RESEARCH COMMUNICATION

P53 Arg72Pro Polymorphism and Bladder Cancer Risk - Meta-analysis Evidence for a Link in Asians but not Caucasians

Ting Xu[1&], Zi-Cheng Xu[1&], Qin Zou[1], Bin Yu[1], Xin-En Huang[2*]

Abstract

Objective: Individual studies of the associations between P53 codon 72 polymorphism (rs1042522) and bladder cancer susceptibility have shown inconclusive results. To derive a more precise estimation of the relationship, we performed this systemic review and meta-analysis based on 15 publications. Methods: We used odds ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of the association. Results: We found that there was no association between P53 codon 72 polymorphism and bladder cancer risk in the comparisons of Pro/Pro vs Arg/Arg; Pro/Arg vs. Arg/Arg; Pro/Pro plus Pro/Arg vs. Arg/Arg; Arg/Arg vs. Pro/Arg plus Arg/Arg (OR=1.06 95%CI 0.81-1.39; OR=1.06 95%CI 0.83-1.36; OR=0.98 95%CI 0.78-1.23; OR=1.06 95%CI 0.84-1.32). However, a significantly increased risk of bladder cancer was found among Asians in the homozygote comparison (Pro/Pro vs. Arg/Arg, OR=1.36 95%CI 1.05-1.75, P=0.790 for heterogeneity) and the dominant model (Arg/Pro plus Pro/Pro vs. Arg/Arg, OR=1.26 95%CI 1.05-1.52, P=0.564 for heterogeneity). In contrast, no evidence of an association between bladder cancer risk and P53 genotype was observed among Caucasian population in any genetic model. When stratifying for the stage of bladder, no statistical association were found (Pro/Pro vs. Arg/Arg, OR=0.45 95%CI 0.17-1.21; Pro/Arg vs. Arg/Arg, OR=0.60 95%CI 0.28-1.27; Dominant model, OR=0.56 95%CI 0.26-1.20; Recessive model, OR=0.62 95%CI0.35-1.08) between P53 codon 72 polymorphism and bladder cancer in all comparisons. Conclusions: Despite the limitations, the results of the present meta-analysis suggest that, in the P53 codon 72, Pro/Pro type and dominant mode might increase the susceptibility to bladder cancer in Asians; and there are no association between genotype distribution and the stage of bladder cancer.

Keywords: P53 codon 72 - bladder carcinoma - meta-analysis - polymorphism - susceptibility

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Introduction

An estimated 386,300 new cases of urinary bladder cancer were diagnosed and 1,520,200 deaths in 2008 worldwide (Jemal et al., 2010). Urinary bladder cancer ranks ninth in worldwide cancer incidence. Risk factors for the development of bladder cancer could be classified into three types: chemical or environment exposure, genetic and molecular abnormalities, and chronic irritation (Williams et al., 2004; Bryan et al., 2005; Kaufman et al., 2009). However, the genetic factors determine the progression to bladder cancer remain to be investigated. The most common type of bladder cancer is transitional cell carcinoma (TCC), which accounts for 90%. Approximately 70% of newly detected cases are exophytic papillary tumors confined largely to the mucosa (Ta) (70%) or, less often, to the submucosa (T1) (30%) (Herr et al., 2001). 10%-20% of those superficial tumors will progress to muscularies propria invasive bladder cancer. Bladder carcinogenesis and progression from non-muscle-invasive type to muscle-invasive type are complex, multistep and multifactor processes, in which genetic factors affect mostly. Tumor suppressor gene P53 is involved in the development and progression of bladder cancer.

The P53 gene located at 17p13, is a prototypical tumor suppressor gene encoding a 53 kDa protein (P53) with important functions in cell cycle control, apoptosis, and maintenance of DNA integrity (Sager et al., 1989; Levine et al., 1997; Xu et al., 2001). The function of P53 is to reduce the incidence of cancers by mediating apoptosis in cells. That has activated oncogenic pathways. DNA damage or genotoxic stress may case the induction of P53, leading to growth arrest or apoptosis(Meek et al., 2004). Although P53 contains several polymorphic sites, the codon 72 polymorphism located on exon 4 is the most common candidate gene. The polymorphism consists of a single base pair change of either arginine (Arg, CGC) or proline (Pro, CCC), which creates three distinct genotypes, including homozygous for arginine (Arg/Arg), homozygous for proline (Pro/Pro) and heterozygote (Pro/Arg) (Klug et al., 2009).

