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SYSTEMATIC REVIEW AND META-ANALYSIS

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Murine Double Minute 2 SNP T309G Polymorphism and Urinary Tract Cancer Risk

A Meta-Analysis

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Abstract: Urinary tract cancer is a common cause of cancer-related death. The etiology and pathogenesis of urinary tract cancer remain unclear, with genetic and epigenetic factors playing an important role. Studies of the polymorphism of murine double minute 2 (MDM2) have shown inconclusive trends in the risk of urinary tract cancer.

To clarify this inconsistency, we conducted updated meta-analyses to evaluate the role of MDM2 T309G polymorphism in urinary tract cancer susceptibility.

Data sources were Pubmed (1966–May 2015), Chinese biomedicine literature database (1978–May 2015), and hand searching of the reference lists of included studies:

(1) research categories case-control study or a nested case-control study; (2) information evaluating the association between the MDM2 SNP309 and urinary tract cancer risk; (3) studies with sufficient data to perform a meta-analysis.

It included the use of odds ratios (ORs) to assess the strength of the association, and 95% confidence intervals (CIs) give a sense of the precision of the estimate. We used I^2 for the assessment of between-study heterogeneity, and publication bias was assessed using the funnel plot and the Egger test. Statistical analyses were performed by Review Manage, version 5.0 and Stata 11.0.

A total of 18 studies met the eligibility criteria and were included in our analyses. Overall, there was no statistical association between MDM2 SNP309 and prostate cancer risk for the allele contrast, the GG genotype, the recessive genetic model, the dominant genetic model, and prostate cancer risk in all subjects (OR = 0.96, 95% CI 0.87–1.05, $P = 0.36$; OR = 0.93, 95% CI 0.75–1.15, $P = 0.50$; OR = 1.00, 95% CI 0.87–1.15, $P = 0.99$; OR = 0.93, 95% CI 0.80–1.07, $P = 0.30$), and between MDM2 SNP309 and bladder cancer risk (the allele contrast: OR = 1.06, 95% CI 0.89–1.27, $P = 0.50$; the GG genotype: OR = 1.12, 95% CI 0.79–1.61, $P = 0.52$; the dominant genetic model: OR = 1.03, 95% CI 0.83–1.28, $P = 0.78$; the recessive genetic model: OR = 1.12, 95% CI 0.84–1.49, $P = 0.45$). However, there was positive association between MDM2 SNP309 and kidney cancer risk for the allele contrast (OR = 1.24, 95% CI 1.05–1.46, $P = 0.01$), the GG genotype (OR = 1.57, 95% CI 1.11–2.20, $P = 0.01$), dominant model contrast (OR = 1.30, 95% CI 1.00–1.68, $P = 0.05$), the recessive genetic model (OR = 1.37, 95% CI 1.02–1.83, $P = 0.04$).

First, only the data of published studies were included in this meta-analysis. Unpublished studies tend to show more negative results; therefore, publication bias may be present. Second, because of the lack of the original data, we did not perform stratification analysis by age, hormone levels, dietary habit, or other variables. This might have caused confounding bias. Third, because the number of studies was relatively small for kidney cancer, the results might not have enough statistical power for us to investigate the association of the polymorphism with kidney cancer susceptibility, and we could not perform subgroup analyses. Finally, there were no studies about Africans in this meta-analysis.

In summary, the results of our meta-analysis suggest an increased risk role of the MDM2 SNP T309G in renal cancer. However, there was no association between the MDM2 SNP T309G and prostate cancer risk or between the MDM2 SNP T309G and bladder cancer risk. Moreover, well-designed studies should estimate different ethnicities, degree of malignancy and clinical progression on the association between MDM2 SNP309 and urinary cancer risk in the future.

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Abbreviations: MDM2 = murine double minute 2.

INTRODUCTION

As is well known, prostate cancer, bladder cancer, and kidney cancer are the most common urologic tumors. According to the 2011 ''Global cancer statistics,''[1] prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males worldwide; bladder cancers are the second most common urologic tumors, with an estimated 386,300 new cases diagnosed worldwide; kidney cancer is the third leading cause of death among urologic tumors, and the rate of incidence is 21.5 per 100,000 in 2008. The present studies[2–6] have demonstrated that genetics and diet are closely related with the occurrence and development of urinary tract cancers. However, the etiology of these tumors is still unclear.

Recently, several studies have indicated that the polymorphism of p53 gene was associated with the urologic tumors. The p53 protein is a key tumor suppressor protein that encoded by the tumor protein 53 gene. The tumor suppression functions

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of p53 are widespread and mediated by various mechanisms, where it regulates the cell cycle and initiates apoptosis in response to severe DNA damage.[7] Several studies have demonstrated that the degradation of p53 is regulated by the ubiquitin–proteasome pathway.[8] Human mouse double-minute 2 protein (MDM2) is a key negative regulator of p53 through several mechanisms. MDM2 directly binds to p53, resulting in the p53 transactivation inactivity.[9–12] Moreover, MDM2 also acts as an ubiquitin protein ligase and controls p53 by targeting it for proteasomal degradation.[9–12] Therefore, overexpression of MDM2 and inactivation of p53 were associated with oncogenesis.

A novel functional single nucleotide polymorphism (SNP, rs2279744) was found that located 309 bp downstream from intron 1 in the promoter of the MDM2 gene (SNP309, T>G).[13] This GG genotype of SNP309 binds stimulatory protein (Sp1) with increased affinity; it can increase the expression of MDM2 and suppress the p53 pathway.[13] For the past few years, a number of epidemiological studies have been done to assess the association between MDM2 SNP309 and tumor risk in different populations. Among the tumor types, urologic tumors including prostate cancer, bladder cancer, and kidney cancer were also evaluated. However, these results were inconsistent.[14,15] And for the relatively small sample size of the published studies, it is necessary to accumulate data from different studies to provide evidence on the association of MDM2 SNP309 genetic polymorphisms with urologic tumors risk. Moreover, more studies and large sample studies have been published in recent years.[16–21] Therefore, we performed a systematic review and meta-analysis to further estimate the overall urinary tract cancers risk caused by the MDM2 SNP309 in patients.

MATERIALS AND METHODS

Publication Search

The following databases were searched: Pubmed (1966–May 2015) and Chinese biomedicine literature database (1978–May 2015) using the following search terms: (''murine double minute 2'' or ''MDM2'') AND ''polymorphism, Genetic'' AND (''prostate cancer'' or ''bladder cancer'' or ''kidney neoplasms'') to identify all relevant articles on the subject. We also searched the references of included studies to identify additional potentially relevant studies. Hand searching of the reference lists of included studies and reviews was undertaken and contact was made with experts in the field, unpublished studies were not sought. The search was not restricted by the publication year or language.

