of results across studies, *Q* test was used together with inconsistency index ($I^2$).

## Results

The frequencies of genotypes of two polymorphisms at 17q12 were compared between groups of 271 PCa patients, 261 BPH patients, and 171 healthy control subjects. The clinical characteristics of PCa and BPH patients and histopathological characteristics of PCa patients are shown in *Table 1*.

| Characteristics | | PCa patients | BPH patients | Controls |
|---|---|---|---|---|
| Number | | 271 | 261 | 171 |
| Age | | 69.77 | 68.87 | 69.08 |
| | | (45–96) | (33–85) | (58–83) |
| Serum PSA (ng/mL) | 0–10 | 49 | 124 | 171 |
| | 10–20 | 39 | 20 | – |
| | >20 | 62 | 6 | – |
| Tumor stage | $T_1$ | 43 | – | – |
| | $T_2$ | 118 | – | – |
| | $T_3$, $T_4$ | 71 | – | – |
| | Unknown | 39 | – | – |
| Gleason score | <7 | 153 | – | – |
| | = 7 | 72 | – | – |
| | >7 | 38 | – | – |
| | Unknown | 8 | – | – |
| Metastasis | Absent | 191 | – | – |
| | Present | 54 | – | – |
| | Unknown | 26 | – | – |
| Risk of progression (D'Amico et al., 1998) | Low | 19 | – | – |
| | Medium | 90 | – | – |
| | High | 150 | – | – |
| | Unknown | 12 | – | – |
| Risk of progression (Medeiros et al., 2002) | Low | 102 | – | – |
| | High | 150 | – | – |
| | Unknown | 19 | – | – |

**Table 1.** The clinical characteristics of patients with PCa and BPH and histopathological characteristics of patients with PCa.

The distributions of rs3760511 and rs7501939 genotypes in both PCa and BPH patient groups, as well as in controls were compatible with HWE.

*Table 2* shows genotype frequencies of two SNPs at 17q12 in PCa patients, BPH patients and controls, as well as the results of tests for association with PCa risk. Results concerning association of 17q12 SNPs with BPH risk are summarized in *Table 3*.

Genotype frequencies of SNP rs3760511 were not found to differ significantly between PCa patients and controls ($p$ = 0.35, for codominant model; AC heterozygote OR = 1.36, 95%CI 0.89–2.07; CC homozygote OR = 1.20, 95%CI 0.63–2.27). Tests for association of this SNP with the risk of PCa yielded $p$ value of 0.16 for the best-fitting genetic model (dominant) according to AIC. The comparison of genotype frequencies in PCa and BPH patients also showed no statistically significant difference for any genetic model tested ($p$ = 0.48, for codominant model; AC heterozygote OR = 0.86, 95%CI 0.60–1.23; CC homozygote OR = 1.18, 95%CI 0.66–2.13).

Statistically significant difference in rs3760511 genotype frequencies was found between BPH patients and controls ($p$ = 0.026, for the best-fitting overdominant model). Men with AC genotype were shown to have 1.58-fold increased risk of BPH compared to men with homozygous genotypes (95%CI 1.05–2.36).

When considering possible association between rs7501939 and PCa risk, the comparison of genotype frequencies in PCa patients and controls yielded statistical significance for the best-fitting log-additive model ($p$ = 0.0032), as well as for codominant, dominant, and recessive models. Minor allele T was shown to confer decreased risk of PCa (OR = 0.66, 95%CI 0.50–0.87). The association between this SNP and PCa risk was not confirmed by comparing genotype distributions among PCa and BPH patients ($p$ = 0.9, for codominant model; CT heterozygote OR = 0.96, 95%CI 0.66–1.38; TT homozygote OR = 0.93, 95%CI 0.52–1.64). The best-fitting model in this comparison could not be assessed since AIC score was the same for recessive and overdominant model of association.

Evidence of association between rs7501939 and the risk of BPH was obtained in comparison of genotype distributions among BPH patients and controls, with the best-fitting model found to be log-additive ($p$ = 0.0023). Aside from being associated with the decreased risk of PCa, rs7501939 allele T was also shown to confer decreased risk of BPH (OR = 0.65, 95%CI 0.49–0.86).

