OncoTargets and Therapy

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ORIGINAL RESEARCH

Polymorphism in *IGFBP3* gene is associated with prostate cancer risk: an updated meta-analysis

This article was published in the following Dove Press journal:
OncoTargets and Therapy
7 July 2016
Number of times this article has been viewed

Yunkai Qie[1,*]
Xuewu Nian[2,*]
Xuesen Liu[1,*]
Hailong Hu[1]
Changwen Zhang[1]
Linguo Xie[1]
Ruifa Han[1]
Changli Wu[1]
Yong Xu[1]

[1]Department of Urology, The Second Hospital of Tianjin Medical University, Tianjin Institute of Urology, [2]Department of Urology, Tianjin Nankai Hospital, Tianjin, People's Republic of China

*These authors contributed equally to this work

Objective: Insulin-like growth factor-binding protein-3 (IGFBP3) is the major protein that binds with insulin-like growth factor-1 (IGF-1) and is considered to be involved in the development and progression of various cancers. We aimed to examine the association between prostate cancer (PCa) and the *IGFBP3* gene-202A/C polymorphism.

Methods: A comprehensive search within PubMed, EMBASE, and Cochrane Library was conducted to identify all case–control studies up to October 30, 2015, for a meta-analysis. Pooled odds ratios (ORs) and the 95% confidence intervals (CIs) were calculated using the fixed or random effects model.

Results: Eighteen studies including 10,538 cases and 10,078 controls were identified. Overall, the CC genotype of *IGFBP3*-202A/C polymorphism was associated with increased risk of PCa in homozygote comparison (CC vs AA – OR =1.16, 95% CI: 1.08–1.25) and in recessive model (CC vs AA+AC – OR =1.11, 95% CI: 1.04–1.17). In dominant model, the CC/AC genotypes also implicated an increased risk of PCa (CC+AC vs AA – OR =1.11, 95% CI: 1.05–1.19). The C allele of *IGFBP3*-202A/C polymorphism was the risk allele for PCa relative to the A allele (OR =1.09, 95% CI: 1.05–1.14). Further stratification analysis revealed that the association between –202A/C polymorphism and PCa risk among Caucasians, but not in other ethnicities, was statistically significant (recessive model, OR =1.10, 95% CI: 1.02–1.19). In addition, the *IGFBP3*-202A/C polymorphism was associated with PCa risk in both population-based and hospital-based studies in homozygote comparison, recessive model, and allele model.

Conclusion: Our meta-analysis indicates that the *IGFBP3*-202A/C polymorphism is associated with the risk of PCa, particularly in Caucasians, with the C allele being the risk allele for PCa.

Keywords: IGFBP3, polymorphism, prostate cancer, meta-analysis

Introduction

Prostate cancer (PCa) is the most commonly diagnosed internal malignancy and the second leading cause of cancer mortality for men in Western industrialized countries, and its incidence is constantly increasing.[1] The mechanisms underlying the occurrence and recurrence of PCa are largely unknown.[2] However, recent evidence suggests that polymorphic genes may be associated with PCa risk via modulating the effects of endogenous androgens or environmental toxicants.[3]

Insulin-like growth factor-binding protein-3 (IGFBP3) is the major protein that binds with insulin-like growth factor-1 (IGF-1) and limits its bioavailability.[4] In addition, IGFBP3 possesses IGF-independent functions, such as inhibition of cell growth and induction of apoptosis.[5] Many studies had reported the correlation between the level of circulating IGFBP3 and PCa risk, yet their outcomes are still controversial.[6–8] The gene encoding IGFBP3 is located at the chromosome 7p14-p12 region[9] and contains a single nucleotide polymorphism (SNP) (A→C) (rs2854744) at the –202 position in the

Correspondence: Changli Wu; Yong Xu
Department of Urology, The Second Hospital of Tianjin Medical University, Institute of Urology, 23 Pingjiang Road, Tianjin 300211, People's Republic of China
Tel/fax +86 22 2827 3211
Email wujygc@163.com; yxurologist@163.com

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http://dx.doi.org/10.2147/OTT.S102452

promoter region. Deal et al[10] found that circulating IGFBP3 levels were higher when the subjects possessed at least one A allele, suggesting that the circulating IGFBP3 level might be regulated by the −202A/C polymorphism. In accordance with Deal et al's finding, two independent studies also showed that the A allele of −202A/C polymorphism correlates with high serum IGFBP3 levels.[11,12]

Although quite a few studies investigated the association between *IGFBP3*-202A/C polymorphism and PCa risk,[13–23] the results from these studies are controversial and inconsistent, and a couple of meta-analyses have been performed to assess the risk of PCa associated with *IGFBP3*-202A/C polymorphism by using previously published case–control studies.[24,25] But their outcomes still varied leading to controversy. In light of that, a number of new cases have been added since the last comprehensive analysis, and hence we feel necessary to perform an updated meta-analysis to examine the association between the *IGFBP3*-202A/C polymorphism and PCa risk.

Materials and methods

Literature search

A search string that included the terms "IGFBP3", "polymorphism", and "prostate cancer" was used for reviewing the published literature until May 30, 2014, from databases PubMed, EMBASE, and Cochrane Library. In addition, studies cited in the reference lists of the identified articles were also reviewed. We checked all associated publications to retrieve the most appropriate studies. Articles were limited to English language journals and research conducted on human subjects. Studies that reported results of different subpopulations were treated as independent data. We excluded abstracts and unpublished reports. When data of the same patient population were included in more than one publication, the most recent or complete study was used for this meta-analysis.

