

Original Article

NUDT11 rs5945572 polymorphism and prostate cancer risk: a meta-analysis

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Abstract: The association between the NUDT10 rs5945572 polymorphism and prostate cancer (PCa) was not clear. We thus conducted a meta-analysis to assess the association between NUDT10 rs5945572 polymorphism and PCa risk. A literature search was carried out using PUBMED, EMBASE, and Cochrane Library Central database before Dec 2014. The strength of the associations between the NUDT10 rs5945572 polymorphism and PCa risk was measured by odds ratios (OR) with 95% confidence intervals (CI). The random-effects model was used. NUDT10 rs5945572 polymorphism was significantly associated with PCa risk (OR = 1.22, 95% CI 1.19-1.26, $P < 0.001$, $I^2 = 0\%$, Figure 2). In the subgroup analysis by ethnicity, a significant association was found among Caucasians (OR = 1.25, 95% CI 1.00-1.57, $P = 0.05$, $I^2 = 0\%$), and Asians (OR = 1.23, 95% CI 1.19-1.28, $P < 0.001$, $I^2 = 0\%$), and Africans (OR = 1.22, 95% CI 1.03-1.45, $P = 0.02$, $I^2 = 48\%$). In conclusion, this meta-analysis found a significant association between NUDT10 rs5945572 polymorphism and prostate cancer.

Keywords: Prostate cancer, NUDT10, meta-analysis, polymorphism

Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy in American men, afflicting one in six men. It is estimated that in the USA, one new case occurs every 2.4 min and a death results every 16.4 min from prostate cancer. The cause of PCa is not well known, but multiple risk factors have been identified, including age, race, and family history of PCa. Many putative risk factors, including androgens, diet, physical activity, sexual factors, inflammation, and obesity, have been investigated, but their roles in PCa etiology remain unclear [1]. Recently, genetic factor was also reported to be an important risk factor for Pca [2-6].

NUDT10 gene is located in Xp11.22. Several genome-wide association (GWA) studies suggested that the susceptibility locus at NUDT10 may be involved in PCa risk [7-19]. However, the results were inconsistent. To our knowledge, no meta-analysis has been conducted to evaluate the association between NUDT10 rs5945572 polymorphism and PCa risk. Thus, we per-

formed a meta-analysis of observational studies to assess the association between NUDT10 rs5945572 polymorphism and PCa risk.

Methods

Publication search

A literature search was carried out using PUBMED, EMBASE, and Cochrane Library Central database before Dec 2014. There were no restriction of origin and languages. Search terms included: "NUDT10" and "Prostate cancer". The reference lists of each comparative study included in this meta-analysis and previous reviews were manually examined to identify additional relevant studies.

Inclusion criteria

Two reviewers independently selected eligible trials. Disagreement between the two reviewers was settled by discussing with the third reviewer. Studies were selected if they met our criteria for study design (cohort study or case-control study), population (patients with PCa), outcome

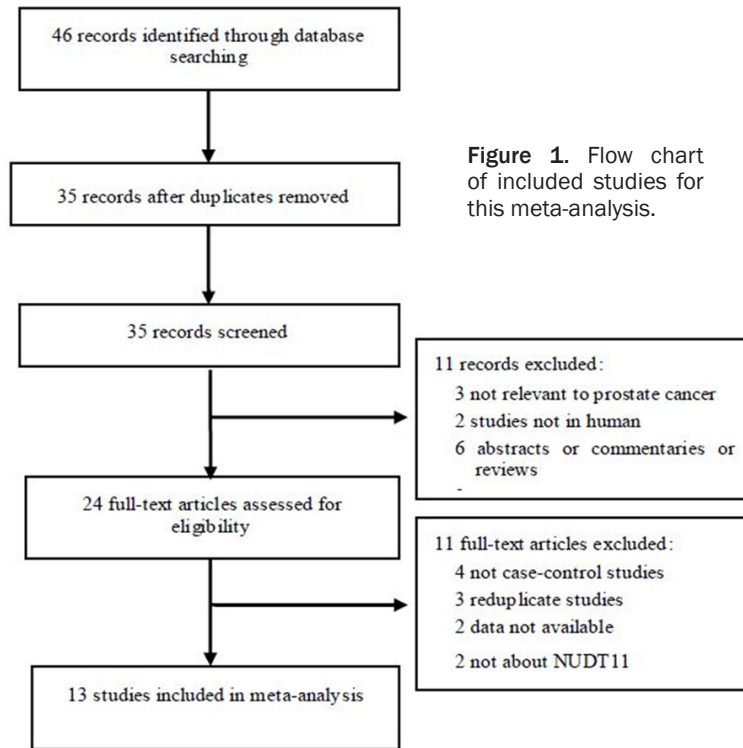


Figure 1. Flow chart of included studies for this meta-analysis.

between the two reviewers was settled by discussing with the third reviewer.