Inclusion and Exclusion Criteria

The included studies met the following criteria: (1) research categories case-control study or a nested case-control study; (2) information evaluating the association between the MDM2 SNP309 and urinary tract cancers risk; (3) studies with sufficient data to perform a meta-analysis. The following studies were excluded: no control population, insufficient available data, duplicated articles, and the genotype distribution of the control population was departure from Hardy–Weinberg equilibrium.

Data Extraction

Data extraction was carried out independently by the same authors using standard data extraction forms. Disagreements were resolved in consultation with the third reviewer. For each study, the following characteristics were collected: first author's name, year of publication, tumor type (prostate cancer, bladder cancer, or kidney cancer), ethnicity, and country of study population, design of experiment (population- or hospital-based controls), number of genotyped cases and controls, genotyping method, p53 mutation status, the characteristics of the controls and quality control. The patient ethnicities were categorized as Caucasian, Asian, or African. When studies included subjects of >1 ethnicity, genotype data were extracted separately according to ethnicities for subgroup analyses.

Statistical Analysis

The strength of association between MDM2 SNP309 and urinary cancer risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs), including the allele G compared with the allele A, the homozygous contrast (GG vs AA), the dominant genetic model [(GG+GA) vs AA], and the recessive genetic model [GG vs (GA+AA)]. The statistical significance of the summary OR was determined using the *Z*-test.

I^2-test and chi-square test were used to evaluate the heterogeneity between the studies. If $P<0.10$, it was considered to have significant heterogeneity in statistics; and the I^2 value was used to test the degree of heterogeneity ($I^2<25\%$, no heterogeneity; I^2 25–50%, moderate heterogeneity; $I^2>50\%$, large or extreme heterogeneity). To test the reliability of the results, the Mantel–Haenszel method (fixed-effects) and the DerSimonian–Laird method (random-effects) were used to estimate the pooled ORs, respectively. Publication bias was assessed using inverted funnel plots. The significance of asymmetry was determined using the *t* test, an asymmetric plot, and $P<0.05$ was considered to indicate a possible publication bias. Funnel plot asymmetry was also examined by using Egger's linear regression test.

As a research using systematic review and meta-analysis, ethical approval of this study is not required. This work was reported according to the PRISMA guidelines.[22] Meta-analyses were performed using Review Manager, version 5.0, software (The Cochrane Information Management System, http://ims.cochrane.org/revman) and Software STATA version 11.0 (Stata Corporation, College Station, TX). $P<0.05$ was considered statistically significant.

RESULTS

Study Characteristics

A total of 18 studies [12,14–21,23–31] investigating the polymorphism of MDM2 SNP309 met our inclusion criteria (Figure 1). The characteristics of each study are summarized in Table 1. These studies were published from 2006 to 2015. Eight studies reported the prostate cancer including 4 Asian populations, 3 European populations and 1 USA populations; 7 studies reported the bladder cancer including 3 Asian populations and 4 European populations; and 3 studies reported the renal cancer including 2 Asian populations and 1 European populations, respectively. In all the studies, all controls were free of prostate cancer, bladder cancer, and kidney cancer.

Quantitative Synthesis

A total of 5165 cases and 4785 controls were used to analyze the association of the MDM2 T309G polymorphism and prostate cancer risk. Seven studies including 1254 advanced cases and 1787 controls were analyzed to study the association between the T309G polymorphism and bladder cancer risk.

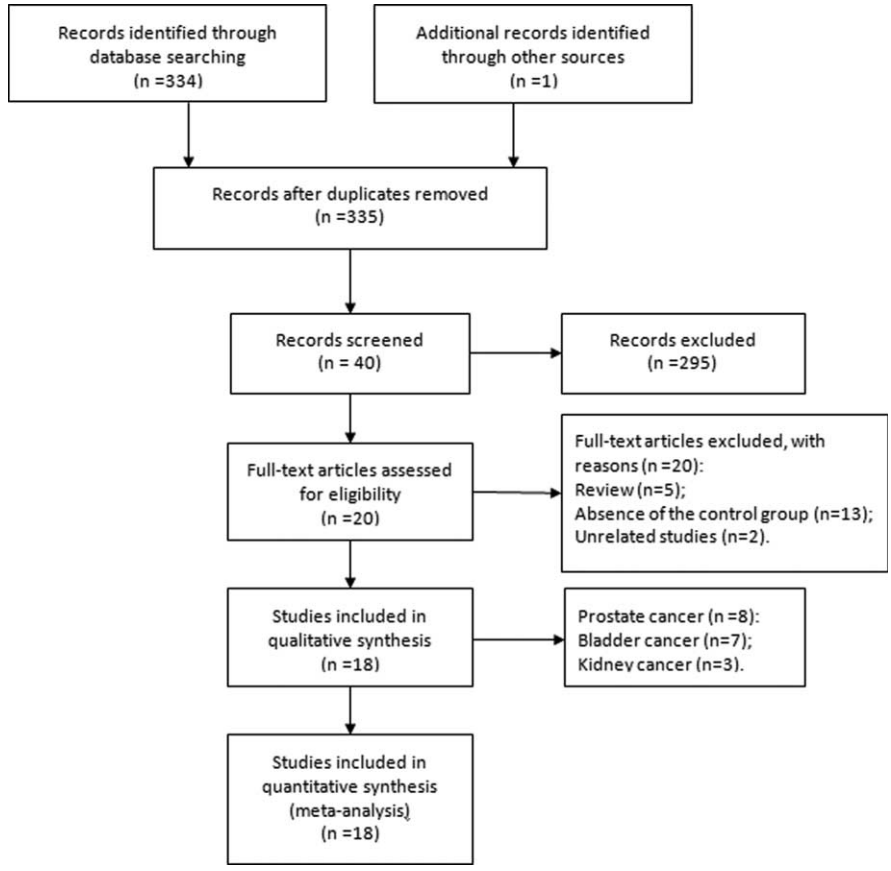

FIGURE 1. Flowchart of meta-analysis.

Three studies including 567 advanced cases and 663 controls were analyzed to study the association between the T309G polymorphism and kidney cancer risk. For prostate cancer and renal cancer, the studies mentioned quality control methods for genotyping, such as randomly repeated assays or validation by directed sequencing. For bladder cancer, 1 study used randomly repeated assays as quality control methods for genotyping.[23] The genotypic and allelic frequencies of the cases and controls for T309G are listed in Table 2. All studies stated that the distribution of genotypes in the control groups were consistent with Hardy–Weinberg equilibrium.