Inclusion and exclusion criteria

To minimize heterogeneity and facilitate the proper elucidation of results, studies that met the following criteria were thought eligible: 1) information on the evaluation of *IGFBP3*-202A/C polymorphism and PCa susceptibility, 2) case–control studies, 3) studies based on histologically or pathologically verified PCa, and 4) studies with sufficient genotype data to calculate the odds ratios (ORs) with 95% confidence interval (CI). The major reasons for exclusion of studies were 1) absence of controls, 2) reviews and duplication of previously published data, and 3) studies that lacked usable data.

Data extraction

Data were systematically extracted from all eligible publications by two independent investigators (Nian and Liu). When the two investigators had disagreement, a third investigator (Qie) intervened to reach an agreement. The following criteria were considered for studies to be deemed eligible: first author's surname, year of publication, country of the trials, source of control, ethnicity, genotyping method, number of cases and controls, number of PCa cases and controls for the *IGFBP3*-202A/C genotypes (AA/AC/CC). When there were more than one populations studied in an article, we treated each of them as a single study.

Statistical analysis

The Hardy–Weinberg Equilibrium (HWE) was calculated by using the goodness-of-fit test, and a $P<0.01$ was considered as a deviation. The strength of the association between *IGFBP3* polymorphism and PCa risk was assessed using crude ORs along with their corresponding 95% CIs. We first examined rs2854744 genotype using homozygote model (CC vs AA), heterozygote model (AC vs AA), dominant model (AC+CC vs AA), recessive model (CC vs AA+AC), and allelic (C vs A) model, respectively. Heterogeneity was measured using the Q-test ($P<0.05$ was considered significant) and quantified with the I^2 metric. If the P-value for heterogeneity was <0.05 or if the I^2 was $\geq 50\%$, the random effects model was adopted to calculate the overall OR value. Otherwise, the fixed effects model was used. Stratified analyses were performed by ethnicity and source of control. Sensitivity analysis was conducted by sequential omission of individual studies to evaluate the stability of the results. Begg's funnel plot and Egger's test were performed to examine the potential influence of publication bias (linear regression analysis). An asymmetric plot was thought to suggest possible publication bias ($P\geq 0.05$ was considered as no bias). All the analyses were done using STATA Version 11.0 (StataCorp LP, College Station, TX, USA).

Results

Literature search and characteristics of the included studies

A total of 377 studies that investigated the association of *IGFBP3* with PCa risk were identified and screened for data retrieval. As shown in Figure 1, after the exclusion of overlapping data, 353 studies were shortlisted for meta-analysis. Further, 308 papers were excluded as they were not relevant to *IGFBP3* polymorphism and PCa, and thus 45 studies were available for further review. Of these 45 studies, 28 studies

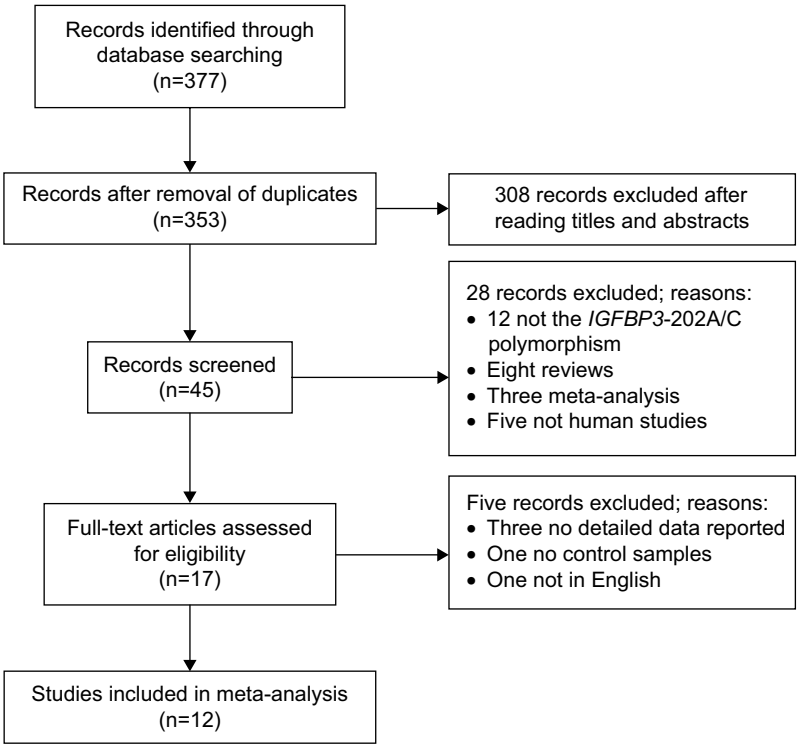

Figure 1 Flowchart of studies included in the meta-analysis.

were excluded because they were reviews or meta-analyses or studies, which were not conducted in human subjects or not relevant to *IGFBP3*-202A/C polymorphism. Among the 17 full-text papers, four studies did not provide sufficient data needed for OR calculation; one had no controls and one was not in English. We thus included 12 independent studies[13–23,26] that enabled data extraction for the present meta-analysis. Since three studies[19–21] had more than one subpopulation, we treated every subpopulation as an independent study. Therefore, 18 separate studies in total were available for our meta-analysis, which included 10,538 cases and 10,078 controls. The main features of these studies are summarized in Table 1. The *IGFBP3*-202A/C polymorphism was reported by four studies in African Americans, four studies in Asians, six studies in Caucasians, one study in Hawaiians, and one study in Latinos. The HWE deviated ($P<0.01$) in three studies in the control group[15,17,19] and were further tested for sensitivity analysis.