Statistical analysis

The strength of the associations between the NUDT10 rs5945572 polymorphism and PCa risk was measured by ORs and 95% CIs. The random-effects model was used. The statistical significance of summary OR was determined with Z test. The Q statistic and the I² statistic were used to assess the degree of heterogeneity among the studies included in the meta-analysis. The distributions of genotypes in controls were tested by Hardy-Weinberg equilibrium (HWE) using the Chi-square test. Subgroup analyses were carried out by ethnicity. Sensitivity analysis and cumulative meta-

(PCa incidence reported) and evaluation of the NUDT10 rs5945572 polymorphism and PCa risk. Studies without PCa assessment were excluded. When there were multiple publications from the same population, only data from the most recent report were included in the meta-analysis and the others were excluded.

Data extraction

The following data was collected by two reviewers independently using a purpose-designed form: name of first author, publishing time, race, age, number of controls, number of PCa cases, and source of controls.

Quality assessment

Newcastle-Ottawa scale (NOS) was used to assess the methodological quality of cohort and case-control studies. The NOS contains eight items that are categorized three categories: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each). A “star” presents a “high-quality” choice of individual study. Two reviewers assessed the methodological quality independently. Disagreement

analysis were performed. The potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested using Egger’s test. All statistical tests were performed using STATA 11.0 software (Stata Corporation, College Station, TX, USA). A P value < 0.05 was considered statistically significant.

Results

Study characteristics

Figure 1 shows the flow diagram for study selection. A total of 46 citations were identified by the initial search. On the base of the titles and abstracts, we identified 24 full-text articles. After further evaluation, 11 studies were excluded. None study was identified from reference lists. At last, a total of 13 eligible studies were identified [7-19]. A total of 76730 male subjects, including 28370 PCa cases and 48360 controls were involved. Most of the studies included Caucasians. The characteristics of the included studies are summarized in **Table 1**. The NOS scores for the included studies ranged from 7 to 9, with a median 8; all these studies were deemed to be of a high quality (shown in **Table 2**).

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Table 1. Main characteristics of included studies

Author	Year	Ethnicity	Age	Cases	Controls	HWE	Source of controls
Eeles 1	2008	Caucasian	61	1854	1894	Yes	Population-based
Eeles 2	2008	Caucasian	59	1960	2104	Yes	Population-based
Eeles 3	2008	Caucasian	61	1308	1262	Yes	Population-based
Gudmundsson 1	2008	Caucasian	NA	1833	21372	Yes	Population-based
Gudmundsson 2	2008	Caucasian	NA	991	2021	Yes	Population-based
Gudmundsson 3	2008	Caucasian	NA	539	1594	Yes	Population-based
Gudmundsson 4	2008	Caucasian	NA	2865	1722	Yes	Population-based
Gudmundsson 5	2008	Caucasian	NA	1516	554	Yes	Population-based
Gudmundsson 6	2008	Caucasian	NA	656	503	Yes	Population-based
Gudmundsson 7	2008	Caucasian	NA	526	612	Yes	Population-based
Gudmundsson 8	2008	Caucasian	NA	1128	500	Yes	Population-based
Camp	2009	Caucasian	73	169	805	Yes	Population-based
FitzGerald	2009	Caucasian	40-64	1308	1267	Yes	Population-based
Lu 1	2009	Caucasian	NA	1527	482	Yes	Population-based
Lu 2	2009	Caucasian	NA	1172	1157	Yes	Population-based
Waters 1	2009	African	64	860	575	Yes	Population-based
Waters 2	2009	Caucasian	64	468	419	Yes	Population-based
Waters 3	2009	Latino	64	603	572	Yes	Population-based
Waters 4	2009	Asian	64	725	684	Yes	Population-based
Waters 5	2009	Hawaiian	64	112	109	Yes	Population-based
Helfand	2010	Caucasian	58	687	777	Yes	Population-based
Hooker	2010	African	66	454	301	Yes	Population-based
Chang	2011	African	NA	1764	1235	Yes	Population-based
Liu	2011	Asian	70	1108	1525	Yes	Population-based
Vijai	2011	Caucasian	68	963	613	Yes	Population-based
Johansson	2012	Caucasian	59	520	988	Yes	Population-based
Lange	2012	Caucasian	50	754	2713	Yes	Population-based

