

Association between *EHBP1* rs721048(A>G) polymorphism and prostate cancer susceptibility: a meta-analysis of 17 studies involving 150,678 subjects

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Background: *EHBP1* rs721048(A) was first identified as a prostate cancer (PCa) risk in Caucasians by genome-wide association study, but subsequent replication studies involving Caucasian and other ethnicities did not produce consistent results. The aim of this study was to obtain a more definite association between rs721048(A) and PCa risk.

Methods: We comprehensively searched several databases updated to September 2014, including PubMed, Web of Science, EBSCO, and Google Scholar. Two authors independently screened and reviewed the eligibility of each study. The quality of the included studies was assessed by the Newcastle–Ottawa scale. The association of rs721048(A) and PCa risk was assessed by pooling odds ratios (ORs) with 95% confidence intervals (CIs).

Results: A total of 17 studies, including 48,135 cases and 102,543 controls, published between 2008 and 2014 were included in the meta-analysis. Overall, the pooled analysis demonstrated that rs721048(A) was significantly associated with the risk of PCa under the allele model (OR=1.14, 95% CI=1.11–1.17, $P=0.000$). Subgroup analysis based on ethnicity revealed a significant association between rs721048(A) and PCa in Caucasian (OR=1.14, 95% CI=1.11–1.16, $P=0.000$), African descent (OR=1.11, 95% CI=1.01–1.23, $P=0.025$), and Asian (OR=1.35, 95% CI=1.12–1.64, $P=0.002$).

Conclusion: Our results provided strong evidence that rs721048(A) could be a risk factor for PCa.

Keywords: *EHBP1*, rs721048, meta-analysis, prostate cancer

Introduction

Prostate cancer (PCa) is a common malignant tumor of the urinary system and the most frequently diagnosed nonskin cancer in men, with over 659,000 cases in developed countries.^{1–4} The incidence of PCa has increased as a result of increased awareness and screening.⁵ The highest PCa incidence rates occur in developed countries, such as Australia and New Zealand, Western and Northern Europe, and Northern America, and the highest mortality rates are among those of African descent in the Caribbean region, whereas the lowest incidence and mortality rates occur in South-Central Asia.⁶ Several risk factors, such as androgen, obesity, diet, smoking, alcohol, race, family history, and advancing age, are associated with the occurrence of PCa. Among them, race, family history of the disease, and advancing age are the only established risk factors for PCa,⁷ indicating genetics as a key factor in the risk of PCa. However, the detailed pathogenesis of this disease is still unclear. Therefore, more researches

are now in progress to look for new risk factors for PCa. Genome-wide association study (GWAS), also known as whole genome association study (WGAS), is widely used in the study of genetic epidemiology. At present, more than 50 susceptibility loci associated with PCa risk have been identified by GWAS. Most of them are located in the introns and noncoding regions of the genes. Among them, eight loci were identified in the Japanese,^{8,9} one locus was identified in African-Americans,¹⁰ and two loci were identified in the Chinese,¹¹ while other susceptibility loci were identified in Europeans.^{12–22}

EHD domain protein 2 (EHD2) binding protein 1 (EHBP1) was first identified and cloned in 3T3-L1 adipocytes, containing a calponin homology domain and five NPF motifs.²³ EHBP1 connects clathrin-mediated endocytosis to the actin cytoskeleton and plays an important role in insulin-stimulated GLUT4 movements and hexose transportation by interacting with EHD2 protein through its NPF motifs.^{23,24} Upregulation of EHBP1 in colorectal cancer is related to the survival of colorectal cancer patients. Moreover, EHBP1 can also mediate the anti-invasive effect of atorvastatin in PTEN-expressing PCa cells.²⁵

rs721048 is an A/G variation, which is located within one of the introns of the *EHBP1* gene on chromosome 2p15, and rs721048(A) was first identified as a risk factor for PCa in Caucasians.¹⁷ Subsequently, extensive replication studies examined the association between rs721048(A>G) polymorphism and PCa risk in Caucasians and other ethnicities, such as those of African descent, Asians, Latinos, Native Hawaiians, and those of Japanese descent, but these studies yielded inconsistent results. Only seven studies yielded similar trends with GWAS analysis, whereas the other nine studies showed no association of rs721048(A) with the risk of PCa. These inconsistent results may have resulted from the different ethnicities in these replication studies. Among them, eight studies assessed the association of rs721048(A) with PCa risk in Caucasians. Four studies yielded similar results to those obtained with GWAS analysis,^{20,26–28} whereas the other four studies yielded opposite results.^{29–32} The first replication study conducted by Waters et al showed an association of rs721048(A) with PCa risk in Latinos, but not in Caucasians, those of African descent, of Japanese descent, and Native Hawaiians.²⁹ Another GWAS conducted by Gudmundsson et al identified four new variants associated with PCa risk. Moreover, one replication study further confirmed that rs721048(A) is a risk factor for PCa in Caucasians.²⁰ Six studies evaluated the association of rs721048(A) with PCa risk in African descent,^{29,33–37} but only one study yielded