IGFBP3-202A/C polymorphism and PCa risk

Q-test of heterogeneity was conducted for overall homozygote comparison, heterozygote comparison, dominant model, recessive model, and allele model, respectively, which turned out that I^2 value was <50% in all these cases. Thus, a fixed effects model was used to calculate values. Overall, the CC genotype of *IGFBP3*-202A/C polymorphism was associated with increased risk of PCa in homozygote comparison (CC vs AA – OR =1.16, 95% CI: 1.08–1.25, I^2=28.7%; Figure 2) and in recessive model (CC vs AA+AC – OR =1.11, 95% CI: 1.04–1.17, I^2=1.10%; Figure 3). In dominant model, the CC/AC genotypes implicated an increased risk of PCa (CC+AC vs AA – OR =1.11, 95% CI: 1.05–1.19, I^2=28.5%; Figure 4). The C allele of *IGFBP3*-202A/C polymorphism was the risk allele for PCa relative to the A allele (OR =1.09, 95% CI: 1.05–1.14, I^2=32.90%; Figure 5).

In stratification analysis by ethnicity, we observed an increased PCa risk associated with the CC genotype of *IGFBP3*-202A/C polymorphism among Caucasians in recessive model (CC vs AA+AC – OR =1.10, 95% CI: 1.02–1.19, I^2=42.9%). We did not find any significant association between *IGFBP3*-202A/C polymorphism and PCa susceptibility in the other ethnicity populations. The detailed data are presented in Table 2. When the identified studies were stratified by the source of controls (population-based or hospital-based), we observed significant association between the *IGFBP3*-202A/C polymorphism and PCa susceptibility with population-based studies in homozygote comparison (CC vs AA – OR =1.13, 95% CI: 1.04–1.22); dominant model (CC+AC vs AA – OR =1.10, 95% CI: 1.03–1.19), recessive

Table 1 Main features of studies included in the meta-analysis

Reference	Year	Country	Control source	Ethnicity	Genotyping methods	Cases/ controls	rs2854744 cases			rs2854744 controls			P_{HWE}
							AA	AC	CC	AA	AC	CC	
Nam et al[23]	2003	Canada	HB	Mixed	PCR-RFLP	483/548	135	233	115	145	274	129	0.98
Wang et al[22]	2003	Japan	HB	Asian	PCR-RFLP	307/272	189	100	18	152	105	15	0.57
Li et al[26]	2004	US	HB	Mixed	PCR-RFLP	440/479	97	217	126	139	225	115	0.20
Schildkraut et al[21]	2005	US	HB	African	PCR-RFLP	50/48	9	30	11	15	21	12	0.40
Schildkraut et al[21]	2005	US	HB	Caucasian	PCR-RFLP	50/44	9	25	16	8	20	16	0.70
Cheng et al[19]	2006	US	PB	African	TaqMan	666/642	217	308	141	224	298	120	0.24
Cheng et al[19]	2006	US	PB	Hawaiians	TaqMan	70/67	22	36	12	24	33	10	0.81
Cheng et al[19]	2006	US	PB	Asian	TaqMan	455/466	264	161	30	282	161	23	1.00
Cheng et al[19]	2006	US	PB	Latinos	TaqMan	637/636	81	277	279	95	257	284	<0.001
Cheng et al[19]	2006	US	PB	Caucasian	TaqMan	451/444	103	220	128	95	205	144	0.17
Chen et al[20]	2006	US	PB	Caucasian	PCR-RFLP	174/174	43	73	58	37	84	53	0.73
Chen et al[20]	2006	US	PB	African	PCR-RFLP	38/38	12	17	9	10	19	9	1.00
Hernandez et al[18]	2007	US	HB	African	PCR-RFLP	401/366	112	196	93	113	183	70	0.79
Park et al[16]	2010	Korea	HB	Asian	PCR-RFLP	225/225	128	76	21	140	76	9	0.74
Johansson et al[17]	2009	Sweden	PB	Caucasian	PCR-PCR	2,633/1,715	891	439	1,303	603	300	812	<0.001
Schumacher et al[15]	2010	US	PB	Caucasian	PCR-RFLP	2,626/2,876	724	556	1,346	888	602	1,386	<0.001
Safarinejad et al[14]	2011	Iran	HB	Caucasian	PCR-RFLP	168/336	23	85	60	89	163	84	0.59
Qian et al[13]	2014	People's Republic of China	HB	Asian	TaqMan	664/702	31	225	408	32	246	424	0.63

Abbreviations: HB, hospital-based; HWE, Hardy–Weinberg equilibrium; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

