RESEARCH ARTICLE

Meta-analysis of Associations between the MDM2-T309G Polymorphism and Prostate Cancer Risk

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Abstract

The mouse double minute 2 (MDM2) gene plays a key role in the p53 pathway, and the SNP 309T/G single-nucleotide polymorphism in the promoter region of MDM2 has been shown to be associated with increased risk of cancer. However, no consistent results were found concerning the relationships between the polymorphism and prostate cancer risk. This meta-analysis, covering 4 independent case-control studies, was conducted to better understand the association between MDM2-SNP T309G and prostate cancer risk focusing on overall and subgroup aspects. The analysis revealed, no matter what kind of genetic model was used, no significant association between MDM2-SNP T309G and prostate cancer risk in overall analysis (GT/TT: OR = 0.84, 95%CI = 0.60-1.19; GG/TT: OR = 0.69, 95%CI = 0.43-1.11; dominant model: OR = 0.81, 95%CI= 0.58-1.13; recessive model: OR = 1.23, 95%CI = 0.95-1.59). In subgroup analysis, the polymorphism seemed more likely to be a protective factor in Europeans (GG/TT: OR = 0.52, 95%CI = 0.31-0.87; recessive model: OR = 0.58, 95%CI = 0.36-0.95) than in Asian populations, and a protective effect of the polymorphism was also seen in hospital-based studies in all models (GT/TT: OR = 0.74, 95%CI = 0.57-0.97; GG/TT: OR = 0.55, 95%CI = 0.38-0.79; dominant model: OR = 0.69, 95%CI = 0.54-0.89; recessive model: OR = 0.70, 95%CI = 0.51-0.97). However, more primary studies with a larger number of samples are required to confirm our findings.

Keywords: MDM2 - polymorphism - prostate cancer risk - meta-analysis

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Introduction

Prostate cancer is one of the most commonly diagnosed male malignancies, and it remains a leading cause of death in most Western countries, especially in elderly men (Detchokul et al., 2011). P53 is a well-known tumor suppressor gene which is negatively regulated by the mouse double minute 2 (MDM2) gene. MDM2 could bind to p53 with high affinity, resulting in down-regulation of p53 (Bouska et al., 2009; Eischen a et al., 2009; Kruse et al., 2009).

A single-nucleotide polymorphism (SNP-T309G) in the promoter region of MDM2 was proved to increase the expression of MDM2, leading to the attenuation of p53 and increased risk of tumorigenesis (Bond et al., 2004; Vassilev et al., 2004; Bond et al., 2005; Liu et al., 2011; Ma et al., 2012). It is reported MDM2-SNP T309G is associated with increased susceptibility to gastric, cervical and liver cancer (Ohmiya et al., 2006; Yoon et al., 2008; Nunobiki et al., 2010). Independent studies have focused on the association between this polymorphism and prostate cancer risk, but their results were inconclusive, which put forward the requirement of a more comprehensive and reliable assessment of the polymorphism and prostate cancer risk.

Here, we performed a meta-analysis of 4 case-control studies (732 cases and 836 controls) to explore their relationship. During which we found that the polymorphism of T→G change in -309 of MDM2 promoter may have no significant overall effect on the risk of prostate cancer, while it probably can be a protective factor to prostate cancer in European population and hospital-based population, though larger number of samples are required to clarify in future.

Materials and Methods

Selection of studies and data collection

We performed a systematic search of literature prior to July 2012 from PubMed and Medline with the terms of "prostate cancer" and "MDM2", resulting in 112 eligible publication candidates. After comprehensive screening, 4 independent studies published from 2008 to 2010 were selected for the meta-analysis, and the references of the 4 were also screened. Specific search workflow is shown in Figure 1. Then the following basic data was extracted from

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those studies for further analysis: first author, published year, source of controls, location, population (ethnicity), sample size and genotype distributions.

Statistical analysis

We performed overall as well as subgroup meta-analysis stratified by ethnicity or source of controls. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for evaluating the association between MDM2-SNP T309G and prostate cancer risk. We applied 4 genetic models (GT/TT, GG/TT, dominant model and recessive model) and 2 mathematical models (fixed effects model and random effects model) to calculate in order to get a more comprehensive analysis. Heterogeneity test was used to determine which mathematical model is more suitable. When the chi-square-based Q-test resulted a P value more than 0.10, fixed effects model was considered to be more precise, otherwise, random effects model was used. Egger's regression test was used to test publication bias and a P value more than 0.05 was considered as absence of publication bias.

