RESEARCH ARTICLE

Prostate Cancer Risk in Relation to a Single Nucleotide Polymorphism in the Insulin-like Growth Factor-binding Protein-3 (IGFBP3) Gene: a Meta-analysis

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Abstract

Insulin-like growth factor-binding protein-3 (IGFBP3) has been identified as a putative tumor suppressor with multifunctional roles in the IGF axis. Recently, there have been a growing body of studies investigating the relation between the IGFBP3 A-202C polymorphism, circulating IGFBP3 and prostate cancer risk, but their outcomes varied leading to controversy. Hence, it is necessary to perform a meta-analysis covering all eligible studies to shed a light on the association of IGFBP3 A-202C and cancer risk. Finally, we included a total of 11 relevant articles between 2003 and 2010 covering 14 case-control studies including 9,238 cases and 8,741 controls for our analysis. Our results showed that A-202C was a marginal risk factor of prostate cancer (allele contrast: OR=1.08, 95% CI :1.01-1.16; dominant model: OR=1.11, 95% CI :1.01-1.22; heterozygote codominant model: OR=1.11, 95% CI :1.03-1.18; homozygote contrast: OR=1.19, 95% CI :1.03-1.37). Stratification analysis revealed that sample size and control source were two major heterogeneous meta-factors especially in the recessive model (source: Population-based control group :p=0.30,I2=16.7%, Hospital-based control group: p=0.20, I2=30.3%; sample size: Small: p=0.22,I2= 32.8%, Medium: p=0.09,I2= 48%, Large p=0.60,I2=0.0%); However, contrary to previous findings, no significance was found in racial subgroups. No significant publication bias was found in our analysis. Considering the robustness of the results and the discrepancy among some studies, there might be some unsolved confounding factors, and further more critical large studies are needed for confirmation.

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

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Introduction

As one of the most prominent public health problems in the western, prostate cancer (PCa) was estimated to have claimed 33,720 deaths in the United States in 2011, ranking the second leading cause of cancer death (Brawley, 2012). In China, PCa is more and more concerned ,for its growing incidence rate leaping from 1.6/105 PY (person per year) in 2002 to 4.3/105 PY in 2008 (Zhang et al., 2011). Although increasing risk factors such as age, family history of the disease, and race/ethnicity have been identified , the etiology of prostate cancer is still complex and elusive.

One of the factors involved is insulin-like growth factor binding protein-3 (IGFBP3), which regulates IGFs bioavailability to facilitate or inhibit IGF—IGF receptor interaction via binding to circulating IGFs (Collett-Solberg et al., 1996; Kelley et al., 1996). Some studies have demonstrated that decreased circulating IGFBP3 concentration portends higher cancer risk including breast, colorectal, lung and gastric cancer (Hankinson et al., 1998; Ma et al., 1999; Yu et al., 1999; Pham et al., 2007), and the individual variation of gene expression level may largely be attributed to genetic factors. IGFBP3 A-202C polymorphisms, an A-C transversion which is located 202 bp upstream of the transcription start site of IGFBP3, has been confirmed to be associated with basal promoter activity both in vitro and in vivo (Rohrbacher et al., 2005; Wagner et al., 2005), The [A] possessing stronger promoter activity yields higher IGFBP3 gene expression, while the [C] allele or A-202C leads to be a lower one (Deal et al., 2001; D'Aloisio et al., 2003; Costalonga et al., 2009).

Recently, more and more studies have focused on A-202C polymorphism and cancer susceptibility. As for PCa, the results are conflicting. The inconsistency might come from various study design, sample size , recruitment criteria or insignificant effect of polymorphisms. Therefore, it is necessary to perform a meta-analysis reviewing all the published case-control studies to reach a more reliable conclusion on the relation between IGFBP3 A-202C polymorphisms and PCa susceptibility.

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Materials and Methods

Literature search

All the publications until Sep.20 2012 in PubMed, Scopus, Web of Science and Chinese National Knowledge Infrastructure (CNKI) were identified with the search terms'IGFBP3' or 'insulin-like growth factor-binding protein-3', 'polymorphism','variants', 'variation' and 'prostate' with restriction of 'Human'. The potentially associated articles as well as their bibliographies were read in full text or abstract to assess the appropriateness.