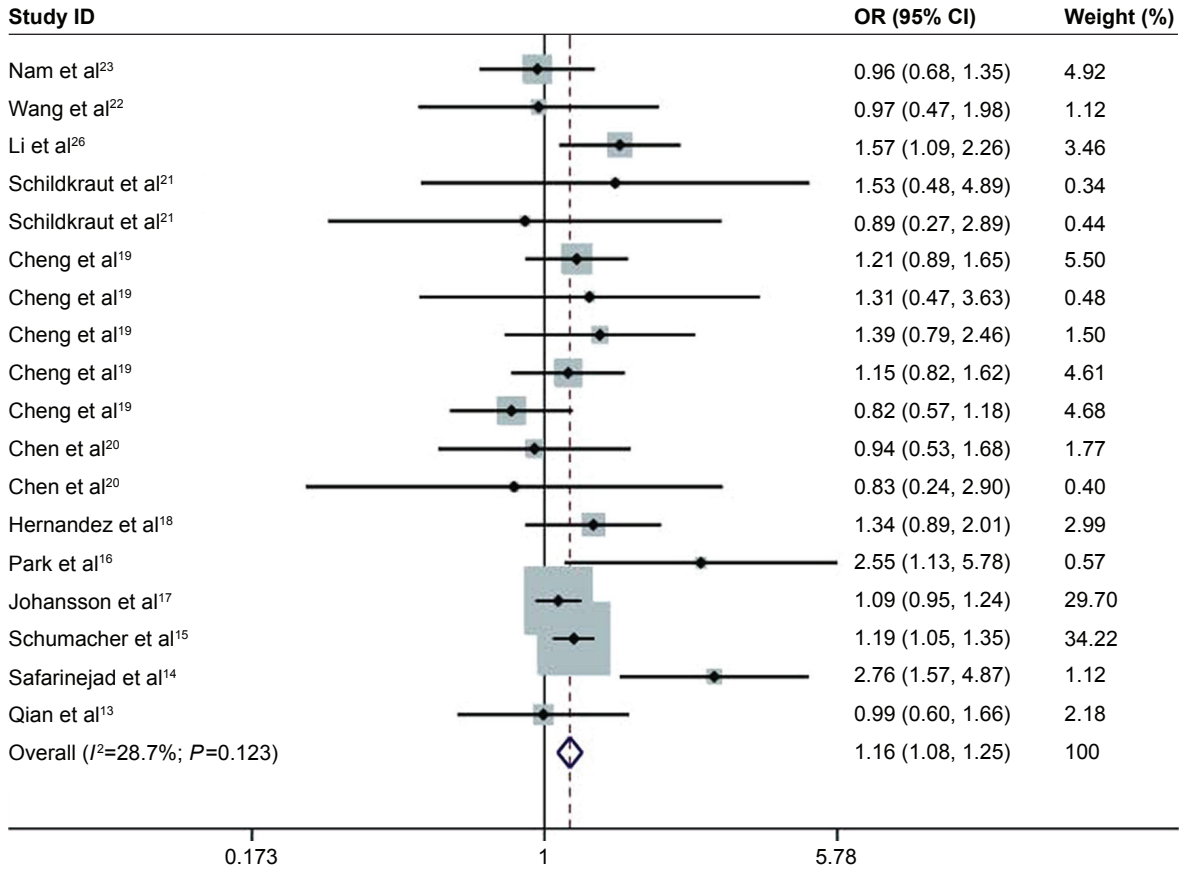

Figure 2 Forest plot of odds ratios with 95% confidence interval for *IGFBP3*-202A/C polymorphism and risk of prostate cancer risk under recessive model (CC vs AA).
Abbreviations: IGFBP3, insulin-like growth factor-binding protein-3; OR, odds ratio; CI, confidence interval.