positive result.³⁴ Three studies evaluated the association of rs721048(A) with PCa risk in Asians,^{38–40} but only one yielded positive result.⁴⁰ Na et al demonstrated that rs721048(A) is a risk factor for PCa and demonstrated that rs721048(A) is associated with high-grade PCa (Gleason score ≥ 8) in Chinese.⁴⁰ Another cause of the inconsistent results could be the small sample size of subjects. There were only 443 samples in Zheng et al's,³⁸ 472 in Wang et al's,³⁶ 1,176 in Nguyen Bentzon et al's,³² and 1,746 in Xu et al's³⁵ study. In addition, publication bias may exist. These three points are likely to be the cause of the inconsistent results.⁴¹ Therefore, we wanted to confirm whether rs721048(A) is a risk factor for PCa.

rs721048(A) was first identified as a risk factor for PCa in Caucasians, but subsequent replication studies in Caucasians yielded inconsistent results and the replication studies in other ethnicities (such as Asian and African descent) also yielded inconsistent results. Thus, we performed a pooled meta-analysis to obtain a more precise prediction for the association between rs721048A>G polymorphism and PCa risk. To the best of our knowledge, our study was the first comprehensive meta-analysis to assess the association of rs721048(A) with PCa risk. In addition, we also evaluated the association between rs721048(A) and PCa risk in different ethnicities in subgroup analysis.

Materials and methods

Search strategy

The meta-analysis was performed according to the PRISMA guidelines.⁴² We searched the articles using the following terms and keywords: “EHD2-binding protein 1” or “EHBP1” or “rs721048” and “prostate cancer” in academic databases, including PubMed, EBSCO, Web of Science, and Google Scholar (last search was dated September 21, 2014). Additionally, reference lists were hand searched from retrieved articles and reviews. Articles were limited to English language. Two investigators (Xiang Ao and Ying Liu) read the abstracts of the retrieved articles to check all relevant studies independently. After that, all investigators further reviewed the full-text articles to identify all appropriate articles upon inclusion and exclusion criteria. Disagreements were solved by discussion among all authors, until an agreement was reached by all parties.

Inclusion and exclusion criteria

To be eligible for inclusion in this meta-analysis, the included studies must meet all the following inclusion criteria: 1) articles about the association between *EHBP1* rs721048(A>G) polymorphism and PCa risk; 2) case-control studies or cohort

studies; 3) studies providing sufficient published data of odds ratio (OR) with 95% confidence interval (CI). Studies were excluded due to the following reasons: 1) reviews; 2) case-only studies; 3) studies about the association between rs721048(A) and PCa progression; 4) studies about the association between rs721048(A) and Gleason grade and stage; 5) the genotype distributions in the controls deviated from Hardy–Weinberg equilibrium ($P \leq 0.05$).

Data extraction

Data extraction was performed by two investigators (Xiang Ao and Ying Liu) independently. The following data were extracted: first author's name, publication year, sample size, country and ethnicity of case-controls, source of control, genotyping method and OR (95% CI). The quality of the included studies was assessed by the Newcastle–Ottawa scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), including selection of groups, comparability of groups, and ascertainment of exposure. The range of NOS score was from 0 to 10 stars. Studies with NOS score above 5 stars were included in the final analysis.

Statistical analysis

Data were analyzed using Stata 12.0. The strength of association between rs721048(A) and PCa risk was measured by OR and 95% CI. Heterogeneity of the included studies was examined by Cochran's Q test. If no heterogeneity was detected in the studies ($P > 0.1$), the fixed-effect model was chosen to calculate the pooled OR and 95% CI. In contrast,

if heterogeneity was detected in the studies ($P \leq 0.1$), the random effect model was adopted. I^2 statistical test was used to calculate the degree of heterogeneity ($I^2 = 0\%–25\%$, no heterogeneity; $I^2 = 25\%–50\%$, moderate heterogeneity; $I^2 = 50\%–75\%$, large heterogeneity; $I^2 = 75\%–100\%$, extreme heterogeneity). For further subgroup analysis, similar method was used to assess the association between rs721048(A) and the risk of PCa in different ethnicities. In the subgroup analysis, different ethnicities or subsets in the study were recognized as individual studies. One-way sensitivity analysis was carried out to evaluate the stability of the results. Cumulative meta-analysis was performed to reflect the trends of the results induced by publication year and sample size. All included studies were ranked according to publication year or sample size. These analyses were performed by adding one new study at a time. Publication bias was examined by the Egger's test and Begg's funnel plot. $z < 1.96$ or $P > 0.05$, indicated no publication bias. Otherwise, publication bias was considered.