Overall and subgroup meta-analysis results

NUDT10 rs5945572 polymorphism was significantly associated with PCa risk (OR = 1.22, 95% CI 1.19-1.26, $P < 0.001$, $I^2 = 0\%$, **Figure 2**). In the subgroup analysis by ethnicity, a significant association was found among Caucasians (OR = 1.25, 95% CI 1.00-1.57, $P = 0.05$, $I^2 = 0\%$), and Asians (OR = 1.23, 95% CI 1.19-1.28, $P < 0.001$, $I^2 = 0\%$), and Africans (OR = 1.22, 95% CI 1.03-1.45, $P = 0.02$, $I^2 = 48\%$). As shown in **Figures 3** and **4**, sensitivity analysis and cumulative meta-analysis suggested that the results of this study were robust and stable.

The potential publication bias was evaluated by funnel plot and Egger's test. No visual publication bias was found in the funnel plot (**Figure 5**). And Egger's test suggested that no publication bias was detected ($P = 0.07$).

Discussion

Many studies have indicated that genetics have a critical role in the prostate cancer [20, 21]. Zhou et al. suggested that short tandem repeat polymorphism of TAAA in the promoter region of PCA3 gene is a risk-increasing factor for prostate cancer in the Chinese population [22]. Xu et al. suggested that IL-1B-511 (rs16944) and IL-1B-31 (rs1143627) are significantly associated with PCa risk [23]. Zhao and colleagues found that eNOS gene 894G>T polymorphism might be a risk factor in the onset of PCa [24]. Chu et al. indicated that there is the significant association between the functional promoter variant rs4705342T>C in miR-143 and PCa risk [25].

This study demonstrates that there is a significant positive relationship between NUDT10 rs5945572 polymorphism and prostate can-

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Table 2. Methodological quality of the included studies

Author	Year	Selection				Comparability	Exposure			Total stars
		Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Eeles 1	2008	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Eeles 2	2008	☆	☆	☆	☆	☆☆	—	☆	☆	8
Eeles 3	2008	☆	☆	☆	☆	☆	☆	☆	—	8
Gudmundsson 1	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 2	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 3	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 4	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 5	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 6	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 7	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Gudmundsson 8	2008	☆	☆	—	☆	☆☆	☆	☆	☆	8
Camp	2009	☆	☆	☆	☆	☆☆	☆	☆	☆	9
FitzGerald	2009	☆	☆	☆	☆	☆	☆	—	☆	8
Lu 1	2009	—	—	☆	☆	☆☆	☆	☆	☆	7
Lu 2	2009	—	—	☆	☆	☆☆	☆	☆	☆	7
Waters 1	2009	☆	☆	—	☆	☆☆	☆	☆	☆	8
Waters 2	2009	☆	☆	—	☆	☆☆	☆	☆	☆	8
Waters 3	2009	☆	☆	—	☆	☆☆	☆	☆	☆	8
Waters 4	2009	☆	☆	—	☆	☆☆	☆	☆	☆	8
Waters 5	2009	☆	☆	—	☆	☆☆	☆	☆	☆	8
Helfand	2010	☆	☆	☆	☆	☆	☆	☆	—	8
Hooker	2010	☆	☆	☆	☆	☆	☆	☆	☆	9
Chang	2011	☆	—	☆	☆	☆	☆	☆	☆	8
Liu	2011	☆	☆	☆	—	☆	☆	—	☆	7
Vijai	2011	☆	☆	☆	☆	☆	☆	☆	☆	9
Johansson	2012	☆	☆	☆	☆	—	☆	☆	☆	8
Lange	2012	☆	☆	☆	☆	☆	☆	☆	—	8