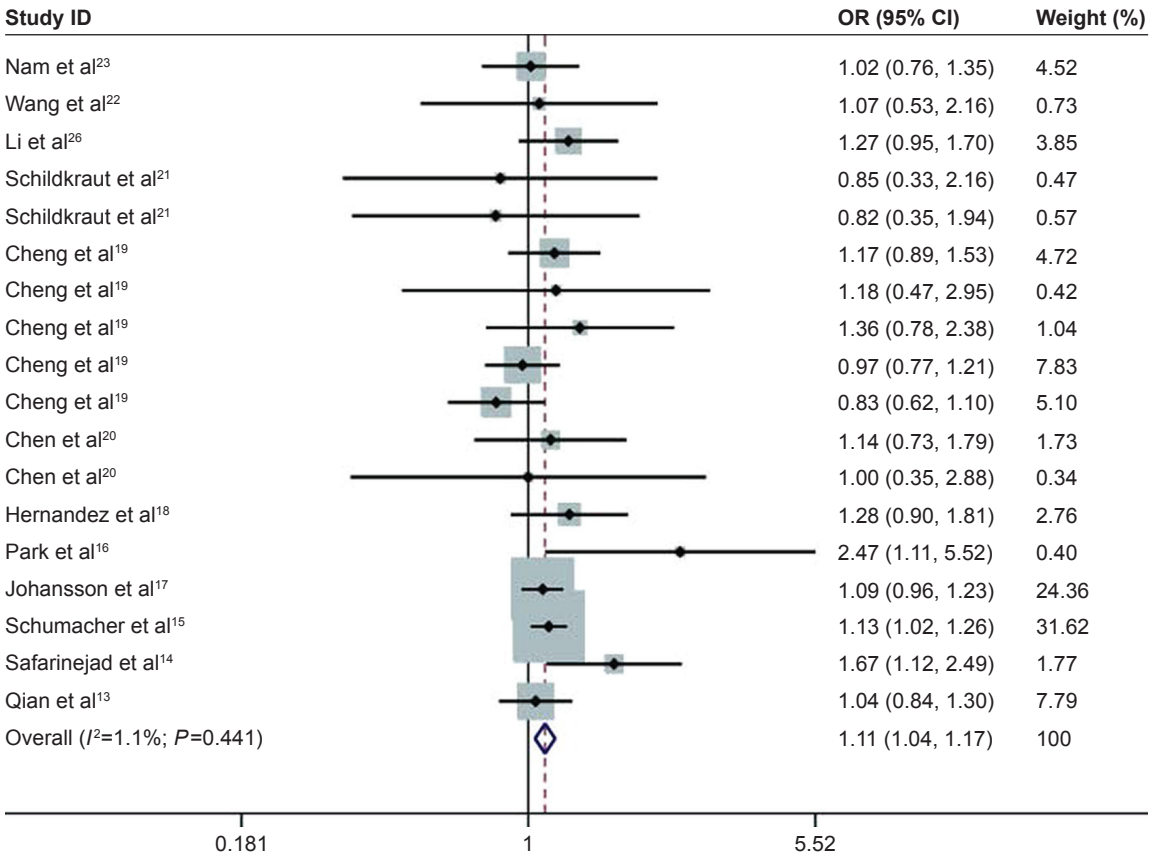

Figure 3 Forest plot of odds ratios with 95% confidence interval for *IGFBP3*-202A/C polymorphism and risk of prostate cancer risk under recessive model (CC vs AA+AC).
Abbreviations: IGFBP3, insulin-like growth factor-binding protein-3; OR, odds ratio; 95% CI, 95% confidence interval.

model (CC vs AA+AC – OR =1.09, 95% CI: 1.01–1.16), and allele model (C vs A – OR =1.08, 95% CI: 1.04–1.14). For hospital-based studies, significant association between the *IGFBP3*-202A/C polymorphism and PCa susceptibility existed in homozygote comparison (CC vs AA – OR =1.33, 95% CI: 1.13–1.58), recessive model (CC vs AA+AC – OR =1.17, 95% CI: 1.03–1.32), and allele model (C vs A – OR =1.13, 95% CI: 1.00–1.29).

Sensitivity analysis

Sensitivity analyses were done by sequential omission of all subjects and subgroups from each study. The statistical significance of the results did not change, although the genotype distributions of the control group in the three studies did not follow HWE (Figure 6). Hence, this suggested that the data of our meta-analysis were relatively stable and credible.

Publication bias

Begg's funnel plot and Egger's linear regression tests were performed to assess the possibility of potential publication bias. For all genetic models, the shape of the funnel plots was symmetrical, and Egger's test showed no evidence of significant publication bias ($P>0.05$), suggesting that there was no apparent publication bias in this meta-analysis (Figure 7).

Discussion

In this meta-analysis, we systematically investigated the relationship between *IGFBP3*-202A/C polymorphism and PCa risk based on 10,538 cases and 10,078 controls. Overall, the *IGFBP3*-202A/C polymorphism was associated with PCa risk, with the carriers of C allele and CC genotype of this SNP being more susceptible to PCa. In stratification analysis, the SNP was found to be associated with PCa risk in Caucasians, but not statistically significant in other ethnicities. With regard to the source of controls, the association of the SNP with PCa risk was also observed for hospital-based studies and population-based studies.

Recently, two meta-analyses have reported the correlation between the *IGFBP3*-202A/C polymorphism and PCa risk, but there are many differences between their outcomes. The study by Mao et al,[25] including 9,238 cases and 8,741 controls, revealed that *IGFBP3* A-202C polymorphisms seemed