Results

Characteristics of eligible studies

The process of including and excluding articles with specific reasons is described in Figure 1. A total of 182 articles were obtained through literature search, each of which was relevant to the search terms. Among them, 65 articles were duplicated. After reading the abstracts of the remaining 117 articles, 77 articles were excluded because they did not meet our specified criteria. The full text of the remaining

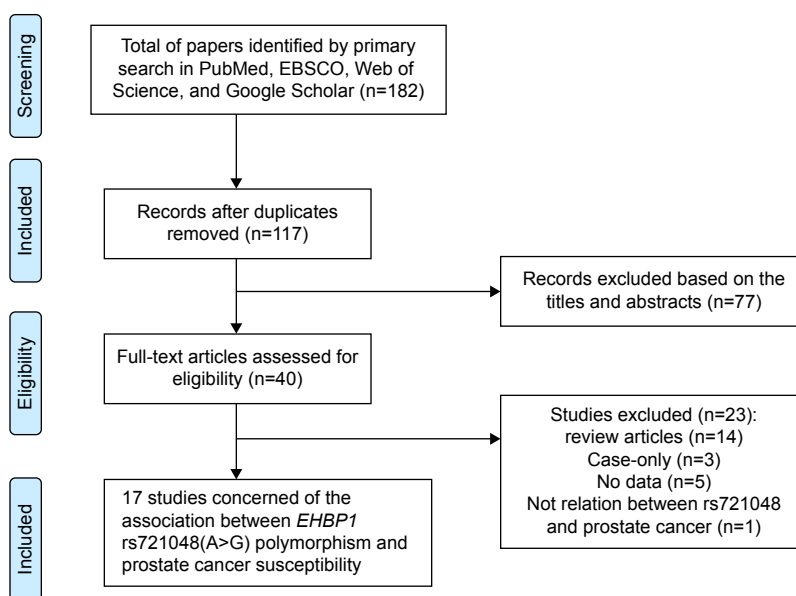


Figure 1 Flow diagram of the inclusion and exclusion of studies.

40 articles was further checked. The reasons for exclusion are listed in Figure 1. Only 17 articles, published between 2008 and 2014, were retained for the meta-analysis because they met our criteria. These articles included a total of 48,135 cases and 102,543 controls. The main characteristics of the 17 eligible studies are summarized in Table 1. GWAS analysis conducted by Gudmundsson et al initially identified the association of rs721048A>G polymorphism with PCa risk.¹⁷ The other 16 articles were replication studies at the population level. Overall, 17 studies were conducted in five different regions, including Europe, USA, UK, Australia, and People’s Republic of China. On the level of ethnicity, the 17 included studies were classified according to previous descriptions:^{43,44} nine studies were of Caucasians (White), four were Asians, six were African descent, one was Japanese descent, one was a Native Hawaiian, and one was the Latino population. Six studies had a NOS score of 8 stars, whereas the other eleven studies had a NOS score of 7 stars. Since most studies only provided an adjusted OR with 95% CI under the allele model, without providing the details of the genotypes in the cases and controls, we extracted the adjusted OR with 95% CI under the allele model in our meta-analysis.

Overall analysis of data and subgroup analysis

A total of 48,135 cases and 102,543 controls were included in this meta-analysis. Given that each of the 17 studies only provided one adjusted OR with 95% CI under the allele model, we calculated the pooled OR under the allele model to assess the association between rs721048A>G polymorphism and PCa risk. The heterogeneity among the 17 studies was measured by Cochran’s *Q* test. No heterogeneity was observed among these studies ($I^2=0.0\%$, $P=0.909$) (Figure 2). Therefore, the meta-analysis was performed in a fixed-effect model. A highly significant association was observed between *EHBP1* rs721048A>G polymorphism and PCa risk in the allele model (OR=1.14, 95% CI=1.11–1.17) (Figure 2). Considering that rs721048(A) was a risk factor for PCa in Caucasian as revealed by GWAS analysis, we performed a subgroup analysis according to ethnicity to examine whether rs721048(A) is also a risk factor in other ethnicities. A significant association between rs721048(A) and the risk of PCa was observed in the subgroups of Caucasian (OR=1.14, 95% CI=1.11–1.16), African descent (OR=1.11, 95% CI=1.01–1.23), and Asian population (OR=1.35, 95% CI=1.12–1.64) under the allele model. In addition, no heterogeneity was observed (Figure 3).