Bulks of epidemiologic studies have addressed the influence of this polymorphism on cancer risk for most common cancer types, including bladder cancer. However,

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small sample sizes and deficiencies in study design might contribute to the conflicting results. To conduct a comprehensive evaluation of the potential association of the P53 codon 72 polymorphism (rs1042522) and bladder cancer susceptivity, we perform this systemic review and meta-analysis of candidate genetic association studies.

Materials and Methods

Literature search strategy

PUBMED, Embase databases were searched to retrieve papers linking P53 codon 72 polymorphism and bladder cancer risk available up to January 2012, using the following keywords: 'P53', 'Polymorphism', 'single nucleotide polymorphism', 'bladder cancer', 'bladder neoplasm' and 'bladder tumor' separately and combined. The research was restricted on human subjects only. We also hand-searched the reference lists for all retrieved studies and relevant review articles for additional data. We only considered studies published in English.

Inclusion and exclusion criteria

Studies using an analytic design (case-control, nested case-control, or cohort) and employing validated genotyping methods to examine the frequency of rs1042522 among bladder cancer patients and controls were eligible for inclusion. Studies should include sufficient genotype data for analysis. Case reports, letters, reviews and editorial articles were excluded. When there was overlapping study population, only the mostly published study was included. Family-based studies were not considered eligible owing to different design considerations.

Data Extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Xu T and Xu ZC) to populate files with the necessary information. The following information was extracted from each of the included articles: first author's surname, year of publication, country of origin, ethnicity, source of control and case groups, genotyping methods, total number of cases and controls, and detailed numbers of Arg/Arg, Arg/Pro and Pro/Pro genotype respectively. Disagreement was resolved by consensus with a third reviewer (Yu B).

Statistic analysis and Publication bias

For our main analysis, the following contrasts for P53 codon 72 polymorphism were evaluated: co-dominant model (homozygote comparison Arg/Arg vs. Pro/Pro, heterozygote comparison Arg/Pro vs. Pro/Pro), dominant model (Arg/Pro plus Pro/Pro vs. Arg/Arg) and recessive model (Arg/Arg plus Arg/Pro vs. Pro/Pro). All associations were presented as odds ratios (OR) with their corresponding 95% confidence intervals (95%CI). Subgroup analyses were conducted on the basis of ethnic group, source of control, genotyping methods, and tumor stage. Between-study heterogeneity was tested using the X2-based Q-test. We separately used random-effects and fixed-effects models to analyze the data for accessing the stability of the results (Mantel et al., 1959; DerSimonian et al., 1986). We also tested whether genotype frequencies of controls were in Hardy-Weinberg equilibrium (HWE) using the chi-square test.

All statistic analyses were carried out using stata software, vision 11.0 (Stata corporation, College Station, TX, USA). To ensure the reliability and the accuracy of the results, two reviewers (Xu T and Xu ZC) inputted the data in statistic software programs independently and obtained the same results. The study group has enough experience in conducting oncological researches, and has published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Publication bias was investigated by Begg's funnel plot, and funnel polt asymmetry was assessed by the Egger linear regression test (Egger et al., 1997); statistical significance was considered when the P value of the Egger test was < 0.05.

Table 1. Characteristics of Studies that Investigated the Association Between TP53 Codon 72 and Cancer Risk

First author	Year	Source Of control	Genotyping method	Ethnicity	No. of case	No. of control	case			control			HWE
							Arg/Arg	Pro/Arg	Pro/Pro	Arg/Arg	Pro/Arg	Pro/Pro	
Zhang	2011	HCC	PCR-RFLP	Asian	120	120	37	59	24	55	47	18	0.141
Santos	2009	PCC	PCR-RFLP	Caucasian	94	159	64	24	6	90	60	9	0.8075
Lin	2011	PCC	PCR-RFLP	Asian	127	427	27	84	16	125	228	74	0.0849
Srivastava	2011	PCC	PCR-RFLP	Caucasian	200	265	103	93	4	141	106	18	0.7478
Pandith	2010	HCC	PCR-RFLP	Caucasian	108	138	22	68	18	59	53	26	0.0295
Ye	2008	PCC	PCR-RFLP	Caucasian	615	598	390	186	39	390	156	52	0.0001
Horikawa	2008	HCC	PCR	Asian	227	266	73	118	36	93	136	38	0.2955
Chung	2008	HCC	PCR-RFLP	Asian	170	402	47	87	36	134	194	74	0.7969
Kuroda	2003	PCC	PCR-RFLP	Asian	112	175	38	38	36	63	77	35	0.2003
Mabrouk	2003	PCC	PCR	African	47	34	21	23	3	13	19	2	0.2538
Souitzis	2002	PCC	PCR	Caucasian	50	99	30	18	2	24	64	11	0.0014
Toruner	2001	HCC	PCR	Caucasian	121	114	43	57	21	42	55	17	0.884
Chen	2000	HCC	PCR	Asian	58	59	26	25	7	25	26	8	0.7659
Brio	2000	PCC	PCR-RFLP	Caucasian	50	145	28	18	4	71	54	20	0.0737
Wu	1995	PCC	PCR	Asian	151	56	69	60	22	26	24	6	0.8957