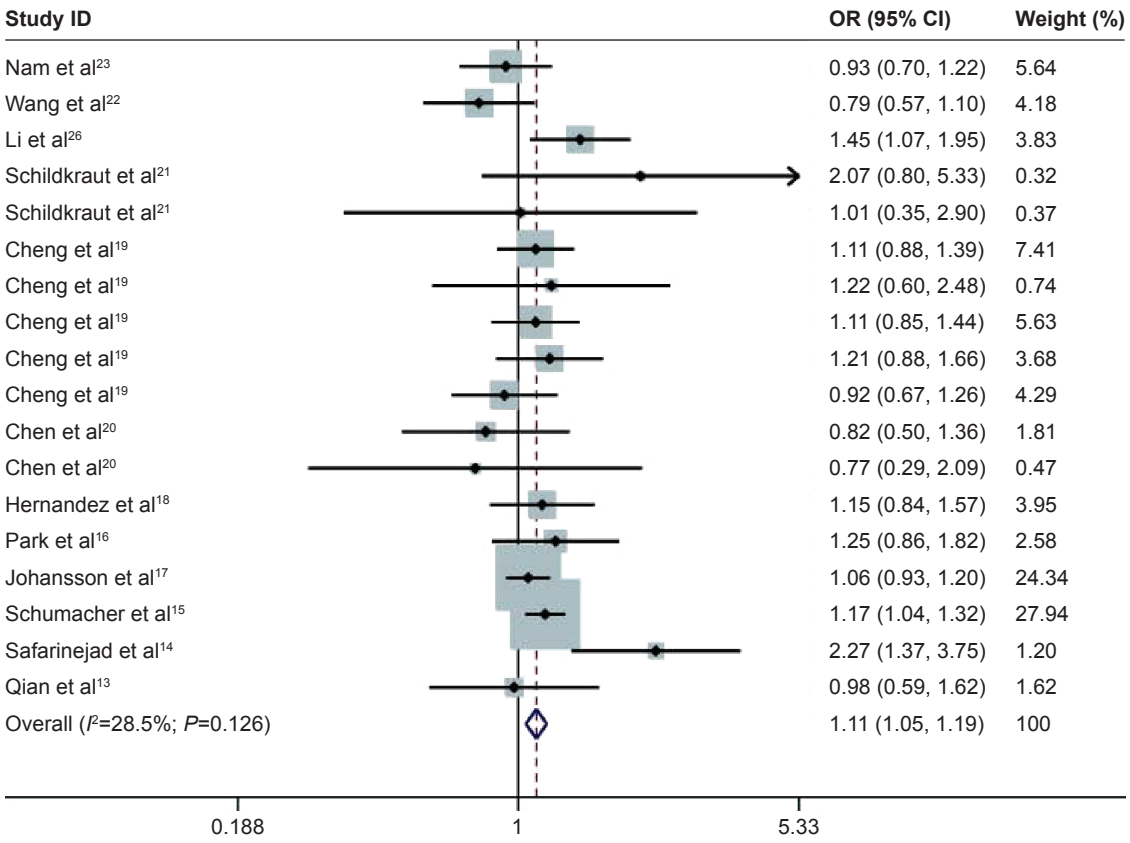

Figure 4 Forest plot of odds ratios with 95% confidence interval for *IGFBP3*-202A/C polymorphism and risk of prostate cancer risk under recessive model (CC+AC vs AA).
Abbreviations: IGFBP3, insulin-like growth factor-binding protein-3; OR, odds ratio; CI, confidence interval.

to increase the risk of PCa, but the effect was not significant. The meta-analysis by Ding et al,[24] which was based on 4,602 PCa cases and 4,880 controls from 16 case–control studies, found a significant association between *IGFBP3* A-202C polymorphisms and PCa risk. Moreover they got different conclusions about the association between *IGFBP3*-202A/C polymorphism and PCa risk in race subgroup comparisons. Mao et al[25] reported that the association of –202A/C polymorphism with PCa risk was observed only in Caucasians in the heterozygous codominant model (OR =1.14, 95% CI: 1.05–1.24). In contrast, Ding et al[24] reported that the *IGFBP3*-202A/C polymorphism was associated with a significantly decreased risk of PCa in Asians, but not in Europeans or African Americans. In addition, the meta-analysis by Mao et al[25] and Ding et al[24] both included a relatively small sample size. Our meta-analysis included the most subjects which may provide the most comprehensive evidence for association of *IGFBP3*-202A/C polymorphism with PCa risk.

In our meta-analysis, with the most PCa cases and controls up to date, we found that the CC genotype of *IGFBP3*-202A/C polymorphism was associated with increased risk of PCa in homozygote comparison, dominant model, and recessive model, and the –202C allele is the risk factor for PCa. In the subgroup analysis by ethnicity, the association of *IGFBP3*-202A/C polymorphism with PCa risk was evident only in Caucasians under the recessive model (CC vs AA+AC – OR =1.10, 95% CI: 1.02–1.19). This result is in accordance to that reported by Mao et al,[25] but incongruent with Ding's study.[24] This discrepancy could result from the possible genetic differences among ethnicities, even distinct populations of the same ethnicity. In addition, the environment factors may also contribute to the discrepancy. Moreover, we realized that the Asian subgroup in our meta-analysis included more cases and controls than did the counterpart in Ding et al's study. The different sample sizes in Asian people might lead to different conclusions between our meta-analysis and that of Ding et al.

After stratification by source of controls, the association between *IGFBP3*-202A/C polymorphism and PCa risk was observed in hospital-based studies and population-based studies. Because some individuals from the control group might develop cancer in subsequent years, even if they showed no clinical symptoms at the time of investigation,