Table 1 Characteristics of all eligible studies included in this meta-analysis

Author	Year	Country	Ethnicity	Case	Control	OR (95% CI)	Source of controls	Genotyping method	NOS score
Gudmundsson et al ¹⁷	2008	Europe, USA	Caucasian	10,093	28,654	1.15 (1.1–1.21)	Population based	Illumina; TaqMan	7
Waters et al ²⁹	2009	USA	Caucasian, Latino, African descent, Japanese descent, Hawaiians	2,768	2,359	1.08 (0.94–1.25)	Population based	Nick-translation PCR	7
Xu et al ³⁵	2009	USA	African descent	868	878	1.2 (0.86–1.68)	Hospital based	Sequenom	7
Gudmundsson et al ²⁰	2009	Europe	Caucasian	1,882	35,145	1.14 (1.05–1.24)	Population based	Illumina	7
Chang et al ³³	2011	USA, UK	African descent	2,083	2,116	1.02 (0.82–1.26)	Population based	Not mentioned	7
Zheng et al ³⁸	2010	People’s Republic of China	Asian	288	155	0.94 (0.41–2.17)	Population based	Sequenom	7
Haiman et al ^{10,34}	2011	USA	African descent	3,621	3,502	1.24 (1.03–1.5)	Population based	Illumina	8
Lindstrom et al ²⁶	2011	Europe, USA	Caucasian	10,160	10,474	1.11 (1.06–1.17)	Population based	TaqMan	8
Sun et al ²⁷	2011	Sweden	Caucasian	2,899	1,722	1.16 (1.11–1.22)	Population based	Not mentioned	7
Liu et al ³⁹	2011	People’s Republic of China	Asian	975	1,658	1.36 (1.01–1.83)	Population based	Sequenom	7
Wang et al ³⁶	2011	USA	African descent	127	345	0.98 (0.4–2.18)	Population based	TaqMan	7
Nguyen Bentzon et al ³²	2012	Denmark	Caucasian	648	526	1.09 (0.88–1.35)	Hospital based	TaqMan	7
Tsilidis et al ²⁸	2012	Europe, USA, Australia	Caucasian	2,921	3,374	1.12 (1.02–1.24)	Population based	TaqMan	8
Klein et al ³⁰	2012	Sweden	Caucasian	943	2,829	1.1 (0.96–1.27)	Population based	Sequenom	7
Kouros et al ³¹	2013	USA	Caucasian	841	1,659	1.2 (1–1.45)	Population based	TaqMan	8
Na et al ⁴⁰	2013	People’s Republic of China	Asian	1,922	2,175	1.39 (1.08–1.8)	Population based	Illumina; Sequenom	8
Han et al ³⁷	2015	USA	African descent	5,096	4,972	1.12 (0.96–1.3)	Population based	Illumina	8

Abbreviations: CI, confidence interval; OR, odds ratio; NOS, Newcastle–Ottawa scale.

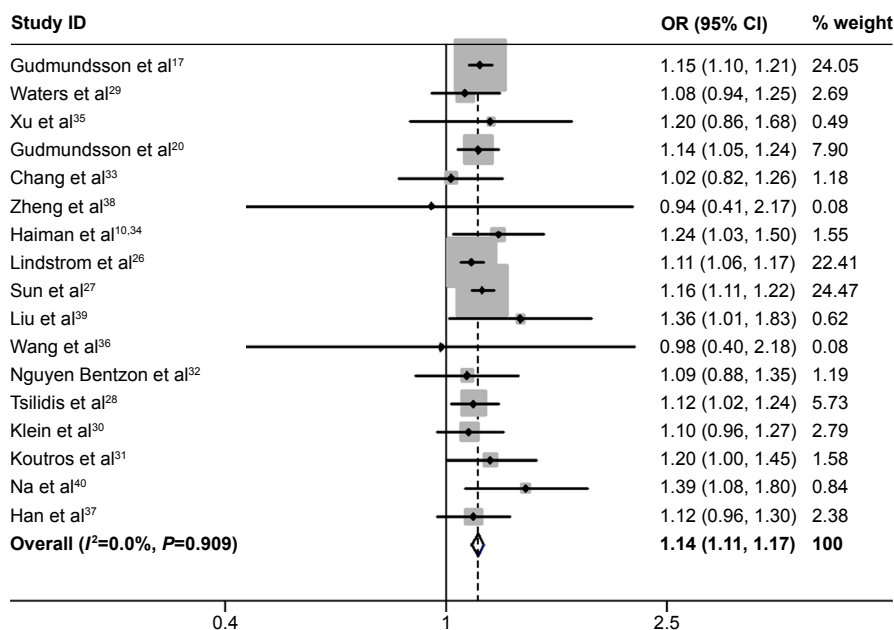


Figure 2 Forest plot of ORs with a fixed-effect model for association between rs721048(A) and the risk of PCa under allele model.