When analyzing whether these two SNPs are in association with PCa progression, no correlation has been found (*Table S2*). Nevertheless, statistical trend of significance was reached when comparing rs3760511 genotype distributions in patients with low and high GS, as well as when assessing the association of this SNP with the risk of cancer progression according to Medeiros et al. for recessive genetic model ($p$ = 0.053 and $p$ = 0.072, respectively).

A meta-analysis across 11 studies and 15 study panels has shown statistically significant reduction in the PCa risk associated with rs7501939 minor allele ($p$ < 0.001; OR = 0.87, 95%CI 0.82–0.92) (*Figure 1*). Similar results were obtained when analysis was restricted to populations of European descent ($p$ < 0.001; OR = 0.84, 95%CI 0.81–0.88) (*Figure S1*). For rs7501939, evidence of significant between-study heterogeneity was obtained ($p$ < 0.001). When considering association of rs3760511 minor allele C with PCa risk, meta-analysis across seven studies and 11 study panels has shown per-allele OR for C versus A allele of 1.19, with 95%CI of 1.16–1.23 (*Figure 1*). The restriction of analysis to populations of European descent yielded practically the same results ($p$ = 0.001; OR = 1.19, 95%CI 1.16–1.23) (*Figure S1*). For rs3760511, there was no evidence of heterogeneity across the studies included in the analysis ($p$ = 0.506).

## Discussion

One of the first Genome-wide association studies (GWAS) on PCa has identified 17q12 as the region carrying PCa susceptibility variants.[7] Together with 8q24, this region remained the most significant region associated with PCa risk and it was replicated in multiple populations and different ethnic groups. Nevertheless,

| SNP | Genetic model | No. of PCa patients (%) | No. of controls (%) | No. of BPH patients (%) | PCa versus controls | | | PCa versus BPH | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | OR (95% CI) | *p* value | AIC | OR (95% CI) | *p* value | AIC |
| **rs3760511** | | | | | | | | | | |
| | Codom. | | | | | | | | | |
| | AA | 123 (45.4) | 84 (52.2) | 112 (43.1) | 1 | 0.35 | 575.1 | 1 | 0.48 | 740.9 |
| | AC | 116 (42.8) | 59 (36.6) | 124 (47.7) | 1.36 (0.89–2.07) | | | 0.86 (0.60–1.23) | | |
| | CC | 32 (11.8) | 18 (11.2) | 24 (9.2) | 1.20 (0.63–2.27) | | | 1.18 (0.66–2.13) | | |
| | Dom. | | | | | | | | | |
| | AA | 123 (45.4) | 84 (52.2) | 112 (43.1) | 1 | 0.16 | 573.3 | 1 | 0.59 | 740.1 |
| | AC + CC | 148(54.6) | 77 (47.8) | 148 (56.9) | 1.32 (0.89–1.95) | | | 0.91 (0.65–1.28) | | |
| | Rec. | | | | | | | | | |
| | AA + AC | 239 (88.2) | 143 (88.8) | 236 (90.8) | 1 | 0.89 | 575.2 | 1 | 0.39 | 739.6 |
| | CC | 32 (11.8) | 18 (11.2) | 24 (9.2) | 1.04 (0.56–1.93) | | | 1.28 (0.73–2.24) | | |
| | Overdom. | | | | | | | | | |
| | AA + CC | 155 (57.2) | 102 (63.4) | 136 (52.3) | 1 | 0.18 | 573.4 | 1 | 0.28 | 739.2 |
| | AC | 116 (42.8) | 59 (36.6) | 124 (47.7) | 1.31 (0.88–1.57) | | | 0.83 (0.59–1.17) | | |
| | Log-add. | | | | | | | | | |
| | – | – | – | | 1.17 (0.88–1.57) | 0.28 | 574 | 1.00 (0.77–1.29) | 0.99 | 740.4 |
| **rs7501939** | | | | | | | | | | |
| | Codom. | | | | | | | | | |
| | CC | 129 (48.1) | 58 (34.5) | 118 (47.6) | 1 | **0.012** | 579.2 | 1 | 0.9 | 721.3 |
| | CT | 107 (39.9) | 78 (46.4) | 103 (41.5) | **0.62 (0.40–0.95)** | | | 0.96 (0.66–1.38) | | |
| | TT | 32 (11.9) | 32 (19.1) | 27 (10.9) | **0.45 (0.25–0.81)** | | | 0.93 (0.52–1.64) | | |
| | Dom. | | | | | | | | | |
| | CC | 129 (48.1) | 58 (34.5) | 118 (47.6) | 1 | **0.006** | 578.4 | 1 | 0.92 | 719.5 |
| | CT + TT | 139 (51.9) | 110 (65.5) | 130 (52.4) | **0.57 (0.34–0.85)** | | | 0.98 (0.70–1.39) | | |
| | Rec. | | | | | | | | | |
| | CC + CT | 236 (88.1) | 136 (81) | 221 (89.1) | 1 | **0.046** | 582.1 | 1 | 0.7 | 719.4 |
| | TT | 32 (11.9) | 32 (19.1) | 27 (10.9) | **0.58 (0.34–0.99)** | | | 1.11 (0.64–1.92) | | |
| | Overdom. | | | | | | | | | |
| | CC + TT | 161 (60.1) | 90 (53.6) | 145 (58.5) | 1 | 0.19 | 584.4 | 1 | 0.73 | 719.4 |
| | CT | 107(39.9) | 78 (46.4) | 103 (41.5) | 0.77 (0.52–1.14) | | | 0.94 (0.66–1.34) | | |
| | Log-add. | | | | | | | | | |
| | – | – | – | – | **0.66 (0.50–0.87)** | **0.0032** | 577.4 | 1.01 (0.79–1.31) | 0.92 | 719.5 |