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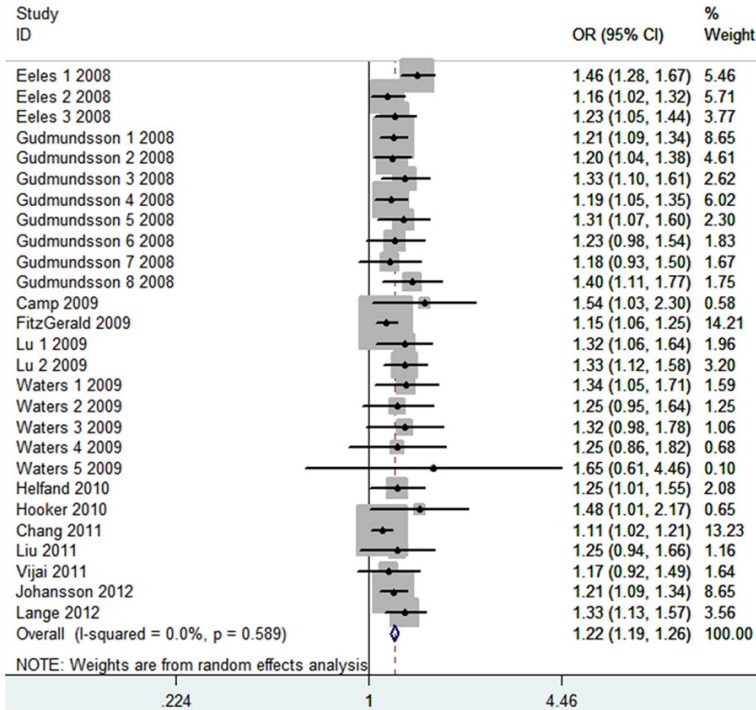


Figure 2. Meta-analyses of the NUDT10 rs5945572 polymorphism and prostate cancer.

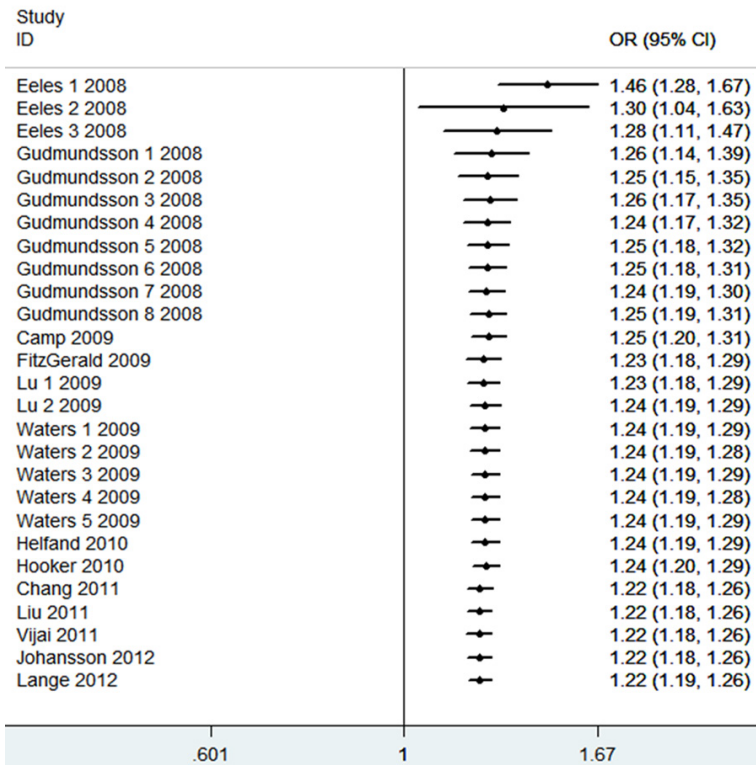


Figure 3. Cumulative meta-analysis of associations between NUDT10 rs5945572 polymorphism and prostate cancer.

cer. This conclusion agrees with many previous epidemiological studies mentioned above [7-19], which indicate that the NUDT10 could promote the prostatic carcinogenesis via multiple signaling pathways. NUDT10 might be involved in inhibiting apoptosis, promoting cell proliferation, and inducing tumor suppressor gene loss. However, the detailed mechanism is not clear and should be investigated in the future studies. In the subgroup analysis of ethnicity, significant associations were observed in Caucasians, Asians, and Africans, suggesting that this polymorphism might play the same role in the prostatic carcinogenesis in different races.

Limitations of this meta-analysis should be noted. First, we did not search for unpublished studies, so only published studies were included in our meta-analysis. Therefore, publication bias may have occurred although no publication bias was indicated from both visualization of the funnel plot and Egger's test. Second, a lack of original data from the eligible studies limited evaluation of the effects of the gene-gene and gene-environment interactions during PCa development. Third, the association between glargine insulin and risk of PCa in Asian population and Africans population was performed with only two studies. So more studies need to further investigate the association in the future.

In conclusion, this meta-analysis found a significant association between NUDT10 rs5945572 polymorphism and prostate cancer.