Abbreviations: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

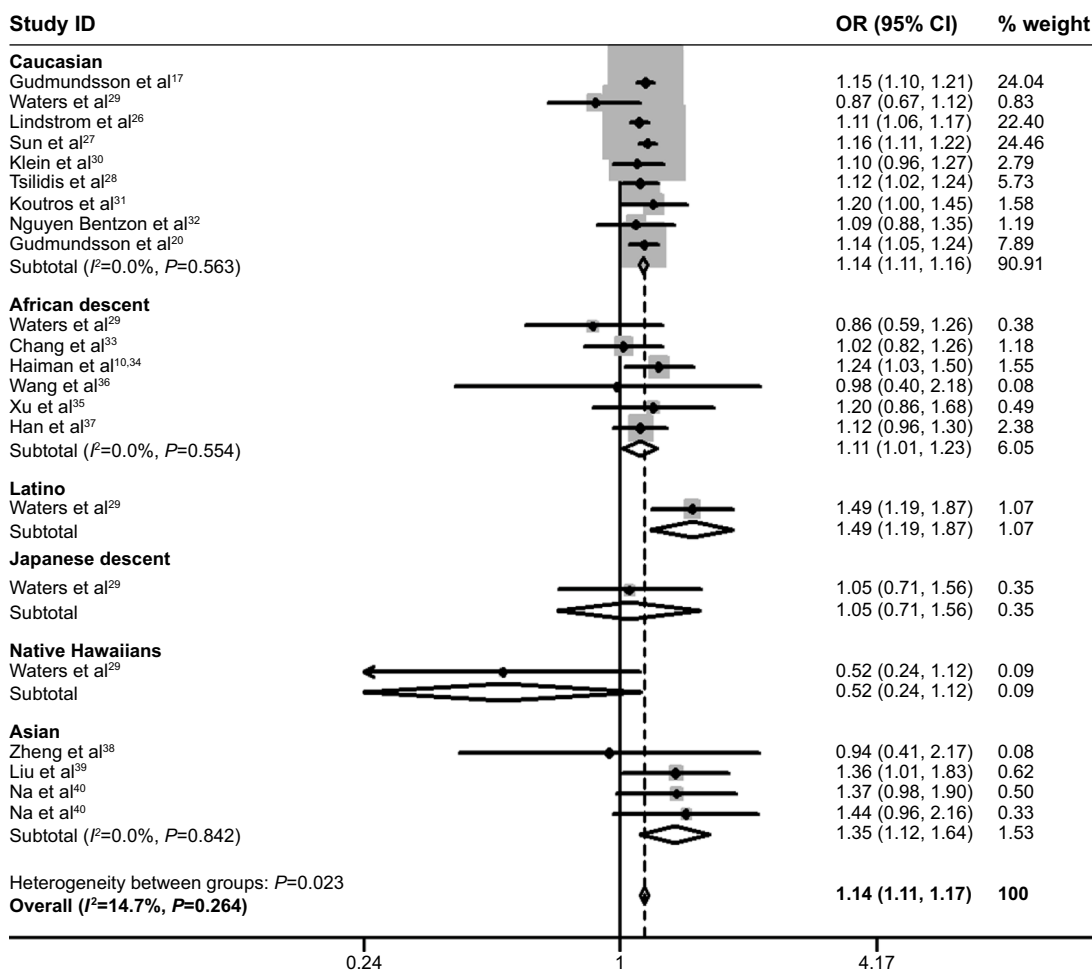


Figure 3 Meta-analysis of the association between rs721048(A) and the risk of PCa stratified for ethnicity under allele model.

Abbreviations: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

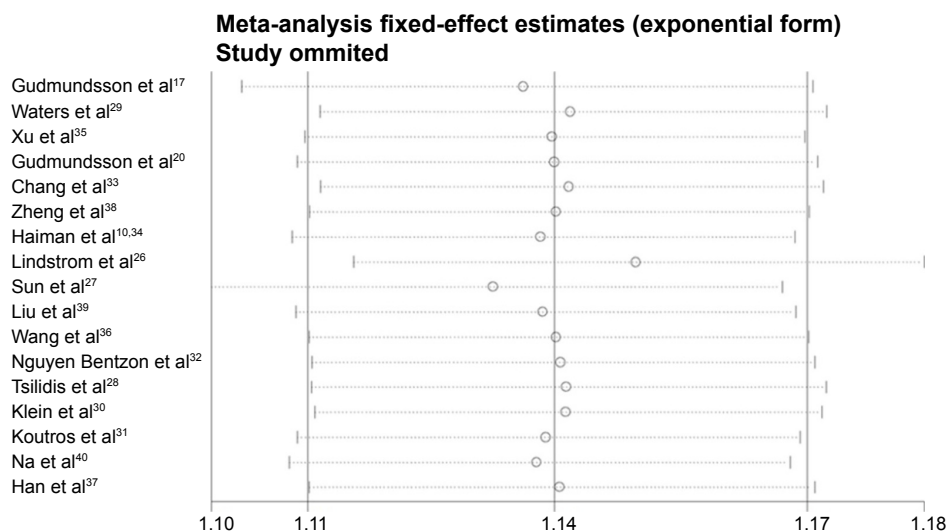


Figure 4 Sensitivity analysis on the association between rs721048(A) and the risk of PCa under allele model.

Abbreviation: PCa, prostate cancer.