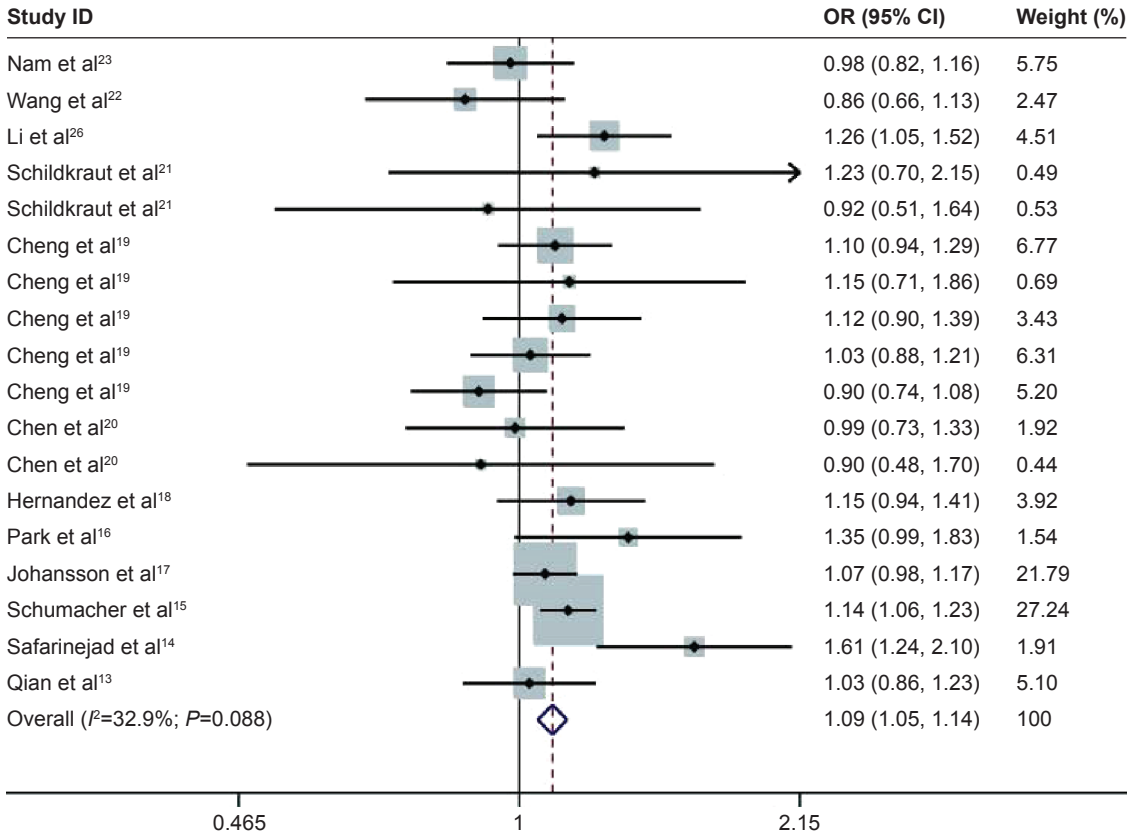

Figure 5 Forest plot of odds ratios with 95% confidence interval for *IGFBP3*-202A/C polymorphism and risk of prostate cancer risk under recessive model (C vs A).
Abbreviations: IGFBP3, insulin-like growth factor–binding protein-3; OR, odds ratio; CI, confidence interval.

and misclassification bias can cause a deviation in the genotype distribution among the controls, the results should be interpreted with caution.

In the present meta-analysis, the potential publications were systematically searched and reviewed. The reliability of the results was further confirmed by sensitivity analysis. Therefore, with the larger sample size than ever before, results from meta-analysis are solid and convincing.

However, our study had some limitations. First, our results were based on unadjusted estimates. More accurate analysis may be achieved with the adjustment of confounders such as age, body mass index, smoking status, drinking status, and environment factors.[27] Second, subgroup analyses

Table 2 Summary of odds ratios (95% confidence interval) and I^2 value for prostate cancer in *IGFBP3*-202A/C genetic model

Variables	CC vs AA		CC vs AC		CC+AC vs AA		CC vs AA+AC		C vs A	
	OR (95% CI)	**I^2 (%)**	**OR (95% CI)**	**I^2 (%)**	**OR (95% CI)**	**I^2 (%)**	**OR (95% CI)**	**I^2 (%)**	**OR (95% CI)**	**I^2 (%)**
Control sources										
HB	**1.33 (1.13–1.58)**	49.10	1.13 (0.99–1.29)	0.00	1.18 (0.96–1.46)[a]	57.10	**1.17 (1.03–1.32)**	20.00	**1.13 (1.00–1.29)[a]**	54.60
PB	**1.13 (1.04–1.22)**	0.00	1.04 (0.96–1.13)	0.00	**1.10 (1.03–1.19)**	0.00	**1.09 (1.01–1.16)**	0.00	**1.08 (1.04–1.14)**	0.00
Ethnicity										
Mixed	1.22 (0.75–1.98)[a]	73.50	1.09 (0.88–1.36)	0.00	1.15 (0.75–1.78)[a]	78.20	1.13 (0.92–1.39)	12.20	1.11 (0.86–1.42)[a]	74.90
Asian	1.27 (0.93–1.72)	31.00	1.14 (0.94–1.39)	15.00	1.02 (0.86–1.21)	20.50	1.14 (0.94–1.37)	34.50	1.06 (0.95–1.19)	38.70
African	1.25 (0.99–1.58)	0.00	1.14 (0.92–1.42)	0.00	1.14 (0.95–1.36)	0.00	1.18 (0.96–1.45)	0.00	1.12 (0.99–1.26)	0.00
Caucasian	1.14 (0.94–1.40)[a]	64.50	1.06 (0.96–1.17)	0.00	1.12 (0.94–1.32)[a]	58.10	**1.10 (1.02–1.19)**	42.90	1.10 (0.97–1.23)[a]	66.10
Hawaiian	1.31 (0.47–3.63)	NA	1.10 (0.42–2.88)	NA	1.22 (0.60–2.48)	NA	1.18 (0.47–2.95)	NA	1.15 (0.71–1.86)	NA
Latino	1.15 (0.82–1.62)	NA	0.91 (0.72–1.16)	NA	1.21 (0.88–1.66)	NA	0.97 (0.77–1.21)	NA	1.03 (0.88–1.21)	NA
Overall	**1.16 (1.08–1.25)**	28.70	1.07 (0.99–1.15)	0.00	**1.11 (1.05–1.19)**	28.50	**1.11 (1.04–1.17)**	1.10	**1.09 (1.05–1.14)**	32.90

Notes: [a]Random-effects estimate. Bold values indicate $P<0.05$, which was statistically significant.
Abbreviations: CI, confidence interval; OR, odds ratio; PB, population-based; HB, hospital-based; IGFBP3, insulin-like growth factor-binding protein-3; NA, not applicable.