MAIN RESULTS OF ALLELE AND SUBGROUP ANALYSIS

Prostate Cancer

Because significant heterogeneity existed among the allele contrast, the homozygous contrast, the recessive genetic model and the dominant genetic model, a random-effects model was used to pool the results. No significant difference was found between the allele contrast and prostate cancer risk, between the GG genotype and prostate cancer risk, between the recessive genetic model and prostate cancer risk, between the dominant genetic model and prostate cancer risk in all subjects (OR = 0.96, 95% confidence interval [CI] 0.87–1.05, $P = 0.36$; OR = 0.93, 95% CI 0.75–1.15, $P = 0.50$; OR = 1.00, 95% CI 0.87–1.15, $P = 0.99$; OR = 0.93, 95% CI 0.80–1.07, $P = 0.30$; Figures 2–5), respectively.

In the subgroup analysis, according to ethnicity, similar effects were detected under the allele contrast (OR = 0.95, 95% CI 0.79–1.14, $P = 0.55$), the homozygous contrast (OR = 0.93, 95% CI 0.67–1.31, $P = 0.69$), the recessive genetic model (OR = 1.00, 95% CI 0.87–1.16, $P = 0.96$), and the dominant genetic model (OR = 0.90, 95% CI 0.63–1.27, $P = 0.55$) in the Asian subgroup; and the allele contrast (OR = 0.95, 95% CI 0.83–1.09, $P = 0.45$), the homozygous contrast (OR = 0.88, 95% CI 0.62–1.26, $P = 0.50$), the recessive genetic model (OR = 0.93, 95% CI 0.67–1.30, $P = 0.68$), and the dominant genetic model (OR = 0.95, 95% CI 0.86–1.05, $P = 0.33$) in the European subgroup. According to study design, similar effects were detected under the allele contrast (OR = 0.90, 95% CI 0.75–1.08, $P = 0.25$), the homozygous contrast (OR = 0.79, 95% CI 0.53–1.18, $P = 0.26$), the dominant genetic model (OR = 0.88, 95% CI 0.66–1.17, $P = 0.39$), and the recessive genetic model (OR = 0.88, 95% CI 0.69–1.13, $P = 0.32$) in the subjects from hospital; and the T309G polymorphism also had no effect on prostate cancer risk in the subjects from population.

Bladder Cancer

A random-effects model was used to pool the results of the allele contrast, the homozygous contrast, the dominant genetic model and the recessive genetic model because of existing significant heterogeneity. The T309G polymorphism had no effect on the allele contrast (OR = 1.06, 95% CI 0.89–1.27, $P = 0.50$), the GG genotype (OR = 1.12, 95% CI 0.79–1.61,

TABLE 1. The Main Characteristics of Included Studies

First Author	Publication Year	Publishing Country	Ethnicity	Case Number	Control Number	Study Design (Case-Control)	HWE Test	Genotyping Method
Prostate cancer								
Stoehr	2008	Germany	European	145	124	Hospital	Yes	PCR-RFLP
Adam	2008	USA	European*	186	220	Hospital	Yes	Pyrosequencing
Hiroshi	2009	Japan	Asian	140	167	Population	Yes	PCR-RFLP
Xu	2010	China	Asian	209	268	Hospital	Yes	PCR-RFLP
Mandal	2010	India	Asian	192	224	Hospital	Yes	PCR-RFLP
Knappskog	2012	Norway	European	666	675	Population	Yes	PCR-DyNazyme EXT
Gansmo	2015	Norway	European	2501	1877	Population	Yes	Light-SNiP assays
Xue	2015	China	Asian	1126	1230	Hospital	Yes	Affymetrix MegAllele
Bladder cancer								
Onur	2006	Turkey	European	75	103	Hospital	Yes	PCR-RFLP
Marta	2007	USA	European*	141	50	Hospital	Yes	PCR-RFLP
Wang	2008	China	Asian	234	253	Hospital	Yes	tagSNPs
Yohei	2008	Japan	Asian	227	266	Hospital	Yes	PCR-RFLP
Ruchika	2010	India	Asian	212	250	Population	Yes	PCR-RFLP
Olsson	2013	Sweden	European	141	725	Population	Yes	Pyrosequencing
Florian (23)	2014	Germany	European	224	140	Hospital	Yes	PCR-RFLP
Renal cancer								
Hiroshi	2007	Japan	Asian	200	200	Population	Yes	PCR-RFLP
Huang	2011	China	Asian	127	254	Hospital	Yes	TaqMan assays; sequencing
Martino	2015	Austria	European	240	209	Hospital	Yes	PCR-RFLP

HWE = Hardy-Weinberg equilibrium, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNP = single nucleotide polymorphism.
* European-American.

$P = 0.52$), the dominant genetic model (OR = 1.03, 95% CI 0.83–1.28, $P = 0.78$), the recessive genetic model (OR = 1.12, 95% CI 0.84–1.49, $P = 0.45$), and bladder cancer risk (Figures 2–5).

In the subgroup analysis, according to ethnicity, similar effects were detected under the allele contrast, the homozygous contrast, the recessive genetic model, and the dominant genetic model in the Asian subgroup or the European subgroup.

TABLE 2. Distribution of MDM2 SNP T309G Genotypes and Alleles

Investigator	Ethnicity/Country	Genotype (T309G T>G)		
		Cases TT/TG/GG	Controls TT/TG/GG	Controls G%
Prostate cancer				
Stoehr, 2008	Germany	61/66/18	41/64/19	41.1
Adam, 2008	USA	85/88/13	90/98/32	36.8
Hiroshi, 2009	Japan	58/56/26	56/79/32	42.8
Xu, 2010	China	44/118/47	68/143/57	47.9
Mandal, 2010	India	67/71/54	53/98/73	54.5
Knappskog, 2012	Norway	297/277/92	305/295/75	33.0
Gansmo, 2015	Norway	988/1169/344	724/905/248	37.3
Xue, 2015	China	227/565/334	272/602/356	53.4
Bladder cancer				
Onat, 2006	Turkey	13/36/26	29/57/17	44.2
Marta, 2007	USA	52/73/16	24/20/6	32.0
Wang, 2008	China	62/121 /51	64/134/55	48,2
Yohei, 2008	Japan	44/116/67	55/132/79	54.5
Ruchika, 2010	India	70/89/53	62/113/75	52.6
Olsson, 2013	Sweden	59/64/18	297/326/102	36.6
Florian, 2014	Germany	75/101/48	51/70/19	38.6
Kidney cancer				
Hiroshi, 2007	Japan	49/89/62	62/98/40	44.5
Huang, 2011	China	19/67/41	49/130/75	55.1
Martino, 2015	Austria	88/117/35	86/97/26	35.6