Sensitivity analysis

In order to evaluate the stability of the results, one-way sensitivity analysis was performed. As shown in Figure 4, when one study was omitted in sequence, no obvious change was observed for the pooled OR and 95% CI, further confirming that rs721048(A) polymorphism was a risk factor for PCa.

Cumulative meta-analysis

Cumulative meta-analyses were conducted to elucidate the variation in ORs and 95% CIs and to find out at which point of the analysis the risk between rs721048(A) polymorphism and PCa would become statistically significant through sorting studies according to publication year or sample size. As shown in Figure 5, rs721048(A) was further confirmed as a significant risk factor for PCa, and this association was not significantly affected by the changes in publication years. Cumulative meta-analysis by sample size showed that the pooled result began to reach statistical significance after the fifth study included (a total number of 2,772 samples), and the range of CIs became more defined with the increased population sizes in the included studies (Figure 6).

Publication bias

In the meta-analysis, publication bias is the most important contributing factor for bias, which can lead to false positive results. The potential publication bias of the 17 studies was determined by Begg's funnel plot and Egger's test. The values of individual ORs were within the range of the standard deviation in the funnel plot (Figure 7) and, therefore, no obvious asymmetry and significant publication bias were observed ($z=0.21$, $P=0.837$). Similar results were obtained

from Egger's test and no evidence of publication bias was observed ($P=0.803$, 95% CI=-0.569 to 0.723) (Figure 8).

Discussion

Currently, more than 50 susceptibility loci associated with the risk of PCa have been identified in Europeans, the Japanese, the Chinese, and African-Americans by GWAS, suggesting that genetic factors could be important factors affecting the risk of PCa. In these susceptibility loci, the polymorphism of rs721048A>G in *EHBPI* gene has attracted a lot of attention. Extensive research has investigated the association between rs721048(A) and the risk of PCa, but these investigations failed to produce consistent results. The lack of consistency among these results may be due to the small sample sizes of the studies, different ethnicities or publication bias. Therefore, we performed a pooled meta-analysis to determine whether rs721048(A) is a risk factor for PCa, and try to find out the underlying cause of these inconsistent results.

To the best of our knowledge, our study was the first comprehensive meta-analysis to demonstrate the significant association between rs721048(A) and the risk of PCa in the population of the overall study. The meta-analysis included 17 studies with a total of 48,135 cases and 102,543 controls. The results confirmed that rs721048A>G polymorphism was significantly associated with PCa risk. The results from subgroup analysis, which were based on ethnicity, showed that the association was significant in Caucasians, those of African descent, and the Asian population. Sensitivity analysis showed that the results of our meta-analysis were stable and reliable. We also examined the heterogeneity in our study given that heterogeneity is a potential factor that may

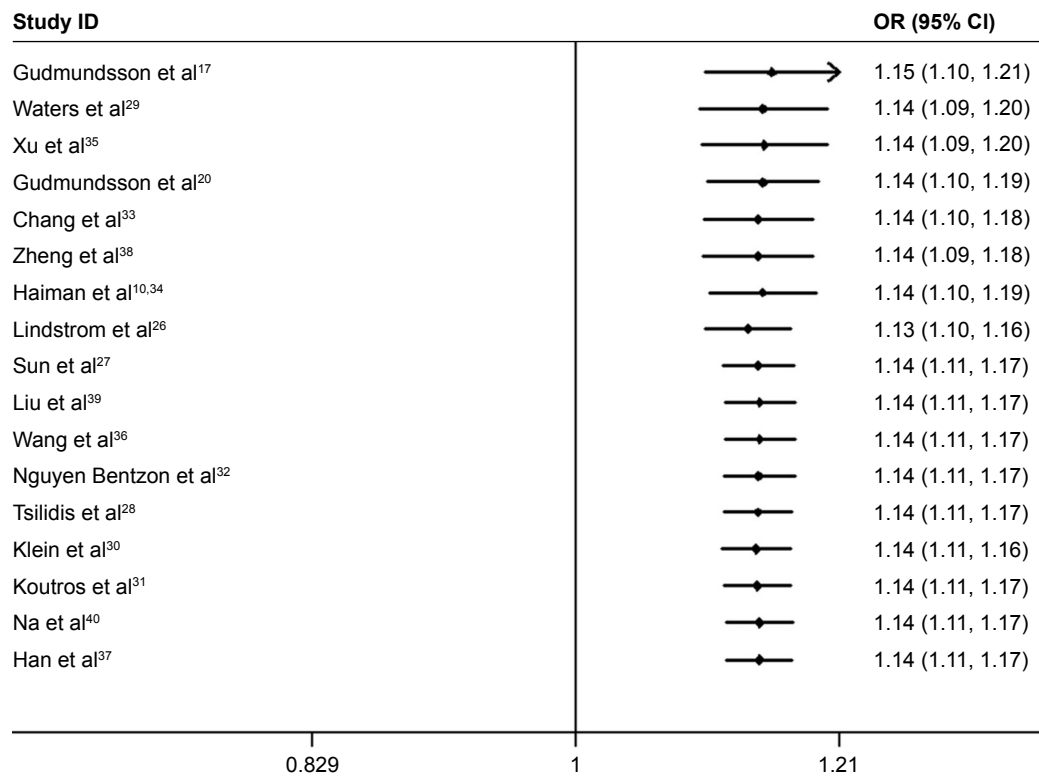


Figure 5 Cumulative meta-analysis of association between rs721048(A) and the risk of PCa under allele model by publication years.
Abbreviations: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