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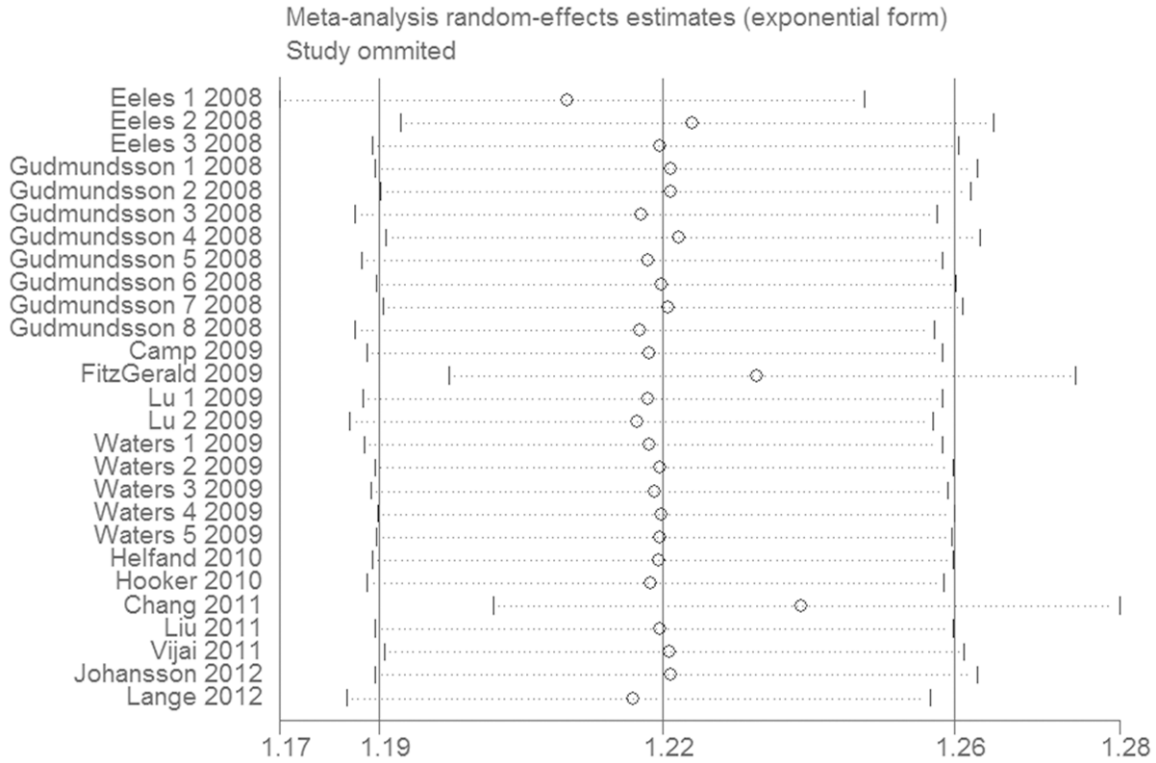


Figure 4. Sensitivity analysis for NUDT10 rs5945572 polymorphism and prostate cancer.

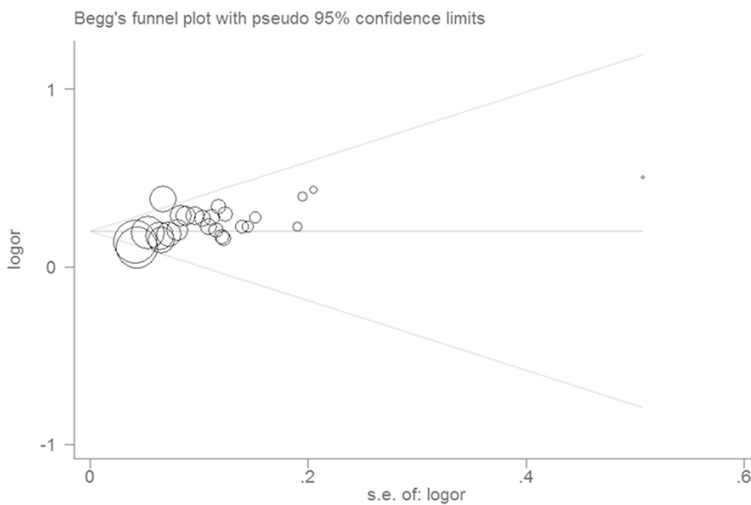


Figure 5. Funnel plot between the NUDT10 rs5945572 polymorphism and prostate cancer.

Disclosure of conflict of interest

None.

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