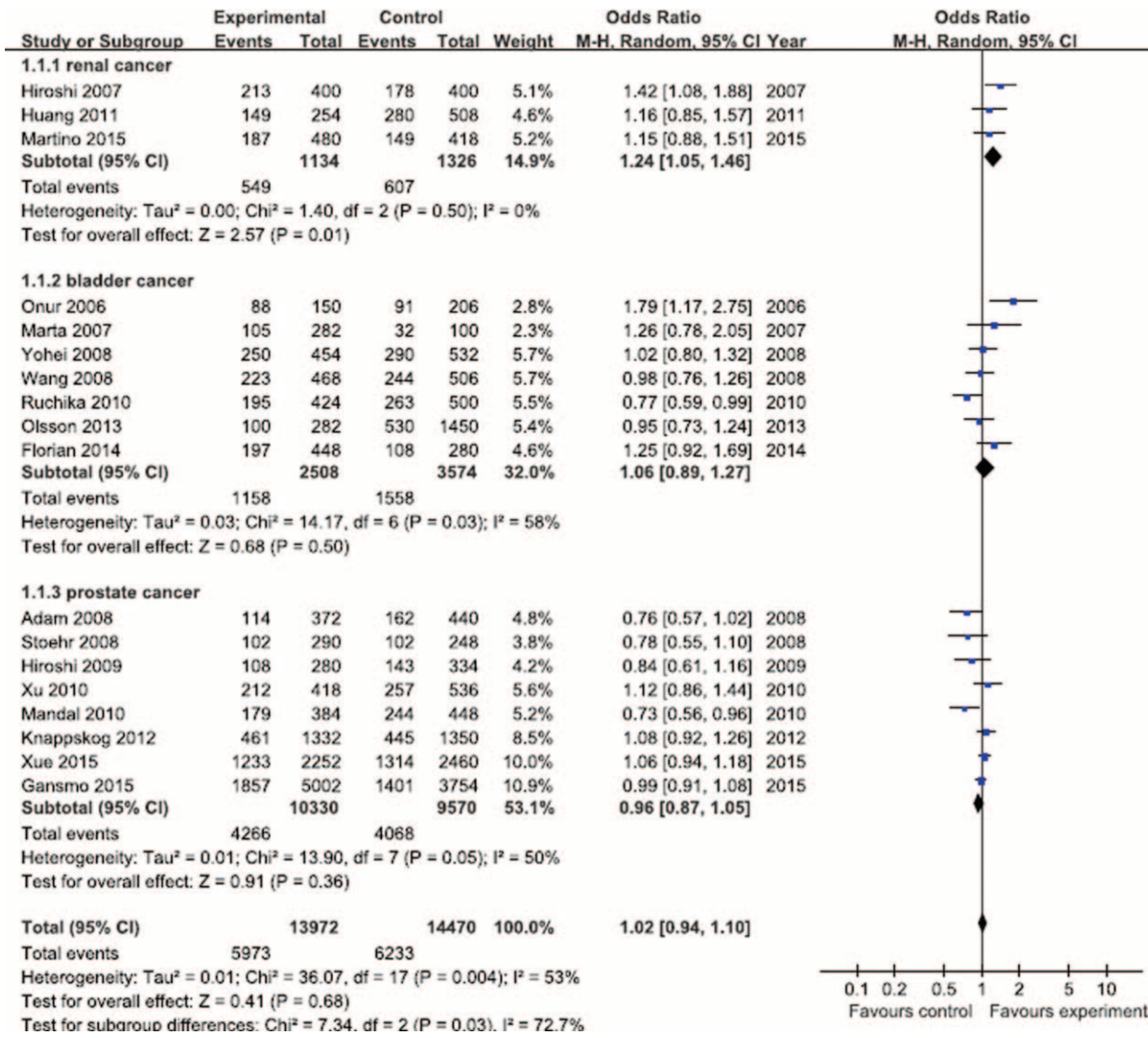

FIGURE 2. The pooled results for allele contrast in investigation of association of MDM2 T309G polymorphisms with urinary cancer.

According to study design, the T309G polymorphism also had no effect on bladder cancer risk in the subjects from population or hospital.

Kidney Cancer

A random-effects model was used to pool the results, and a significantly increased effect was found for the allele contrast (OR = 1.24, 95% CI 1.05–1.46, $P = 0.01$), the GG genotype (OR = 1.57, 95% CI 1.11–2.20, $P = 0.01$), the dominant genetic model (OR = 1.30, 95% CI 1.00–1.68, $P = 0.05$), the recessive genetic model (OR = 1.37, 95% CI 1.02–1.83, $P = 0.04$), and kidney cancer risk in all subjects (Figures 2–5).

Publication Bias

Begg's funnel plot and Egger's test were performed to assess publication bias. Egger's test was used to provide statistical evidence for funnel plot symmetry. For prostate cancer, bladder cancer and kidney cancer, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models including the allele contrast, homozygote model, dominant genetic model and recessive genetic model, the funnel plots of dominant genetic model were showed in Figures 6–8; Egger's results did not show any evidence of publication bias.

DISCUSSION

In the present study, we performed a systematic review and meta-analysis to evaluate the association between MDM2 T309G polymorphism and the risk for prostate cancer, bladder cancer and renal cancer based on all available studies. The results demonstrated that there were no significant association between MDM2 SNP T309G and prostate cancer or bladder cancer risk in Asian or European populations, and there was positive association between MDM2 SNP T309G and kidney cancer risk.

MDM2 plays an important role in the cellular p53 pathway. The MDM2 T309G polymorphism has been shown to increase the synthesis of MdM2 and it has been found to be correlated with the risk of cancer at various organ sites.[32] Bond et al[13] showed that the MDM2 T309G can strengthen the