Inclusion criteria

The eligible studies should be case-control ones pertaining to IGFBP3 A-202C polymorphisms and PCa, with sufficient data for odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI) calculation. All the eligible studies with full text articles were retrieved.

Data extraction

The following data were carefully extracted from every identified article independently by two authors including: first author's name, publication year, ethnicity, subject source, number of cases and controls, IGFBP3 A-202C genotypes distribution frequency. Necessary data for calculation in two articles were retrieved by email, if omitted by the authors . Ethnicity covered in this paper was classified as 'Caucasian', 'Asian', and 'Mixed' which could be further divided in subgroup analysis. Population-based and hospital-based studies were two kinds of subject source.

Statistical analysis

For the meta-analysis, association between IGFBP3 A-202C and PCa risk was demonstrated with pooled OR ±95% confidence intervals (CI) ,based upon A-202C genotype distribution and allele frequency in each case and control. The fixed-effects model (the Mantel-Haenszel method) or the random effects model (the DerSimonian and Laird method) was selected to calculate the pooled OR, according to Q-statistic and further I2 metric in heterogeneity test (Lau et al., 1997; Higgins et al., 2002); if a significant heterogeneity between studies was found ($P<0.10$), random effects model was employed for the pooled OR calculation (Mantel et al., 1959; DerSimonian et al., 1986). The overall associations in every genetic model (dominant model, recessive model, heterozygote codominant model, allele contrast and homozygote contrast) were also examined by pooled odds ratio (ORs, 95% CI). Subgroup analysis was used to investigate the possible factor contributing to heterogeneity . Sensitivity analysis was performed by calculating the pooled ORs in the absence of every single study to indicate that study's influence on overall results (Tobias, 1999). Publication bias was presented as funnel plots and assessed by Egger's and Begg's linear regression tests (Egger et al., 1997). Hardy-Weinberg equilibriums (HWE) of genotype distribution in all the control groups were performed by chi-square test. All the statistical analyses were performed through Stata software (Stata Corporation, College Station, TX).

Results

Summary statistics

Figure 1 presents the flowchart showing selection and identification process of eligible studies with specific reasons. A total of 11 case-control studies focusing on relation between IGFBP3 A-202C polymorphism and PCa susceptibility between 2003 and 2010, with 9,238 cases and 8,741 controls, were finally included. The sample sizes between studies varied widely ranging

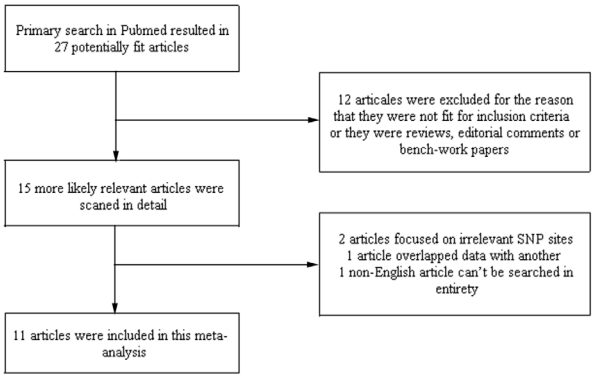

Figure 1. The Flowchart for Article Screening

Table 1. Main Characteristics for All Eligible Studies

Author	Year	Ethnicity	Control source	Genotyping meathod	Sample size	Case no.	Control no.	P_{HWE}
Nam	2003	Mixed	HBC	RFLP	Large	483	548	0.98
Wang	2003	Asian	HBC	RFLP	Medium	307	272	0.57
Li	2004	Mixed	PBC	RFLP	Medium	440	479	0.21
Schildkraut	2005	Mixed	HBC	RFLP	Small	100	92	0.3
Chen	2006	Mixed	HBC	RFLP	Small	213	213	0.69
Cheng	2006	Asian	PBC	RFLP	Medium	455	466	0.99
Cheng	2006	Caucasian	PBC	RFLP	Medium	451	444	0.16
Cheng	2006	Afriacan	PBC	RFLP	Large	666	642	0.24
Cheng	2006	Hawaiian	PBC	RFLP	Small	70	67	0.81
Hernandez	2007	Caucasian	HBC	RFLP	Medium	401	366	0.79
Park	2009	Asian	HBC	RFLP	Small	225	225	0.74
Johansson	2009	Caucasian	PBC	QPCR	Large	2633	1715	0.35
Schumacher	2010	Caucasian	PBC	RFLP	Large	2626	2876	0.15
Safarinejad	2011	Caucasian	HBC	RFLP	Medium	168	336	0.59