Codom. = codominant; Dom. = dominant; Rec. = recessive; Overdom. = overdominant; Log-add. = Log-additive; AIC = akaike information criterion.
Statistically significant results are shown in bold.

**Table 2.** Association of two SNPs at 17q12 with prostate cancer risk, as assessed in comparison of genotype distributions between patients with prostate cancer and controls, as well as between patients with prostate cancer and benign prostatic hyperplasia.

analysis regarding the association of SNPs located at 17q12 has not been conducted in eastern European populations.

This study conducted in Serbian population suggests association of rs7501939 with PCa risk. These results are in concordance with previous studies in various populations of European descent, as well as in Korean population, which show that minor allele T of rs7501939 confers the decreased risk of developing PCa.[7,12–20,32] In contrast with these findings, no evidence of association between rs7501939 and PCa risk was shown in populations of African descent,[14,18,19] nor in the cohort of subjects from Spanish population included in the study by Gudmundsson et al.[7] Furthermore, our results did not differ from results obtained by meta-analysis of previously published studies and this study on association between rs7501939 and PCa risk, when concerning the direction and the significance of association, but showed even larger effect of minor allele T on the risk decrease. These findings qualify rs7501939 as potential genetic marker in PCa risk prediction in populations of European, but not African descent.

When considering association between rs3760511 and PCa risk, the data obtained in our study showed no statistical significance. These results were consistent with data obtained in populations of African descent and in Spanish cohort included in the study by Gudmundsson et al.[7,14] However, in other populations of European descent and Koreans C allele of rs3760511 was