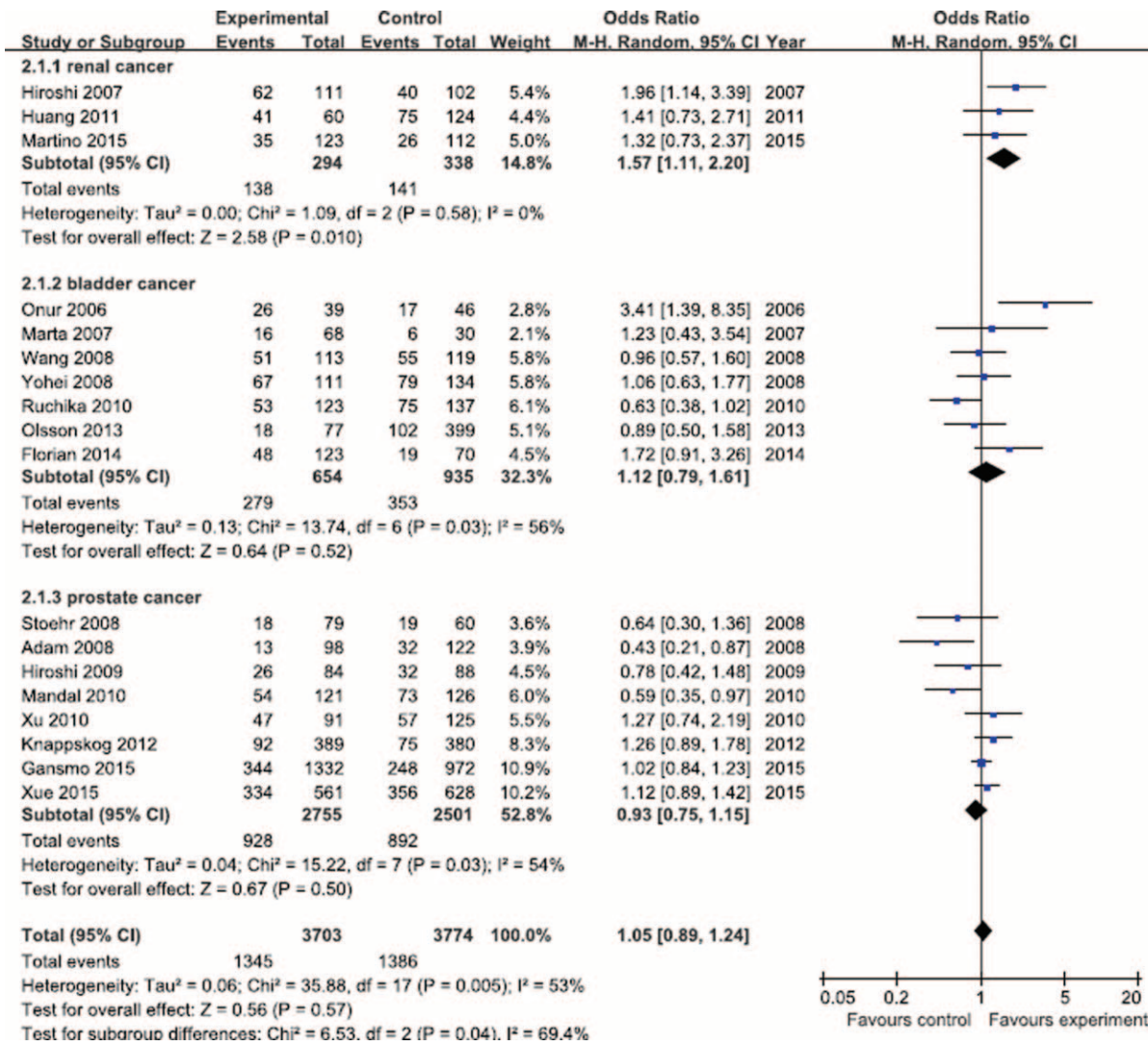

FIGURE 3. The pooled results for GG genotype in investigation of association of MDM2 T309G polymorphisms with urinary cancer.

affinity between MDM2 gene and the transcriptional activator Sp1, then increase the expression of MDM2 protein, attenuates the p53 pathway, and ultimately accelerates tumor formation in human bodies. Based on the above theory, we supposed that the MDM2 T309G polymorphism was associated with urinary cancer risk. Zhao et al[33] reported that an increased breast cancer susceptibility for GT versus TT (OR = 1.31, 95% CI = 1.03–1.67, $P = 0.03$) in Asian population and for GT versus TT (OR = 1.31, 95% CI = 1.03–1.66, $P = 0.03$) in African population, respectively. Li et al[34] found that the GG genotype of MDM2 SNP309 was significantly associated with the increased endometrial cancer risk (OR = 1.54, 95% CI = 1.21–1.95, $P = 0.0004$). However, Phang et al[35] reported that the MDM2 SNP309G allele was associated with reduced risk of leukemia. Kang et al[36] reported that the MDM2 SNP309G allele significantly decreased the risk of epithelial ovarian cancer in Chinese. However, our current pooled data suggested there was no risk effect of the GG genotype under homozygote contrast and the dominant genetic model (OR = 0.87, 95% CI 0.67–1.13, $P = 0.30$; OR = 0.89, 95% CI 0.75–1.04, $P = 0.14$) for prostate cancer. This showed that the MDM2 309G allele could not influence the prostate cancer risk. In subgroups analysis, we did not find that MDM2 SNP T309G polymorphism could increase or decrease prostate cancer risk, regardless of both Asian and European or both population-based study and hospital-based study. Meanwhile, the findings are inconsistent with the variant of the T309G in previous meta-analysis about prostate cancer. Chen et al and Yang et al reported that MDM2 SNP T309G polymorphism probably decreased prostate cancer risk in European population and hospital-based population.[37,38] Importantly, a limited number of participants were enrolled in most individual reports. In addition, the case-control design of many studies may imply potential biased comparisons between patients and control groups, and a publication bias in favor of studies reporting positive results cannot be excluded. However, in our meta-analysis, the number of participants is high compared to other studies that have addressed MDM2 SNP T309G and prostate cancer risk. In addition, Yang et al reported that the MDM2 T309G was associated with lower malignant degree