HCC, Hospital-based case-control; PCC, Population-based case-control; PCR, polymerase chain reaction; PCR-RFLP, restriction fragment length polymorphism

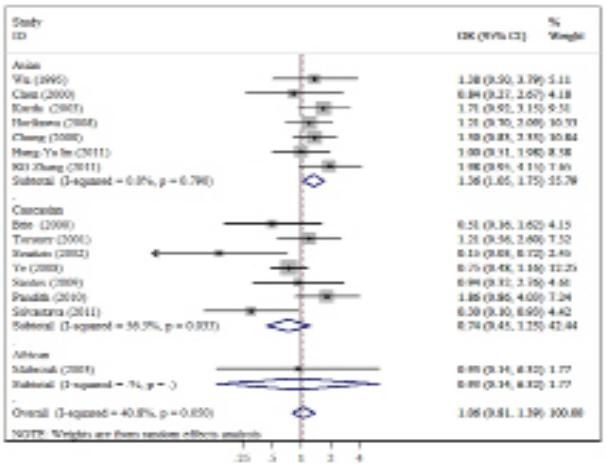

Figure 1. Forest Plots of Cancer Risk Associated with the P53 Codon 72 Polymorphisms in the Stratified Analyses by Ethnicities and Overall Cancer Risk. The plots of Pro/Pro vs. Arg/Arg were given

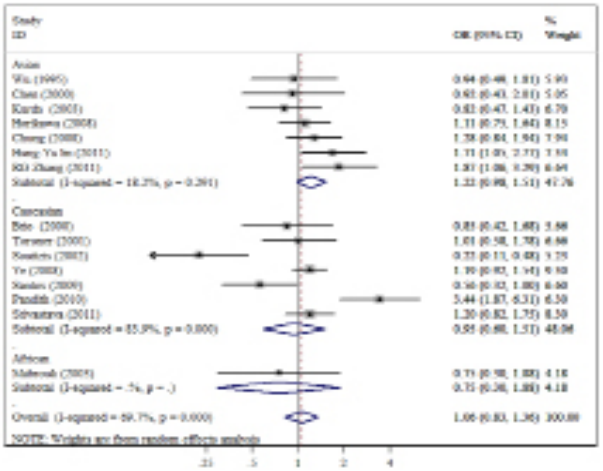

Figure 2. Forest Plots of Cancer Risk Associated with the P53 Codon 72 Polymorphisms in the Stratified Analyses by Ethnicities and Overall Cancer Risk. The plots of Pro/Arg vs. Arg/Arg were given

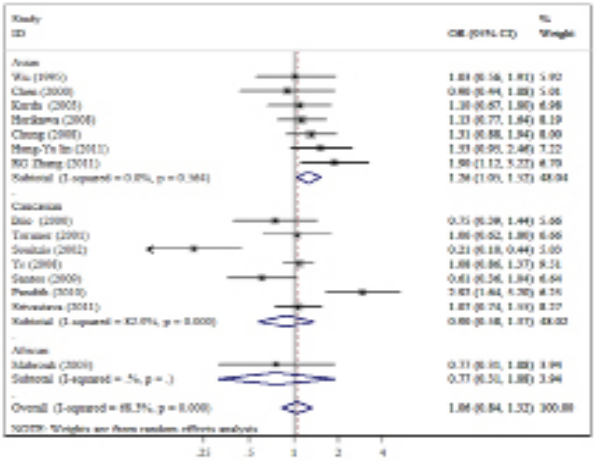

Figure 3. Forest Plots of Cancer Risk Associated with the P53 Codon 72 Polymorphisms in the Stratified Analyses by Ethnicities and Overall Cancer Risk. The plots of dominant model were given