HCC, hospital-based case-control; PCC, population-based case-control; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; q PCR, quantitative polymerase chain reaction; HWE, Hardy-Weinberg equilibrium

Table 2. IGFBP3 A-202C Genotype Distribution and Allele Frequency in Cases and Controls

	Case Genotypes (N,%)			Control Genotypes (N,%)			Allele frequency (N,%)			
	AA	AC	CC	AA	AC	CC	Case A	Case C	Control A	Control C
Nam 2003	135(28)	115(24)	233(48)	145(26)	129(24)	274(50)	503(52)	463(48)	564(51)	532(49)
Wang 2003	189(62)	18(6)	100(33)	152(56)	15(6)	105(39)	478(78)	136(22)	409(75)	135(25)
Li 2004	97(22)	126(29)	217(49)	139(29)	115(24)	225(47)	411(47)	469(53)	503(53)	455(47)
Schildkraut 2005	18(18)	27(27)	55(55)	23(25)	28(30)	41(45)	91(46)	109(55)	87(47)	97(53)
Chen 2006	55(26)	67(31)	91(43)	47(22)	63(30)	103(48)	201(47)	225(53)	197(46)	229(54)
Cheng 2006-Af	217(33)	308(46)	141(21)	224(35)	298(46)	120(19)	742(56)	590(44)	746(58)	538(42)
Cheng 2006-C	103(23)	220(49)	128(28)	95(21)	205(46)	144(32)	426(47)	476(53)	395(44)	493(56)
Cheng 2006-As	264(58)	161(35)	30(7)	282(61)	161(35)	23(5)	689(76)	221(24)	725(78)	207(22)
Cheng 2006-H	22(31)	36(51)	12(17)	24(36)	33(49)	10(15)	80(57)	60(43)	81(60)	53(40)
Hernandez 2007	112(28)	93(23)	196(49)	113(31)	70(19)	183(50)	420(52)	382(48)	409(56)	323(44)
Park 2009	128(57)	21(9)	76(34)	140(62)	9(4)	76(34)	332(74)	118(26)	356(79)	94(21)
Johansson 2009	891(34)	439(17)	1303(49)	603(35)	300(17)	812(47)	3085(59)	2181(41)	2018(59)	1412(41)
Schumacher 2010	724(28)	556(21)	1346(51)	888(31)	602(21)	1386(48)	2794(53)	2458(47)	3162(55)	2590(45)
Safarinejad 2011	23(14)	60(36)	85(51)	89(26)	84(25)	163(49)	131(39)	205(61)	341(51)	331(49)

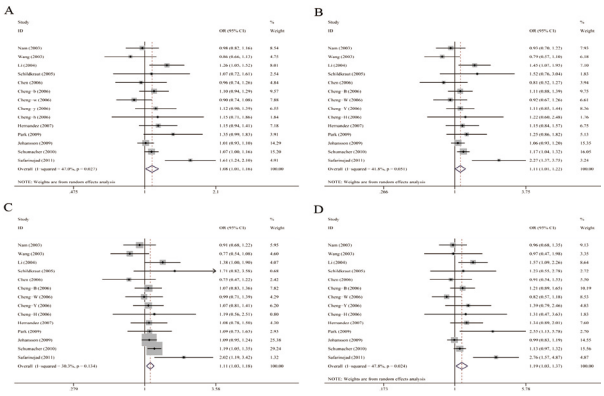

Figure 2. Forest Plots of Cancer Risk Associated with IGFBP3 A-202C Polymorphism in Different Genetic Models (A. allele contrast, B. dominant model, C. codominant model, D. homozygote contrast). The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (CI). The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI

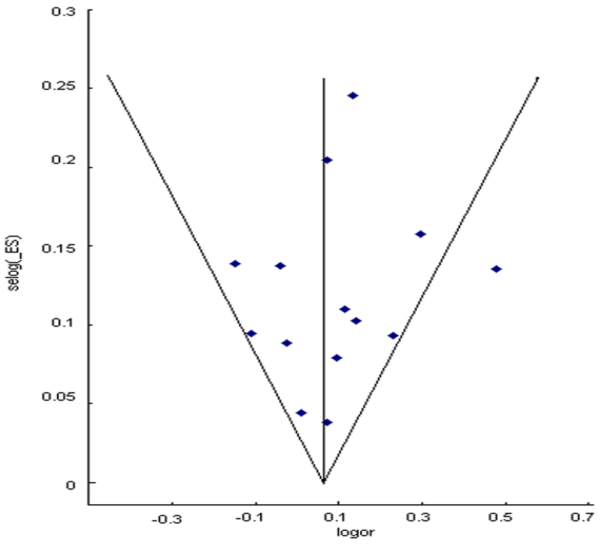

Figure 3. Funnel Plot for IGFBP3 A-202C Polymorphism and Cancer Risk

from approximately 100 to 5000, so we further classified them as follows: 'Small' denoted studies with numbers less than 500,'Medium'for those between 500 and 1000 and'Large'for those more than 1000. For ethnicity, there were 4 studies of Caucasian, 2 Asian and 5 mixed populations. Three articles with duplication on sample group and irrelevant IGFBP3 polymorphism sites were therefore excluded (Friedrichsen et al., 2005; Hoyo et al., 2007; Sarma et al., 2008). The main characteristics of the selected articles were all listed in Table 1. Basically, all the controls (n =8,741) were in consistent with HWE (p>0.05), except for one study which contained a minority subgroup with disequilibrium (Cheng et al., 2003).Then, it was treated as four racial subdivisions independently but rather as a whole for analysis, due to the specialty of MEC (the Multiethnic Cohort study) (Kolonel et al., 2000).

Main results

Table 2 showed both case and controls' genotypes distribution and allele frequency of every available study in the form of number and percentage. By intuitive judgment, we found a slightly favorable distribution of [A] allele and [AA] genotype for the controls, and a similar trend of [C]/[CC] for the cases .Table 3.indicated the main result of this meta-analysis. When all the 14 studies were pooled together, a moderate heterogeneity was revealed in the allele contrast and every genetic model (allele contrast: Q-statistic p= 0.03, I^2= 47.0%; dominant model: *p*= 0.05, I^2= 41.8%; recessive model: *p*= 0.12, I^2= 31.5%; heterozygote codominant model: *p*= 0.13, I^2= 30.3%; homozygote contrast: *p*= 0.02, I^2= 47.8%). The pooled calculation (Figure 2) by random-effects model resulted in significant influence of A-202C polymorphism on cancer risk across all the genetic models except the recessive one (allele contrast: OR=1.08, 95% CI :1.01-1.16; dominant model: OR=1.11, 95% CI :1.01-1.22; heterozygote codominant model: OR=1.11, 95% CI :1.03-1.18; homozygote contrast: OR=1.19, 95% CI :1.03-1.37).

To explore the source of heterogeneity, we performed subgroup analyses stratified by control source, sample size and ethnicity respectively. The stratification analysis identified both 'Control source' and 'Sample size' as two major heterogeneous meta-factors especially in the recessive model (source: PBC: p=0.30,I2=16.7%, HBC: *p*=0.20, I^2=30.3%; size: Small: *p*=0.22, I^2= 32.8%, Medium: *p*=0.09, I^2= 48%, Large *p*=0.60, I^2=0.0%); the

'Ethnicity' is another factor especially in the heterozygote codominant model (African : p= 0.41, I^2=0.0%, Caucasian: p=0.13, I^2=41.0%, Asian: p=0.27, I^2=23.0%) as well as in the recessive model. By stratification, significant associations between A-202C and cancer risk were found mainly within 'population-based control' group (allele contrast: OR=1.06, 95% CI : 1.01-1.11; dominant model: OR=1.13, 95% CI : 1.05-1.21; heterozygote codominant model: OR=1.13, 95% CI : 1.05-1.22; homozygote contrast: OR=1.11, 95% CI : 1.00-1.22), and 'large' sample group (allele contrast: OR=1.07, 95% CI : 1.02-1.11; dominant model: OR=1.10, 95% CI : 1.02-1.19; heterozygote codominant model: OR=1.11, 95% CI :1.03-1.21). In the race subgroup, the association was only found in Caucasians in the heterozygote codominant model (OR=1.14, 95% CI : 1.05-1.24).