In this study, we used R software (version 2.12.1) and the Meta package for R (www.r-project.org) to conduct all the analysis.

Results

Study characteristics

4 case-control studies (Kibel et al., 2008; Stoehr et al., 2008; Mandal et al., 2010; Xu et al., 2010), including 732 cases and 836 controls, published from 2008 to 2010 investigated the association between MDM2-SNP T309G and prostate cancer risk. The main characteristics of the four studies were shown in Table.1. Two of the studies carried out their research in Asian population while one in European population, the rest one by Adam was conducted in St.Louis, Missouri, USA, but they reported those subjects were all European descendants, thus, in the subgroup analysis, we considered them as European. Three of the studies recruited controls from hospital, which was used as another stratification criterion in subgroup analysis.

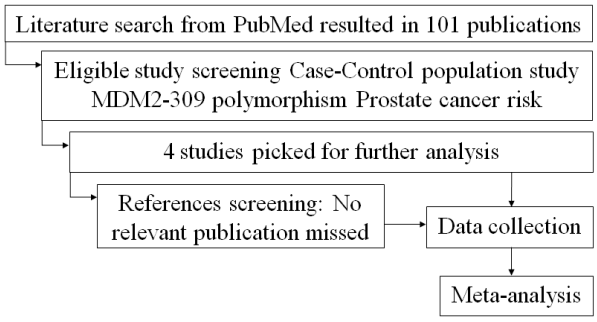

Figure 1. Workflow of the Meta-analysis

Overall and subgroup meta-analysis

The overall analysis of the studies revealed no significant association of MDM2-SNP T309G with prostate cancer risk no matter what kind of genetic model was used (Figure 2A), the pooled ORs and corresponding 95% confidence intervals were respectively: GT/TT OR=0.84, 95%CI=0.60-1.19; GG/TT OR=0.69, 95%CI=0.43-1.11; Dominant OR=0.81, 95%CI= 0.58-1.13; Recessive OR=1.23, 95%CI= 0.95-1.59. In subgroup analysis based on ethnicity, SNP T309G seemed to be protective factor in European population when additive (GG/TT) and recessive (GG/GT+TT) models were applied (GG/TT: OR=0.52, 95%CI=0.31-0.87; Recessive: OR=0.58, 95%CI=0.36-0.95), but no such effect was

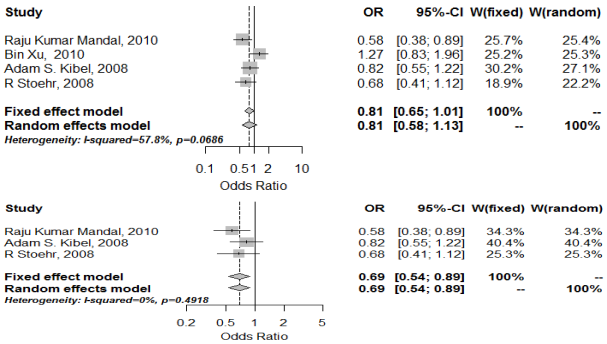

Figure 2. Forest Plot of Meta-analysis. A. Forest plot of overall meta-analysis under dominant model. B. Forest plot of subgroup meta-analysis of hospital-based population under dominant model

Table 1. Main Characteristics of the Four Case-Control Studies Included in the Meta-analysis

Study (First Author, Year)	Source of controls	Study Location	Population	Sampe Size (case/control)	Genotype Distribution (TT/TG/GG) Case	Control	Ref No.
Raju Kumar Mandal, 2010	Hospital	Lucknow, India	Asian	192/224	67/71/54	53/98/73	10
Bin Xu, 2010	Population	Nanjing, China	Asian	209/268	44/118/47	68/143/57	11
Adam S. Kibel, 2008	Hospital	St.Louis, Missouri, USA	European-descendant	186/220	85/88/13	90/98/32	12
R Stoehr, 2008	Hospital	Regensburg, Germany	European	145/124	61/66/18	41/64/19	13