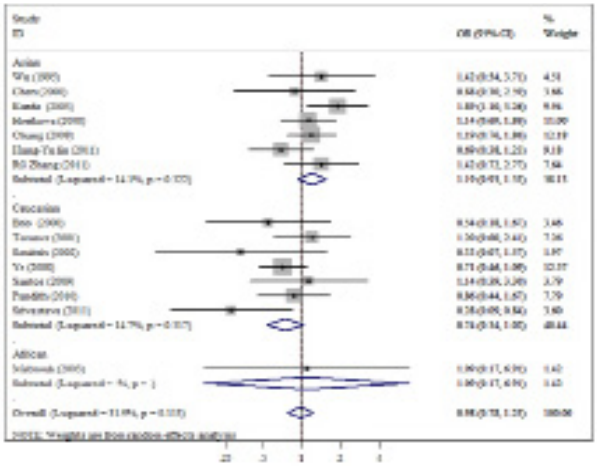

Figure 4. Forest Plots of Cancer Risk Associated with the P53 Codon 72 Polymorphisms in the Stratified Analyses by Ethnicities and Overall Cancer Risk. The plots of recessive model were given

Results

Study characteristics

According to the inclusion and exclusion criteria, 15 studies were evaluable in the meta-analysis (Wu et al., 1995; Biro et al., 2000; Chen et al., 2000; Toruner et al., 2001; Soulitzis et al., 2002; Kuroda et al., 2003; Mabrouk et al., 2003; Chung et al., 2008; Horikawa et al., 2008; Ye et al., 2008; Pandith et al., 2010; Srivastava et al., 2010; Lin et al., 2011; Santos et al., 2011; Zhang et al., 2011). The first one was published in 1995 (Wu et al., 1995) and the last in 2011 (Lin et al., 2011). Detailed study characteristics are presented in Table 1. A total of 15 studies investigated 2,250 bladder cancer cases and 3,057 controls were included in the analysis. All studies were case-control studies that evaluated the association between P53 codon 72 polymorphism and bladder cancer risk. Seven studies were conducted on Asian population, 1 was in African, and the remaining seven studies were conducted in Caucasians population. Restriction Fragment Length Polymorphism was performed in 9 publications, polymerase chain reaction (PCR) was performed in the remaining 6 studies. The distribution of genotypes in the controls of all studies was consistent with HWE except for three studies (Soulitzis et al., 2002; Ye et al., 2008; Pandith et al., 2010) (Pandith et al., P=0.0295; Ye et al., P=0.0001; Souitzis et al., P=0.0014).

Meta-analysis results

A summary of the meta-analysis findings of the association between P53 codon 72 polymorphism and bladder cancer is listed in Table 2. Meta-analytic results showed that there was no association between P53 codon 72 polymorphism and bladder cancer risk in the comparisons of Pro/Pro vs Arg/Arg; Pro/Arg vs. Arg/Arg; Pro/Pro plus Pro/Arg vs. Arg/Arg; Arg/Arg vs. Pro/Arg plus Arg/Arg (OR=1.06 95%CI 0.81-1.39; OR=1.06 95%CI 0.83-1.36; OR=0.98 95%CI 0.78-1.23; OR=1.06 95%CI 0.84-1.32; Table 2) (Figure1-4).

In the stratified analyses by ethnicity, source of control, genotyping methods, the results are also shown in Table2. A significantly increased risk of bladder cancer was found among the Asians in the homozygote comparison (Pro/Pro vs. Arg/Arg, OR=1.36 95%CI 1.05-1.75, P=0.790 for heterogeneity) and the dominant model (Arg/Pro plus Pro/Pro vs. Arg/Arg, OR=1.26 95%CI 1.05-1.52, P=0.564

Table 2. The Main Results of the Meta-analysis of p53 Arg72Pro Polymorphism and Bladder Carcinoma Risk