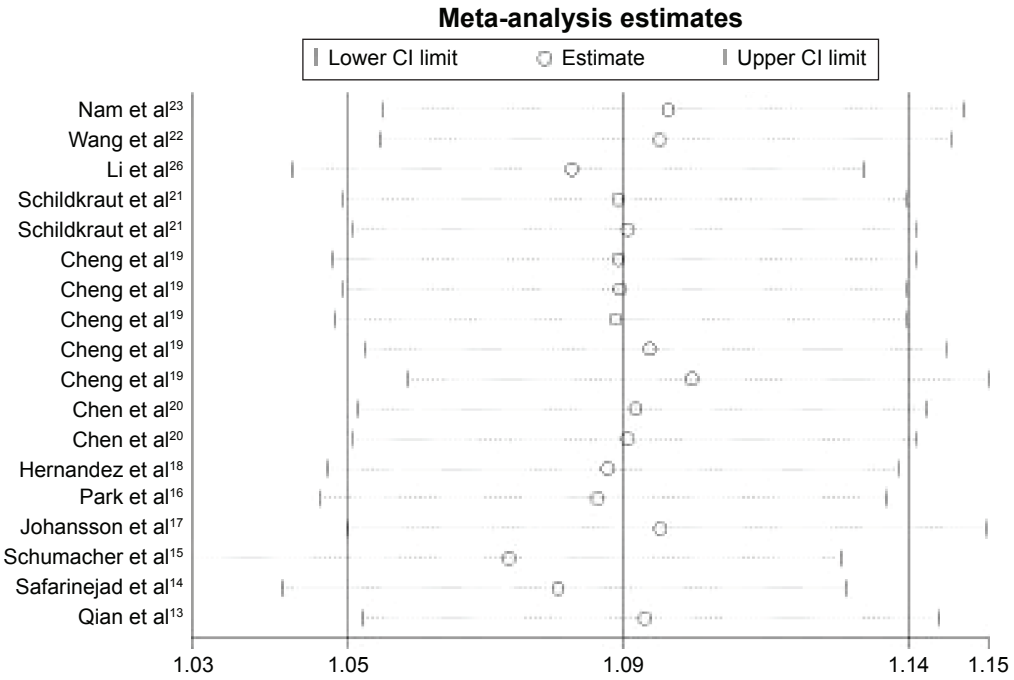

Figure 6 Summary of sensitivity analyses of the odds ratio coefficients and the association between the *IGFBP3*-202A/C polymorphism and risk of prostate cancer under allele model (A vs C).
Abbreviations: IGFBP3, insulin-like growth factor-binding protein-3; CI, confidence interval.

stratified by age, sex, and other factors were not done in the present study, because relevant data were unavailable from the primary publications for meta-analysis. Third, our analysis might overlook the possibility of gene–gene or SNP–SNP interactions or linkage disequilibrium between polymorphisms. Moreover, this gene polymorphism association has not been associated with PCa-specific mortality, which is a much more clinically useful association if it is to be used in any form of screening or general clinical risk stratification. Further investigations on the haplotype effect of a gene and the study of multiple polymorphisms in different genes within the same pathway and different pathways are expected.

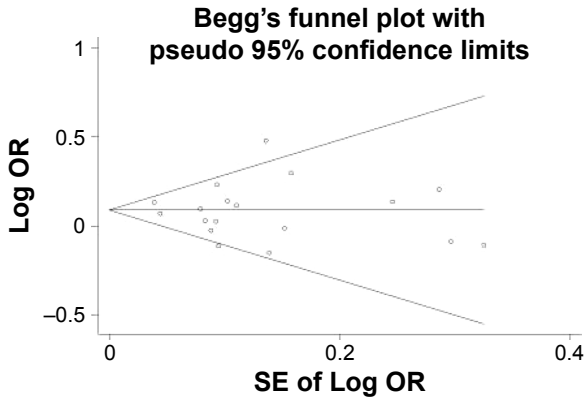

Figure 7 Publication bias represented by Begg's funnel plot for the association between the *IGFBP3*-202A/C polymorphism and risk of prostate cancer under allele model (A vs C alleles).
Note: Each point represents a separate study for the indicated association.
Abbreviations: IGFBP3, insulin-like growth factor-binding protein-3; OR, odds ratio; SE, standard error.

Conclusion

This meta-analysis suggests that *IGFBP3*-202A/C polymorphism is associated with the risk of PCa, particularly in Caucasians, suggesting that *IGFBP3*-202A/C polymorphism could be a marker for PCa development. Additional large-scale studies are warranted to provide a more definitive conclusion on the association between *IGFBP3*-202A/C polymorphism and PCa risk in distinct ethnicity populations.

Acknowledgments

This study was supported in part by the National Natural Science Foundation of China (number 81472416) and the Tianjin Municipal Science and Technology Commission (number 12ZCDZSY16600).

Disclosure

The authors report no conflicts of interest in this work.

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