Table 2. Overall and Subgroup Meta-analysis Under Four Genetic Models

Genetic model	Overall		Subgroup (ethnicity)						Subgroup (source of controls)			
			Asian		European(-descendant)		Hospital		Population			
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P		
GT/TT	0.84(0.60, 1.19)	0.084	0.86(0.39, 1.88)	0.016	0.84(0.61, 1.17)	0.353	0.74(0.57, 0.97)*	0.273	— —			
GG/TT	0.69(0.43, 1.11)	0.070	0.86(0.40, 1.84)	0.039	0.52(0.31, 0.87)*	0.459	0.55(0.38, 0.79)*	0.718	— —			
GT+GG/TT	0.81(0.58, 1.13)	0.069	0.86(0.40, 1.86)	0.011	0.76(0.56, 1.04)	0.558	0.69(0.54, 0.89)*	0.492	— —			
GG/GT+TT	1.23(0.95, 1.59)	0.196	0.93(0.68, 1.26)	0.361	0.58(0.36, 0.95) *	0.247	0.70(0.51, 0.97)*	0.311	— —			

*Effect is significant stastically

found in Asian population, Table 2. Interestingly, another subgroup analysis of hospital-based studies also revealed SNP T309G to be an anti-cancer polymorphism in all genetic models (GT/TT: OR=0.74, 95%CI=0.57-0.97; GG/TT: OR=0.55, 95%CI=0.38-0.79; GT+GG/TT: OR=0.69, 95%CI=0.54-0.89; GG/GT+TT: OR=0.70, 95%CI= 0.51-0.97), the forest plot of dominant model is shown in Figure 2B.

Publication bias test

No publication bias was found by Egger's regression test in each model (GT/TT: P=0.4707; GG/TT: P=0.6022; dominant model: P=0.8045; recessive model: P= 0.3164).

Discussion

MDM2 could bind to the N-terminal transactivation domain of p53, which functions as the principal endogenous E3-ligase with high specificity, thereby negatively modulates its transcriptional activity and stability (Bouska et al., 2009; Eischen et al., 2009; Kruse et al., 2009). SNP T309G, found in the MDM2 promoter, could increase the affinity of the transcriptional activator Sp1, leading to increased expression of MDM2 the subsequent down-regulation of p53(Bond et al., 2004). It is reported the MDM2-SNP T309G is associated with not only increased risk of gastric carcinoma, cervical cancer and liver cancer but also poor prognosis of several cancer types (Ohmiya et al., 2006). However, some studies showed absence of significant effect of SNP T309G on tumorigenesis. Brenda et al found the polymorphism was not statistically associated with breast cancer risk among African American or Caucasian women (Boersma et al., 2006), while data from a Chinese group showed no close connection between SNP T309G and breast cancer either (Ma et al., 2006).

Four independent studies were involved in the relationship between MDM2-SNP T309G and prostate cancer risk. Two of them (Kibel et al., 2008; Mandal et al., 2010) suggested the polymorphism acted as risk-reduced factor in developing prostate cancer and the rest two found no significant association. Besides, Jaboin reported the polymorphism was not associated with clinicopathologic variables, recurrence risk, and overall survival outcome in prostate cancer (Jaboin et al., 2011). Our meta-analysis of them revealed, overall, MDM2-SNP T309G did not increase the susceptibility to prostate cancer, while in European population, two genetic models found MDM2-SNP T309G to be a protective factor against prostate cancer which was different from that of Asian population. It indicated that the polymorphism probably played different role in different populations and compensatory mechanism was likely to exist in the P53 pathway, making the relationship between MDM2-SNP T309G and prostate cancer distinct from other cancer types. Meanwhile, another subgroup analysis considered the polymorphism to reduce prostate cancer risk in hospital-recruited population, and the result needed careful interpretation because of the relative small pooled sample size. However, a study carried out in a more reliable sample size of Caucasian population(Sun et al., 2010) could partially support our results, they found the Mdm2 SNP309 T allele was associated with earlier onset prostate cancer (P = 0.004), higher Gleason scores (P = 0.004), and higher stages in men undergoing a radical prostatectomy (P = 0.011).

In summary, this analysis provided a more comprehensive understanding of relation between MDM2-SNP T309G and prostate cancer risk. We found the T→G change in +309 of MDM2 promoter have no significant overall effect on the risk of prostate cancer, however, the polymorphism probably can be a protective factor to prostate cancer in European population and hospital-based population despite a larger number of samples are required to testify.

Acknowledgements

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