	No.	Pro/Pro vs. Arg/ Arg			Pro/Arg vs. Arg/ Arg			Dominant model			Recessive model		
	studies	OR (95%CI)	P*	I^2(%)	OR (95%CI)	P*	I^2(%)	OR (95%CI)	P*	I^2(%)	OR (95%CI)	P*	I^2(%)
Random model													
All studies	15	1.06(0.81, 1.39)	0.05	40.8	1.06(0.83,1.36)	0.000	69.7	0.98(0.78,1.23)	0.13	31.9	1.06(0.84,1.32)	0.000	68.3
Race													
Asian	7	1.36(1.05, 1.75)	0.790	0.0	1.22(0.98,1.51)	0.291	18.2	1.26(1.05,1.52)	0.564	0.0	1.19(0.93,1.53)	0.322	0.0
Caucasian	7	0.74(0.45, 1.23)	0.033	56.3	0.95(0.60,1.51)	0.000	83.9	0.90(0.58,1.37)	0.000	82.9	0.74(0.54,1.02)	0.317	82.9
Control source													
HCC		1.39(1.06, 1.84)	0.772	0.0	1.42(1.00,2.03)	0.021	62.5	1.13(0.89,1.45)	0.927	0.0	1.41(1.03,1.91)	0.046	55.7
PCC		0.81(0.33, 1.22)	0.056	47.2	0.87(0.63,1.20)	0.001	71	0.82(0.55,1.25)	0.030	52.8	0.87(0.65,1.16)	0.001	68.3
Detecting method													
PCR-FLFP		1.09(0.77, 1.55)	0.031	52.6	1.26(0.95,1.66)	0.001	68.4	0.93(0.67,1.28)	0.026	54.0	1.22(0.96,1.57)	0.004	64.5
PCR		0.99(0.62, 1.58)	0.241	25.8	0.77(0.49,1.20)	0.013	65.2	1.09(0.78,1.52)	0.729	0.0	0.78(0.49,1.24)	0.004	70.6
Fixed model													
All studies	12	1.16(0.93,1.45)	0.341	10.6	1.10(0.95,1.28)	0.170	28.0	1.08(0.89,1.31)	0.179	27.0	1.11(0.96,1.28)	0.253	19.4
Race													
Asian	7	1.36 (1.05, 1.75)	0.790	0.0	1.23(1.01, 1.49)	0.291	18.2	1.27(1.06, 1.52)	0.564	0.0	1.19(0.95, 1.48)	0.322	14.1
Caucasian	4	0.71(0.44, 1.14)	0.200	35.3	0.95(0.73, 1.22)	0.181	38.5	0.90(0.71, 1.15)	0.320	14.4	0.75(0.48, 1.17)	0.126	47.6
Control source													
HCC	7	1.16(0.93,1.45)	0.749	0.0	1.22(0.97,1.52)	0.499	0.0	1.24(1.01,1.53)	0.424	0.0	1.19(0.91,1.55)	0.963	0.0
PCC	5	0.98(0.71,1.37)	0.171	37.7	1.02(0.83,1.25)	0.103	43.2	1.01(0.83,1.23)	0.260	22.2	0.96(0.71,1.29)	0.031	56.7
Detecting method													
PCR-FLFP	7	1.16(0.88,1.52)	0.066	49.2	1.16(0.96,1.39)	0.032	56.6	1.15(0.97,1.37)	0.053	51.8	1.04(0.82,1.33)	0.024	58.8
PCR	5	1.17(0.80,1.71)	0.974	0.0	1.01(0.70,1.30)	0.952	0.0	1.04(0.81,1.33)	0.943	0.0	1.15(0.82,1.63)	0.978	0.0

Dominant model, Pro/Pro+ Pro/Arg vs. Arg/ Arg; Recessive model, Arg/ Arg vs. Pro/Arg + Arg/ Arg; P*,value of Q-test for heterogeneity

Table 3. Stratified Analyses of TP53 Codon 72 Polymorphism on Bladder Cancer (Stratified by stage of bladder cancer)

	No.	Pro/Pro vs. Arg/ Arg			Pro/Arg vs. Arg/ Arg			Dominant model			Recessive model		
	studies	OR (95%CI)	P*	I^2(%)	OR (95%CI)	P*	I^2(%)	OR (95%CI)	P*	I^2(%)	OR (95%CI)	P*	I^2(%)
superficial vs. invasive	6	1.06(0.81,1.39)	0.05	40.8	0.60(0.28,1.27)	0.002	73.0	0.56(0.26,1.20)	0.001	77.3	0.62(0.35,1.08)	0.203	30.9

for heterogeneity) (Figure1, 3). Nevertheless, no evidence of an association between bladder cancer risk and P53 genotype was observed among Caucasian population in any genetic model. A marked increased risk was also observed by hospital-based studies in all genetic model (Pro/Pro vs. Arg/Arg, OR=1.39 95%CI 1.06-1.84; Pro/Arg vs. Arg/Arg, OR=1.42 95%CI 1.00-2.03; Dominant model, OR=1.24 95%CI 1.01-1.53; Recessive model, OR=1.41 95%CI 1.03-1.91).