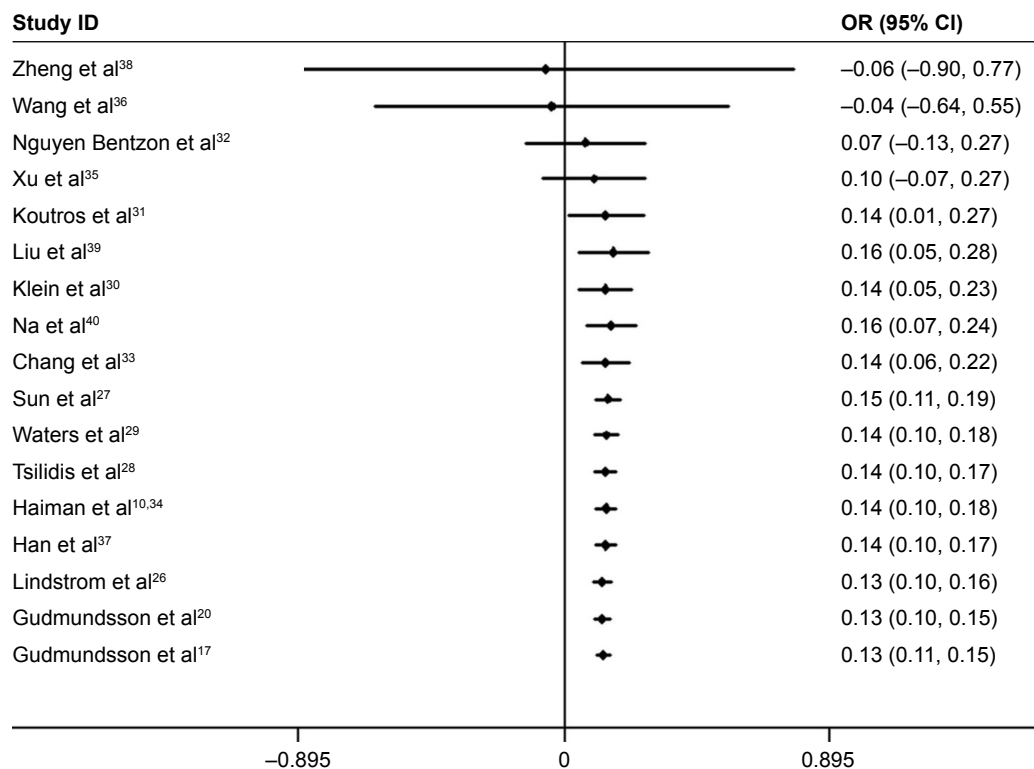


Figure 6 Cumulative meta-analysis of association between rs721048(A) and the risk of PCa under allele model by sample size.
Abbreviations: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

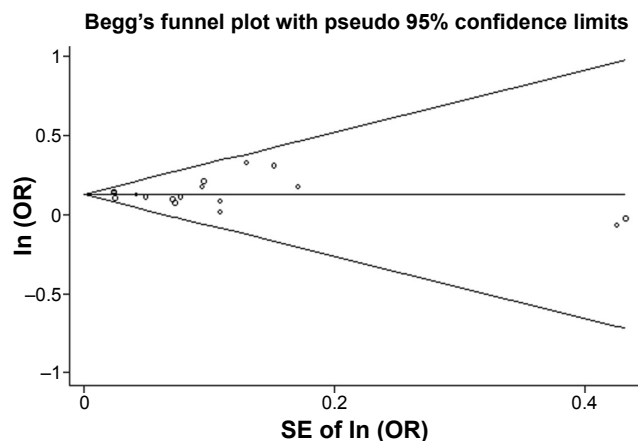


Figure 7 Begg's funnel plot was applied and there were no significant publication bias. Each point represents a separate study for the indicated association.

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

affect the accuracy of the results. Fortunately, no statistically significant heterogeneity was detected in the meta-analysis. In addition, no publication bias was detected, indicating that the eligible studies were unbiased. The association of rs721048(A) with PCa risk was further confirmed by cumulative meta-analyses. When five studies were included, the analysis results reached statistical significance and became stable with further increases in sample size.

