RESEARCH ARTICLE

Meta-analysis of the Relation Between the VDR Gene TaqIpolymorphism and Genetic Susceptibility to Prostate Cancer in Asian Populations

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Abstract

Background: Polymorphisms of the Taq I gene have been associated with prostate cancer risk. Methods: We applied a fixed-effects model to combine odds ratios (ORs) and 95% confidence intervals (95% CI). The Egger's test was carried out to evaluate potential publication bias. Results: A total of 10 case-control studies enrolling 1,141 prostate cancer patients and 1,685 controls were included in this meta-analysis. Compared with the T allele, the OR for the C allele was 0.81 (0.70-0.94). The ORs for CT and CC+CT genotypes were 0.86 (0.74-1.01) and 0.84 (0.73-0.97) compared to wide type genotype (homozygote TT). Conclusions: The present meta-analysis suggests that the TF gene Taq I polymorphism may reduce the prostate cancer risk in Asian populations.

Keywords: Vitamin D receptor - Taq I - prostate cancer - Asian populations - meta-analysis

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Introduction

Prostate cancer is one of the most common malignancies which harm men's health in United States and Europe; it is also the second largest tumor causing male deaths. It is estimated by American Cancer Society that the new prostate cancer patients were 192,000 cases in 2009 in U.S, and 27,000 cases died of prostate cancer (Jemal et al., 2009). In Europe, new cases of prostate cancer were about 260 million every year, the patients with prostate cancer accounted for 11% of total male patients with cancer, and the patients died of prostate cancer accounted for 9% of total male patients died of any cancer. With the aging of our population and the improvement of diagnostic techniques, the morbidity and mortality of prostate cancer showed an increasing trend. The morbidity of prostate cancer has exceeded lung cancer, and ranks first; the mortality of prostate cancer ranks second after lung cancer (Ming et al., 2009). The pathogenesis of prostate cancer is complex, it is widely recognized that age, race and family history of cancer are the risk factors (Zhang et al., 2012). With the development of molecular biological techniques, it is recognized that the pathogenesis of prostate cancer may be the result of role of multiple genes (Schaid et al., 2004).

The human vitamin D receptor (VDR) is a nuclear receptor gene with 75 kb, located in the long arm of chromosome 12, and consists of 11 exons and 11 introns (Zmuda et al., 2000). Schwartz, et al believed that low dose ultraviolet radiation was a risk factor for prostate cancer (Schwartz et al., 1990; Moon et al., 2005). The skin produced vitamin D after exposure to UV, then the vitamin D was hydroxylated to D3[25(OH)D_3] in liver, next, the D3[25(OH)D_3] was transformed to biologically active D3[1,25(OH_2)D_3] in kidney; in addition, VDR is not only expressed in kidney and bone, it is also detected in prostate cells(Hidalgo et al.,2007). It has been reported that 1,25(OH_2)D_3 could promote differentiation, enhance immune regulation, and inhibit cell necrosis, tumor invasion and metastasis in prostate (Krishnan et al., 2003; Bao et al., 2006), all these biological effects were mediated by VDR(Schwartz 2012). Corder et al. (1993) believed that 1,25(OH_2)D_3 in peripheral blood was decreased significantly in prostate cancer susceptible population. Lots of gene polymorphism of VDR3' end have been discovered so far, such as ApaI, BsmI, TaqI, Tru9I, EcoRV, in which TaqI(rs731236) has been widely studied. TaqIpolymorphism located at codon 352, the wild-type T allele was transformed into the mutant C allele (ATT-ATC) (Vieira et al., 2006).

There was controversy in the researches of VDR and susceptibility to prostate cancer; in this study, we collected all literatures about VDR gene TaqI polymorphism and Asian men with prostate cancer, and analyzed them with Meta-analysis to evaluate comprehensively the relationship of VDR gene TaqI polymorphism and genetic susceptibility to prostate cancer in Asian men.

Materials and Methods

Literature collection

Search the key words "VDR" or "Vitamin D receptor", "polymorphism" and "prostate cancer" in

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Table 1. General Data of Study

author	Published year	Country	Cases (prostatic cancer/control)	Protatic cancer			control		
				CC	CT	TT	CC	CT	TT
Bai	2009	China	122/130	0	10	112	0	9	121
Onsory	2008	India	100/100	5	40	55	9	48	43
Huang	2004	China	160/205	0	14	146	0	26	179
Chaimuangraj	2006	Bangkok	28/74	0	6	22	1	14	59
Liu	2004	China	103/226	0	10	93	0	22	204
Suzuki	2003	Japan	81/105	2	20	59	2	20	83
Hamasaki	2001	Japan	115/133	2	22	91	8	34	91
Hamasaki	2002	Japan	110/173	2	21	87	9	41	123
Habuchi	2000	Japan	222/337	2	44	176	3	81	253
Watanabe	1999	Japan	100/202	2	18	80	6	36	160

Pubmed database; at the same time, search the Chinese key words in VIP, WanFang, CBM and CNKI database until September, 2010. Collect the potentially relevant literatures through manual literature retrospective way.