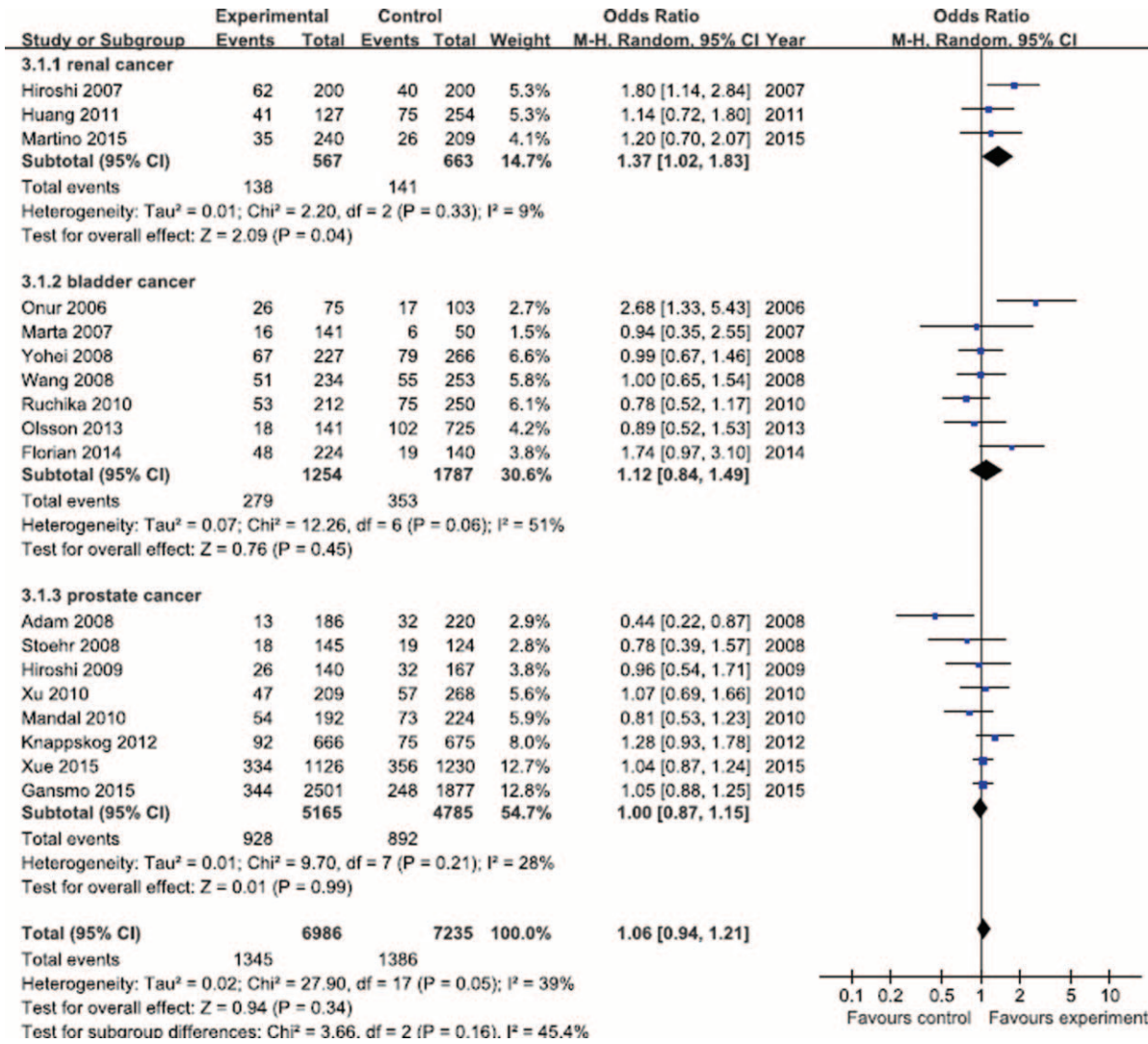

FIGURE 4. The pooled results for the recessive genetic model in investigation of association of MDM2 T309G polymorphisms with urinary cancer.

and slower clinical progression in Caucasians;[37] however, we deem the results are not convincing because most study's data were not available. Recently, Knappskog and Lonning[39] reported a possible confounding factor SNP285 (rs117039649) in occurrence of cancer, located just 24 bp upstream of SNP309. Because the C-allele of SNP285 has been shown to counteract the effect of SNP309G in vitro, SNP285C/309G haplotype might produce different effects between ethnic groups or cancers. The previous studies[20,40] have showed that the SNP285C variant could reduce the risks of breast, ovarian, and endometrial cancer. However, for prostate cancer risk, no association of SNP285C was found in Caucasian either among individuals harboring the SNP309TG or the GG genotype. In future, large sample studies are needed to deeply explore the effects of SNP285C on SNP309 in other ethnics.

For bladder cancer, there were controversial results about MDM2 T309G polymorphism. Onat et al[26] reported that patients with the GG genotype exhibited a 2.68-fold increase in the bladder cancer risk compared with the TT and TG in a Turkish population. Horikawa et al[27] reported that there were no significant associations between the polymorphism and bladder cancer risk. The previous meta-analysis indicated that the genotype of the MDM2 SNP309T > G polymorphism may be associated with genetic susceptibility to bladder cancer among Caucasians, not Asians.[41] However, our results of meta-analysis demonstrated that there was no risk effect of the GG genotype under homozygote contrast and the dominant genetic model for bladder cancer. Compared to the previous studies, the number of participants is high that have addressed MDM2 SNP T309G and bladder cancer risk in our meta-analysis. MDM2 SNP309 polymorphism might affect the clinical outcome of bladder cancer in a different way between superficial and invasive bladder cancer. In superficial bladder cancer, the TT patients tended to have a longer recurrence-free survival than the TG or GG patients after transurethral resection. It needs further investigation for the relationships between MDM2 SNP T309G and bladder cancer grading or staging in future.