| SNP | Genetic model | No. of BPH patients (%) | No. of controls (%) | OR (95% CI) | *p* value | AIC |
|---|---|---|---|---|---|---|
| **rs3760511** | | | | | | |
| | Codominant | | | | | |
| | AA | 112 (43.1) | 84 (52.2) | 1 | 0.083 | 563.1 |
| | AC | 124 (47.7) | 59 (36.6) | **1.58 (1.04–2.41)** | | |
| | CC | 24 (9.2) | 18 (11.2) | 1.00 (0.51–1.98) | | |
| | Dominant | | | | | |
| | AA | 112 (43.1) | 84 (52.2) | 1 | 0.068 | 562.8 |
| | AC + CC | 148 (56.9) | 77 (47.8) | 1.45 (0.97–2.15) | | |
| | Recessive | | | | | |
| | AA + AC | 236 (90.8) | 143 (88.8) | 1 | 0.52 | 565.7 |
| | CC | 24 (9.2) | 18 (11.2) | 0.81 (0.42–1.54) | | |
| | Overdominant | | | | | |
| | AA + CC | 136 (52.3) | 102 (63.4) | 1 | **0.026** | 561.1 |
| | AC | 124 (47.7) | 59 (36.6) | **1.58 (1.05–2.36)** | | |
| | Log-additive | | | | | |
| | - | - | - | 1.18 (0.87–1.61) | 0.27 | 564.9 |
| **rs7501939** | | | | | | |
| | Codominant | | | | | |
| | CC | 118 (47.6) | 58 (34.5) | 1 | **0.0097** | 559.9 |
| | CT | 103 (41.5) | 78 (46.4) | **0.64 (0.41–0.98)** | | |
| | TT | 27 (10.9) | 32 (19.1) | **0.41 (0.23–0.76)** | | |
| | Dominant | | | | | |
| | CC | 118 (47.6) | 58 (34.5) | 1 | **0.0079** | 560.2 |
| | CT + TT | 130 (52.4) | 110 (65.5) | **0.58 (0.39–0.87)** | | |
| | Recessive | | | | | |
| | CC + CT | 221 (89.1) | 136 (81) | 1 | **0.021** | 561.8 |
| | TT | 27 (10.9) | 32 (19.1) | **0.52 (0.30–0.91)** | | |
| | Overdominant | | | | | |
| | CC + TT | 145 (58.5) | 90 (53.6) | 1 | 0.32 | 566.2 |
| | CT | 103 (41.5) | 78 (46.4) | 0.82 (0.55–1.22) | | |
| | Log-additive | | | | | |
| | - | - | - | **0.65 (0.49–0.86)** | **0.0023** | 557.9 |

Statistically significant results are shown in bold.

**Table 3.** Association of two SNPs at 17q12 with the risk of benign prostatic hyperplasia.

found to confer increased risk of PCa.[7,12,14,16,17,30] Meta-analysis also confirmed the mentioned association, whereas the OR for allele C versus allele A found in Serbian population differed only slightly from overall results of meta-analysis, even though statistical significance level was not reached.

Both rs3760511 and rs7501939 were found to be associated with the risk of developing BPH in Serbian population. These results could not be compared with the ones obtained in other populations because none of the previously published studies included the cohort of patients with BPH. Our observations suggest that analyzed SNPs could possibly represent the markers not specific for PCa, but for prostatic diseases in general. In order to make further conclusions, analysis of association between these SNPs and BPH risk should be conducted in other populations.

We found that the values of parameters of PCa progression were independent of rs3760511 and rs7501939 PCa-susceptibility SNPs in Serbian population. Furthermore, these variants were not found to be associated with the risk of cancer progression. Previous study by Berndt et al. which included subjects of European ancestry has also shown no evidence of association between these SNPs and PCa aggressiveness,[16] while in the population of Ashkenazi Jewish ancestry rs7501939 was not found to be associated with the clinical end points.[21] In order to confirm the obtained results, further increase in the sample size is required. It is possible that after expanding study groups the association between rs3760511 and the risk of PCa in Serbian population would reach statistical significance. Furthermore, additional studies would provide the results necessary for making