Other results

To examine the publication bias, Begg's and Egger's tests for the alleles comparison were performed with a Begg's funnel plot (Figure 3) provided for visual judgment. Both tests revealed no publication bias in this analysis (Begg's z=0.44 p=0.66, Egger's t=0.84 p=0.42), and no significant asymmetry was found in the funnel plot. To explore whether the ORs were sufficiently robust under various genetic model and contrasts, the sensitivity tests were performed where the remaining studies were pooled after every single one was deleted; The results showed that none of the studies could considerably affect the overall risk estimates in our meta-analysis (data were not shown).

Discussion

This meta-analysis including 9,238 cases and 8,741 controls represents the largest study to date investigating the association between IGFBP3 A-202C polymorphisms and PCa susceptibility as far as we know. Our results revealed that C allele/[CC] genotype were slightly more frequent than A allele/[AA] genotype at IGFBP3 A-202C SNP site and A-202C is a potential risk factor for PCa, which was especially more prominent within 'population-based control' and 'large' subgroups with negligible heterogeneity. This finding is generally in line with some former reports, but in discrepancy with Li's result derived from a smaller sample size and a sole stratification (Li et al., 2010). An increased cancer risk of C allele carriers among the PBC groups but rather among HBC ones could be attributed to suboptimal representativeness of hospital controls with potential disease conditions involving the SNP polymorphisms under investigation and potential biases producing significant heterogeneity. One available population-based study including 2,626 cases and 2,876 controls screened from seven well-established cohort studies as the largest weight in our analysis swayed the overall calculation to some extent (Schumacher et al., 2010). Hence, a large population-based control is more reliable in meta-analysis. For race stratification, we didn't find any regular genotype distribution or association between different races especially in Africans

Despite a comprehensive study with substantial data and insignificant publication bias, there were still some limitations in our study: First, heterogeneity of various levels existed among most subgroups and genetic models, which meant some heterogeneity factors were yet to be analyzed. One of the reasons might come from inconformity of raw data that should be adjusted by age, smoking status, drinking status, obesity, and environmental/lifestyle factors. Second, unavailable details of race sub-distribution in two studies prevented themselves from inclusion for subgroup analysis, which lead to insufficient samples in Africans and Asians subgroups compared with Caucasians (Nam et al., 2003; Li et al., 2004). Besides, it should be noteworthy that our conclusion actually owed much to Safarinejad's report (Safarinejad et al., 2011) with the most prominently positive result of all. While most other included studies yielded insignificant results, which meant our conclusion was seemingly less robust. Recently, it has been reported that IGFBP3 as a multifunctional anti-proliferative protein gets involved in benign prostatic hyperplasia (BPH) development in a similar way with PCa (Neuhouser et al., 2008; Safarinejad et al., 2011), suggesting that it was possible for some BPH cases to be improperly grouped as controls, not to mention the asymptomatic or underdiagnosed PCa cases. On the other hand, the widely accepted hypothesis that circulating concentration of IGFBP3 runs inversely with PCa risk has been more and more challenged by case-control studies (Severi et al., 1999; Li et al., 2004; Hong et al., 2008). Recently, one study has focused on intracellular level of instead of circulating level of IGFBP3 and identified a high expression of IGFBP3 in nucleus as a poor prognostic biomarker (Seligson et al., 2012). If it is further strengthened, the significance of IGFBP3 A-202C should be re-defined.

In conclusion, our meta-analysis indicated that there is a marginal association between IGFBP3 A-202C polymorphisms and PCa risk. However, further studies using well-defined large-scale controls, adjusted data should be carried out critically with more detailed stratifications. Only in this way, a more comprehensive and insightful understanding of the IGFBP3 A-202C polymorphism could be obtained.

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