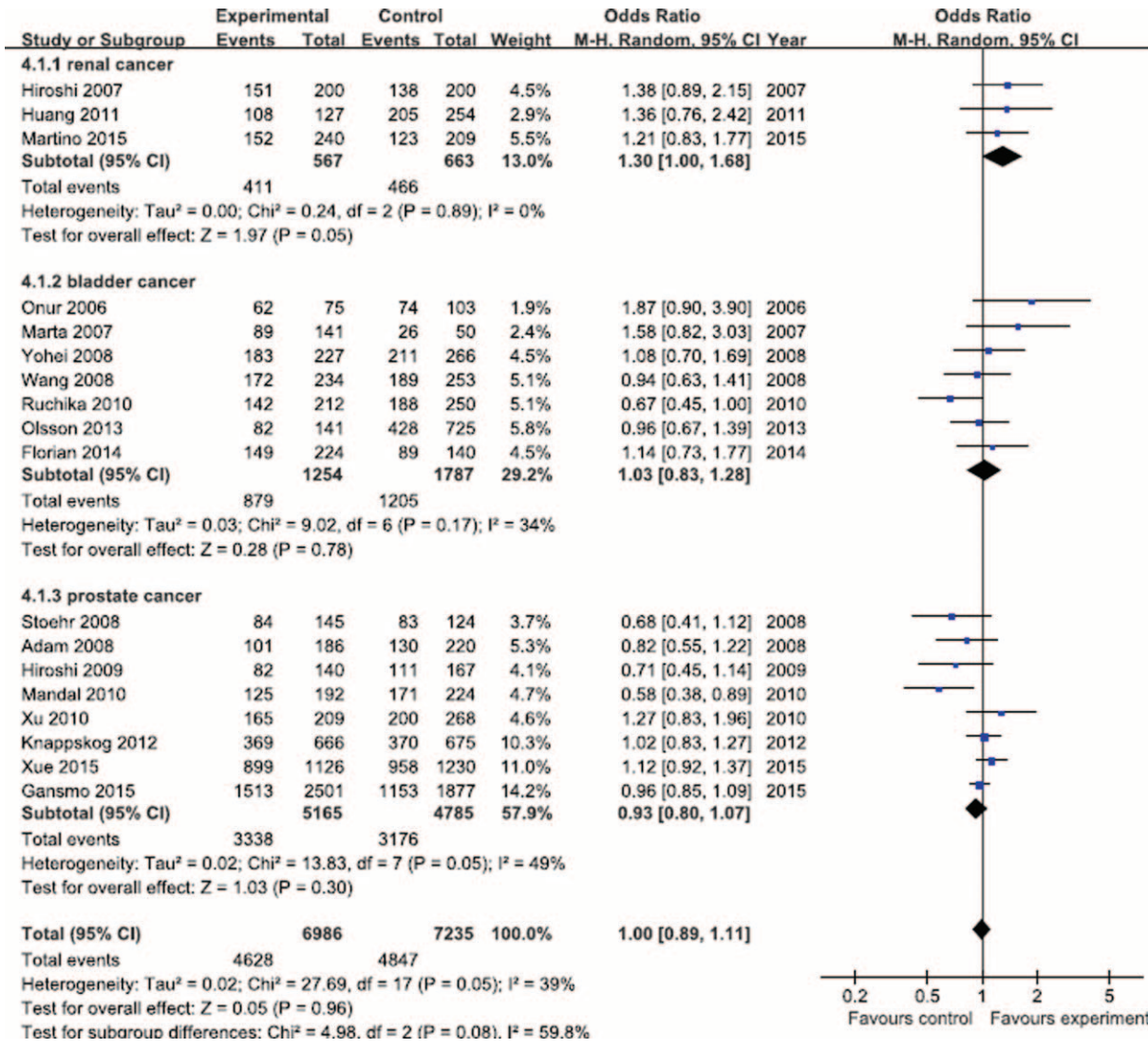

FIGURE 5. The pooled results for dominant model contrast in investigation of association of MDM2 T309G polymorphisms with urinary cancer.

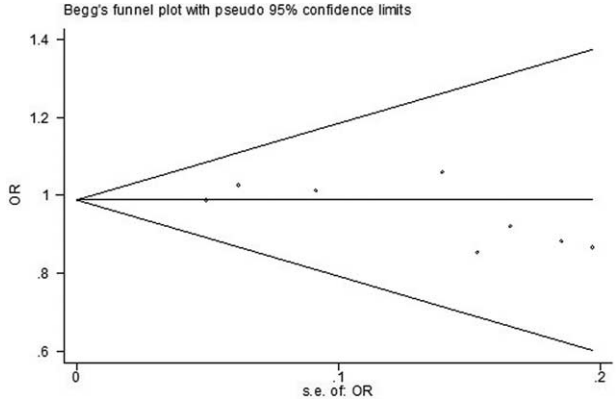

FIGURE 6. The funnel plots of publication bias in prostate cancer studies.

In this meta-analysis, 3 articles reported the relationships between the MDM2 SNP T309G and kidney cancer risk. Our pooling results showed that the patients with MDM2 SNP T309G mutation had high risk of kidney cancer. It is inconsistent with prostate cancer or bladder cancer patients. However, the following reasons may produce an effect on the results: (1) two of all included studies were from Asia, and another study was from Europe. (2) The included patients were from a low arsenic exposure area in 1 study,[28] this indicated that the environmental factor may take participate in kidney cancer formation. So, more studies are needed to confirm the positive correlation between the MDM2 SNP T309G and kidney cancer risk in future.

Our meta-analysis had some limitations. First, only the data of published studies were included in this meta-analysis. Unpublished studies tend to show more negative results; therefore, publication bias may be present. For example, we found an obvious publication bias for bladder cancer caused by Onat et al

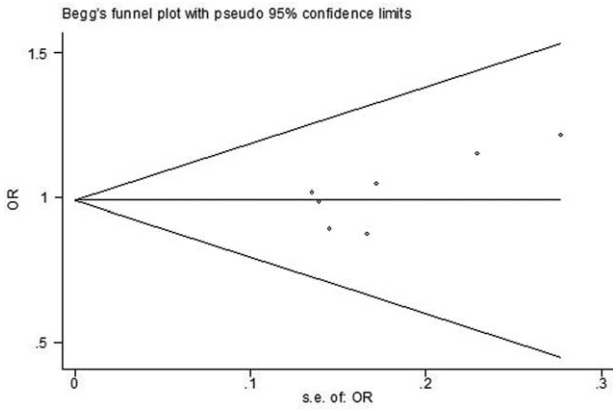

FIGURE 7. The funnel plots of publication bias in bladder cancer studies.

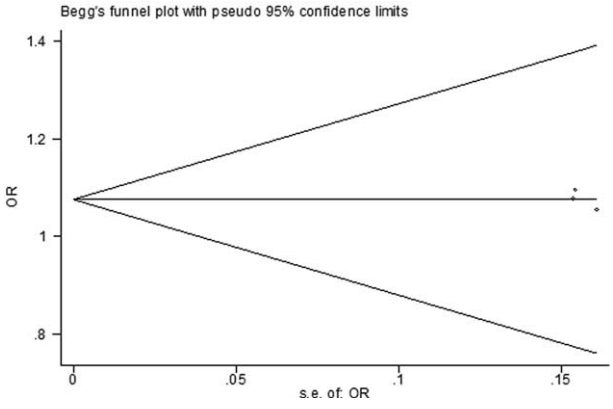

FIGURE 8. The funnel plots of publication bias in kidney cancer studies.

's study.[26] Second, because of the lack of the original data, we did not perform stratification analysis by age, hormone levels, dietary habit or other variables. This might has caused confounding bias. Third, because the number of studies was relatively small for kidney cancer, the results might not have enough statistical power for us to investigate the association of the polymorphism with kidney cancer susceptibility, and we could not perform subgroup analyses. Finally, there were no studies about Africans in this meta-analysis.