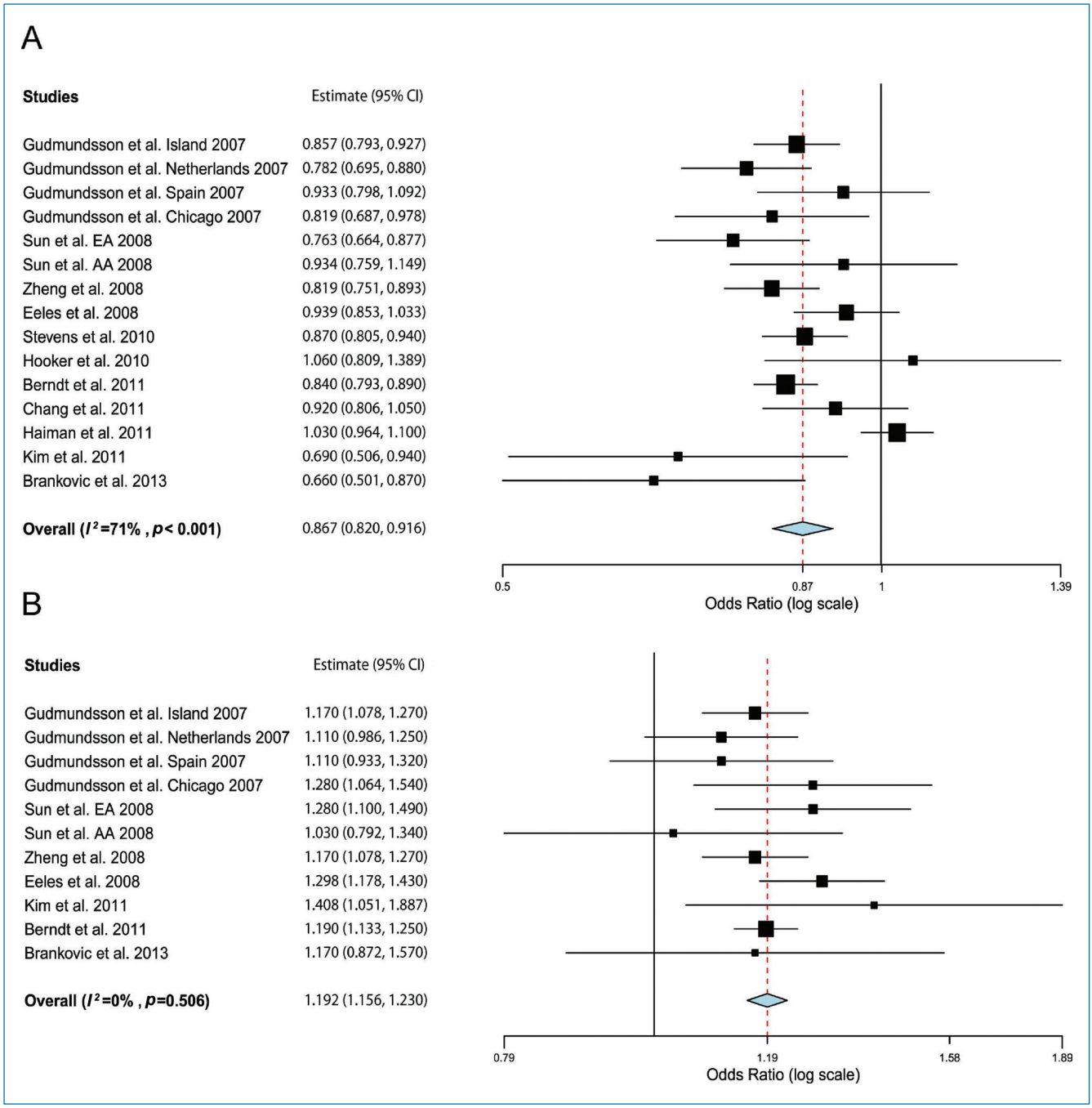


**Figure 1.** Meta-analysis of SNPs at 17q12 and prostate cancer risk. (A) rs7501939 T allele versus C allele and prostate cancer risk across 15 panels from 11 studies; (B) rs3760511 C allele versus A allele and prostate cancer risk across 11 panels from seven studies.

definite conclusions about possible involvement of 17q12 variants in the pathogenesis of other prostatic diseases. Based on presently available data, these variants do not seem to be associated with the parameters of PCa progression and the disease aggressiveness.

## Conclusion

Our study shows association between SNPs at locus 17q12 and the risk of prostatic diseases in Serbian population. At the same time, results of meta-analysis suggest the association of these SNPs with PCa risk.

## Conflicts of Interest

The authors declare that there is no conflict of interest.

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## Supporting Information

Additional supporting information may be found in the online version of this paper.

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