When stratifying for the stage of bladder, no statistical association were found (Pro/Pro vs. Arg/Arg, OR=0.45 95%CI 0.17-1.21; Pro/Arg vs. Arg/Arg, OR=0.60 95%CI 0.28-1.27; Dominant model, OR=0.56 95%CI 0.26-1.20; Recessive model, OR=0.62 95%CI 0.35-1.08) between P53 codon 72 polymorphism and bladder cancer in all comparisons (Table 3).

We assessed the source of heterogeneity and we found there were three studies (Chen et al., 2000; Soulitzis et al., 2002; Ye et al., 2008) whose controls deviated from Hardy-Weinberg equilibrium were the main origin of heterogeneity. After excluding the three investigations, the heterogeneity was effectively decreased and the crude ORs were still stable, all the comparisons were performed under both random-effects model and fixed-effects model; as shown in Table 2.

Publication bias

The publication bias of the meta-analysis of the association between P53 codon 72 polymorphism and bladder cancer risk was detected by Begg's test and Egger's test. All graphical funnel plots of the included studies appeared to be symmetrical. The Egger test also showed that there was non-significance in all evaluation of publication bias ($P > 0.05$). Information concerning the Egger publication bias test is given in figure.

Discussion

Many studies have investigated the association between P53 codon 72 polymorphism and bladder cancer risk in the last two decades, but the results were inconclusive. Soulitzis et al. (2002) found individuals harboring the Arg/Arg genotype have an increased risk ($P < 0.00002$; OR=4.69 95%CI 2.13-10.41) of developing bladder cancer in whites. But Zhang et al.' (2011) research data suggest that P53 codon 72 Arg/Arg genotype and Arg allele are associated with a lower risk (P=0.02, OR=0.53 95%CI 0.31-0.89) of bladder cancer in Asian population.

The polymorphism of TP53 codon 72 occurs in a proline-rich region that has been reported to play a vital role in the growth repression and apoptotic functions of P53 protein (Dumont et al., 2003). The polymorphic variants from Arg to Pro, differ in their capability of binding the transcriptional protein, activating transcription, and suppressing the transformation (Chang et al., 2002). Arg variant was reported to induce cell apoptosis and suppress transformation more efficiently than Pro variant do, which may be due to the ability of the Arg variant to localize in mitochondria that regulates the release of cytochrome C, which plays an important role in apoptosis (Dumont et al., 2003). However, in our meta-analysis based on 15 studies, there was no association between P53 codon 72

polymorphism and bladder cancer risk in the comparisons of Pro/Pro vs. Arg/Arg; Pro/Arg vs. Arg/Arg; Pro/Pro plus Pro/Arg vs. Arg/Arg; Arg/Arg vs. Pro/Arg plus Arg/Arg.

The discrepancy between the results of Asians and Caucasians might be due to differences of genetic backgrounds and the environment existed among different races, we further conducted subgroup analysis by ethnicity. We found that patients with bladder cancer had a significantly higher frequency of Pro/Pro, Pro/Pro plus Pro/Arg than none cancer patients among Asians. The hospital-based studies showed an increased risk in all genetic model, which may be caused by selection bias. Considering possible impact of P53 codon 72 polymorphism on the development and progression of bladder cancer, we extracted data concerning stage of bladder cancer which divided into two groups: superficial and invasive, and further performed meta-analysis. The results failed showing a significant association of P53 codon 72 polymorphisms with stage of bladder cancer, suggesting that P53 codon 72 polymorphism might not contribute to progression of developing bladder cancer.

However, there are several limitations in this meta-analysis. First, the controls were not uniformly defined; some controls were hospital-based. Hence, non-differential misclassification bias is possible. Secondly, all published studies written in English. It is possible that some related published or unpublished studies that might meet the inclusion criteria were missed. Hence, some inevitable publication bias might exist in the results, though the funnel plots as well as Egger's linear regression tests indicated on remarkable publication biases in the meta-analyses. Third, in the subgroup analysis by ethnicity, the population of Caucasians comes from three continents involving North American, South American and Europe, which may cause the selection bias. It may be underpowered to explore the real association. Only one study reported on African (Horikawa et al., 2008), reflecting the current lack of epidemiologic studies in these populations. Furthermore, we were also unable to examine the interactions among gene-environment, lacking of the original data of the included studies limited our further evaluation of potential interactions, which may be an important component of the association between P53 codon 72 polymorphism and environment and bladder cancer risk.

In summary, despite the limitations, the results of the present meta-analysis suggest that, in the P53 codon 72, Pro/Pro type and dominant mode might increase the susceptibility to bladder cancer in Asians; and there are no association between genotype distribution and the stage of bladder cancer.

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