In summary, the results of our meta-analysis suggest an increased risk role of the MDM2 SNP T309G in renal cancer. However, there was no association between the MDM2 SNP T309G and prostate cancer risk or between the MDM2 SNP T309G and bladder cancer risk. Moreover, well-designed studies should estimate different ethnicities, degree of malignancy, and clinical progression on the association between MDM2 SNP309 and urinary cancer risk in the future.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Xu B, Tong N, Chen SQ, et al. Contribution of HOGG1 Ser (3)(2)(6)Cys polymorphism to the development of prostate cancer in smokers: meta-analysis of 2779 cases and 3484 controls. *PLoS One.* 2012;7:e30309.
3. Gong M, Dong W, An R. Glutathione S-transferase T1 polymorphism contributes to bladder cancer risk: a meta-analysis involving 50 studies. *DNA Cell Biol.* 2012;31:1187–1197.
4. Wang J, Wang B, Bi J, et al. MDR1 gene C3435T polymorphism and cancer risk: a meta-analysis of 34 case-control studies. *J Cancer Res Clin Oncol.* 2012;138:979–989.
5. Hurst R, Hooper L, Norat T, et al. Selenium and prostate cancer: systematic review and meta-analysis. *Am J Clin Nutr.* 2012;96:111–122.
6. Mao QQ, Dai Y, Lin YW, et al. Milk consumption and bladder cancer risk: a meta-analysis of published epidemiological studies. *Nutr Cancer.* 2011;63:1263–1271.
7. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell.* 1997;88:323–331.
8. Brooks CL, Gu W. p53 ubiquitination: Mdm2 and beyond. *Mol Cell.* 2006;21:307–315.
9. Haupt Y, Maya R, Kazaz A, et al. Mdm2 promotes the rapid degradation of p53. *Nature.* 1997;387:296–299.
10. Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. *Nature.* 1997;387:299–303.
11. Bond GL, Hu W, Levine A. A single nucleotide polymorphism in the MDM2 gene: from a molecular and cellular explanation to clinical effect. *Cancer Res.* 2005;65:5481–5484.
12. Hirata H, Hinoda Y, Kikuno N, et al. MDM2 SNP309 polymorphism as risk factor for susceptibility and poor prognosis in renal cell carcinoma. *Clin Cancer Res.* 2007;13:4123–4129.
13. Bond GL, Hu W, Bond EE, et al. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. *Cell.* 2004;119:591–602.
14. Xu B, Xu Z, Cheng G, et al. Association between polymorphisms of TP53 and MDM2 and prostate cancer risk in southern Chinese. *Cancer Genet Cytogenet.* 2010;202:76–81.
15. Stoehr R, Hitzenbichler F, Kneitz B, et al. Mdm2-SNP309 polymorphism in prostate cancer: no evidence for association with increased risk or histopathological tumour characteristics. *Br J Cancer.* 2008;99:78–82.
16. Gansmo LB, Knappskog S, Romundstad P, et al. Influence of MDM2 SNP309 and SNP285 status on the risk of cancer in the breast, prostate, lung and colon. *Int J Cancer J Int Cancer.* 2015;137:96–103.
17. de Martino M, Taus C, Wessely IS, et al. The T309G murine double minute 2 gene polymorphism is an independent prognostic factor for patients with renal cell carcinoma. *DNA Cell Biol.* 2015;34:107–112.
18. Hitzenbichler F, Stoehr CG, Rogenhofer M, et al. Mdm2 SNP309 G-variant is associated with invasive growth of human urinary bladder cancer. *Pathobiology.* 2014;81:53–59.
19. Olsson H, Hultman P, Rosell J, et al. MDM2 SNP309 promoter polymorphism and p53 mutations in urinary bladder carcinoma stage T1. *BMC urology.* 2013;13:5.
20. Knappskog S, Trovik J, Marcickiewicz J, et al. SNP285C modulates oestrogen receptor/Sp1 binding to the MDM2 promoter and reduces the risk of endometrial but not prostatic cancer. *Eur J Cancer (Oxford, England: 1990).* 2012;48:1988–1996.
21. Xue L, Han X, Liu R, et al. MDM2 and P53 polymorphisms contribute together to the risk and survival of prostate cancer. *Oncotarget.* 2015. DOI:10.18632/oncotarget.3923. [Epub ahead of print].
22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
23. Gangwar R, Mittal RD. Association of selected variants in genes involved in cell cycle and apoptosis with bladder cancer risk in North Indian population. *DNA Cell Biol.* 2010;29:349–356.

24. Kibel AS, Jin CH, Klim A, et al. Association between polymorphisms in cell cycle genes and advanced prostate carcinoma. *Prostate.* 2008;68:1179–1186.

25. Mandal RK, Mittal RD. Are cell cycle and apoptosis genes associated with prostate cancer risk in North Indian population? *Urol Oncol.* 2012;30:555–561.

26. Onat OE, Tez M, Ozcelik T, et al. MDM2 T309G polymorphism is associated with bladder cancer. *Anticancer Res.* 2006;26:3473–3475.

27. Horikawa Y, Nadaoka J, Saito M, et al. Clinical implications of the MDM2 SNP309 and p53 Arg72Pro polymorphisms in transitional cell carcinoma of the bladder. *Oncol Rep.* 2008;20:49–55.

28. Huang CY, Su CT, Chu JS, et al. The polymorphisms of P53 codon 72 and MDM2 SNP309 and renal cell carcinoma risk in a low arsenic exposure area. *Toxicol Appl Pharmacol.* 2011;257:349–355.

29. Hirata H, Hinoda Y, Kikuno N, et al. Bcl2-938C/A polymorphism carries increased risk of biochemical recurrence after radical prostatectomy. *J Urol.* 2009;181:1907–1912.

30. Sanchez-Carbayo M, Socci ND, Kirchoff T, et al. A polymorphism in HDM2 (SNP309) associates with early onset in superficial tumors, TP53 mutations, and poor outcome in invasive bladder cancer. *Clin Cancer Res.* 2007;13:3215–3220.

31. Wang M, Zhang Z, Zhu H, et al. A novel functional polymorphism C1797G in the MDM2 promoter is associated with risk of bladder cancer in a Chinese population. *Clin Cancer Res.* 2008;14:3633–3640.

32. Hu Z, Jin G, Wang L, et al. MDM2 promoter polymorphism SNP309 contributes to tumor susceptibility: evidence from 21 case-control studies. *Cancer Epidemiol Biomarkers Prev.* 2007;16:2717–2723.

33. Zhao E, Cui D, Yuan L, et al. MDM2 SNP309 polymorphism and breast cancer risk: a meta-analysis. *Mol Biol Rep.* 2012;39:3471–3477.

34. Li Y, Zhao H, Sun L, et al. MDM2 SNP309 is associated with endometrial cancer susceptibility: a meta-analysis. *Hum Cell.* 2011;24:57–64.

35. Phang BH, Linn YC, Li H, et al. MDM2 SNP309 G allele decreases risk but does not affect onset age or survival of Chinese leukaemia patients. *Eur J Cancer.* 2008;44:760–766.

36. Kang S, Wang DJ, Li WS, et al. Association of p73 and MDM2 polymorphisms with the risk of epithelial ovarian cancer in Chinese women. *Int J Gynecol Cancer.* 2009;19:572–577.

37. Yang J, Gao W, Song NH, et al. The risks, degree of malignancy and clinical progression of prostate cancer associated with the MDM2 T309G polymorphism: a meta-analysis. *Asian J Androl.* 2012;14:726–731.

38. Chen T, Yi SH, Liu XY, et al. Meta-analysis of associations between the MDM2-T309G polymorphism and prostate cancer risk. *Asian Pac J Cancer Prev.* 2012;13:4327–4330.

39. Knappskog S, Lonning PE. Effects of the MDM2 promoter SNP285 and SNP309 on Sp1 transcription factor binding and cancer risk. *Transcription.* 2011;2:207–210.

40. Knappskog S, Bjornslett M, Myklebust LM, et al. The MDM2 promoter SNP285C/309G haplotype diminishes Sp1 transcription factor binding and reduces risk for breast and ovarian cancer in Caucasians. *Cancer Cell.* 2011;19:273–282.

41. Wang HG, Wu QY, Zhou H, et al. The MDM2 SNP309T>G polymorphism increases bladder cancer risk among Caucasians: a meta-analysis. *Asian Pac J Cancer Prev.* 2014;15:5277–5281.