The *EHBP1* gene encodes the EHBP1 protein, which is known to associate with PCa risk in humans.¹⁷ However, the detailed mechanisms of EHBP1 in the initiation and progression of PCa are still poorly characterized. It has been reported that EHBP1 is essential for the anti-invasive effect of atorvastatin in PTEN-expressing PCa cells. EHBP1 connects the statin-induced P2X7 signaling with aggressive PCa by interacting with P-Rex1 in response to atorvastatin and by regulating the invasiveness of PTEN-positive PCa cells.²⁵ However its role in PTEN-negative PCa cells has not been

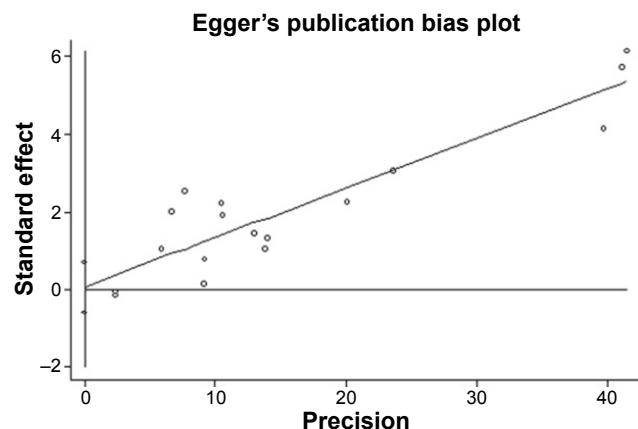


Figure 8 Egger's plot was applied and there were no significant publication bias. Each point represents a separate study for the indicated association.

reported. PTEN is a phosphatase with both protein and lipid phosphatase activities, and it functions as a tumor suppressor. PTEN acts as a negative regulator of the PI3K/AKT signaling pathway by dephosphorylating phosphatidylinositol (3,4,5)-trisphosphate, which is a potent activator of AKT.⁴⁵ EHBP1 may affect PI3K/AKT signaling pathway through direct interaction with PTEN and subsequent modulation of cellular processes, such as cell metabolism, proliferation, migration, and cell cycle. In addition, EHBP1 is also involved in insulin-stimulated rapid receptor trafficking and the translocation of GLUT4 in 3T3-L1 adipocytes,²³ suggesting a possible role for EHBP1 in mediating the translocation of proteins in PCa. The above evidence appeared to support a possible involvement of the *EHBP1* gene in P2X7 signaling and invasiveness regulation of PCa cells in humans.

Several features of our study are worth highlighting. First, the sample size of the analysis (a total of 48,135 cases and 102,543 controls) was large enough to minimize error, significantly increasing the statistical power of the analysis. Moreover, no heterogeneity was observed in the pooled meta-analysis and subgroup analysis, suggesting a high level of homogeneity in the population of the overall study. The adjusted OR with 95% CI for each study was used to calculate the pooled effect, which increased the accuracy of the estimate. Furthermore, our meta-analysis suggested that rs721048(A), which was initially identified as a PCa risk in Caucasians, was also associated with PCa risk in the overall population, especially in Caucasians, Asians, and those of African descent. Finally, cumulative meta-analysis, sensitivity analysis, and publication bias results indicated that the results were stable and accurate in the overall study, which comprises of different ethnic populations.

Some potential limitations should be noted in this study. 1) Since our data were extracted from published articles that just included OR with 95% CI under the allele model, and only the allele model was used to assess the association of rs721048(A) with PCa risk. Thus, the distributions of gene in other genetic models are required for further evaluation. 2) We analyzed the association of rs721048(A) with the risk of PCa, not considering SNP-SNP and SNP-environment interactions, or other environmental factors.⁴⁶ 3) The association between SNP rs721048(A) and PCa grade or stage has been confirmed in only four of the 17 included articles.^{17,26,33,40} Thus, the meta-analysis examining the association of rs721048(A) with PCa grade or stage was not conducted. 4) Our results showed that rs721048(A) was significantly associated with the risk of PCa in the overall

population. However, as only one study was included in each subgroup (Latinos, Native Hawaiians, and Japanese descent), the pooled result was not observed in these three subgroups. Thus, further studies of Latinos, Native Hawaiians, and those of Japanese descent and the other ethnicities need to be conducted in the future.

In conclusion, the data from our meta-analysis demonstrated that *EHBP1* rs721048(A) polymorphism is a risk factor for PCa in the overall population of the study. Although this SNP was initially identified as a risk factor for PCa in Caucasians, subsequent replication studies yielded inconsistent results. Our meta-analysis strongly demonstrated that rs721048(A) is the risk factor for PCa in Caucasians. A lot of replication studies involving Asian and African descent subjects yielded inconsistent results. The pooled analysis that we performed clearly demonstrated that rs721048(A) is a risk factor for PCa in the overall study population, including Caucasians, Asian, and those of African descent. Our finding provided an important basis for the early screening and clinical treatment of PCa. In addition, the functions and mechanisms of *EHBP1* and rs721048A>G polymorphism in PCa also need to be elucidated in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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