Inclusion and exclusion criteria

The inclusion criteria are as followings: 1) the study is based on analysis of the relationship of VDR gene TaqI polymorphism and genetic susceptibility to prostate cancer; 2) case-control study; 3) genotype frequency distribution; 4) age matching between treatment group and control group; the literature must be full-text. The exclusion criteria are as followings: 1) no control group; 2) no genotype frequency distribution; 3) duplicated research; 4) there is a serious bias.

Data extraction and statistical analysis

Each article was evaluated independently by two reviews; the relevant information was extracted and inputted to computer to create the database. The relevant information included the first author, publication year, countries, the source of controls, genotype frequency and the total number of treatment group and control group.

Three models were chosen to analyze the VDR gene TaqIpolymorphism and genetic susceptibility to prostate cancer: allele model (C vs. T), heterozygous model (CT vs. TT) and dominant model (CC+CT vs. TT). In this study, the included studies were analyzed with heterogeneity test (q test), then select the appropriate combination method according to q test results: if $P<0.05$, use fixed effect model (DerSimonian and Laird) to calculate the pooled OR and 95% confidence interval (Dersimonian et al., 1986); if $P>0.05$, use random effect model (Mantel-Haenszel) to calculate the pooled OR and 95% confidence interval (Jose et al., 2008), and finally make a forest graph. The publication bias is indentified by funnel plot and linear regression proposed (Williamson et al., 2005), a $P<0.05$ was considered to be publication bias. Data were analyzed with Stata 10.0 software.

Results

Basic information

Through literature retrieval, we found 27 literatures were about the VDR gene TaqI polymorphism and genetic susceptibility to prostate cancer. In which the objects were Asian population in 12 articles; and one was not

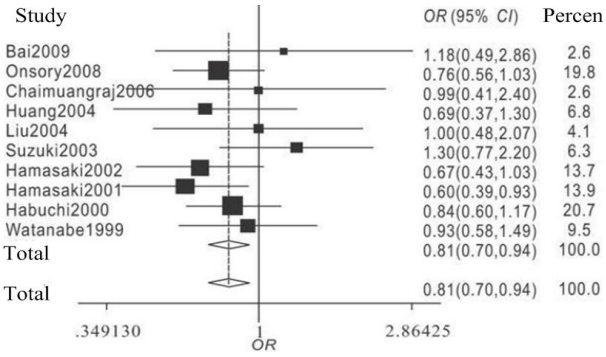

Figure 1. A Meta Analysis of Relation Between Taq I Polymorphism and Prostatic Cancer Susceptibility. (C vs T)

control study (Bid et al., 2005); two shared the prostate cancer cases (Jianhe et al., 2004a; Jianhe et al., 2004b), so we only chose one according to our exclusion criteria (Jianhe et al., 2004a). At last, 10 articles were included in Meta-analysis (Watanabe et al., 1999; Habuchi et al., 2000; Hamasaki et al., 2001; Hamasaki et al., 2002; Suzuki et al., 2003;Huang et al., 2004; Jianhe et al., 2004a; Chaimuangraj et al., 2006; Onsory et al., 2008; Bai et al., 2009), including 1141 cases and 1685 control. The basic information are shown in Table 1. The objects were divided into three groups in 4 literatures (Habuchi et al., 2000; Hamasaki et al., 2002; Jianhe et al., 2004a; Chaimuangraj et al., 2006): group prostate cancer, group prostatic hyperplasia and control group, we combined the cases of group prostatic hyperplasia and normal control group as control group.

Analysis of data combination

Due to the variables used to adjust OR value were different in each study, we only combined the crude OR values of each study. $P_{heterogeneity}>0.05$, it can't be considered significant heterogeneity among all studies, so we used fixed effect model to combine the studies. The mutant allele C of TaqI might be related to reduce prostate cancer risk compared to allele T (OR=0.81, 95%CI: 0.70-0.94, Pheterogeneity=0.578, Figure 1). There was no correlation between wild-type TT genotype and mutant CT genotype of TaqI (OR=0.86, 95%CI: 0.74-1.01, $P_{heterogeneity}=0.820$), however, TaqIcarried the dominant CC+CT genotype might be associated with decrease of prostate cancer risk compared to wild-type TT genotype (OR=0.84, 95%CI: 0.73-0.97, $P_{heterogeneity}=0.702$, Figure 2).

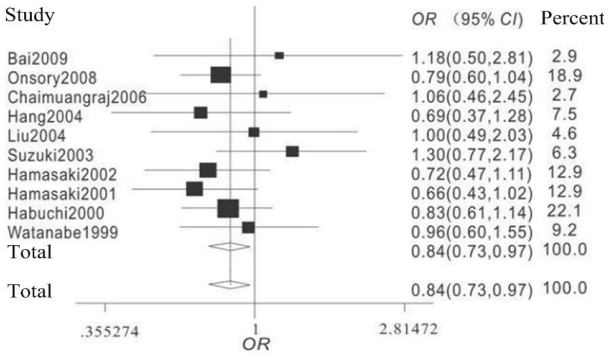

Figure 2. A Meta Analysis of Relation Between Taq I Polymorphism and Prostatic Cancer Susceptibility. (CC+CT vs TT)

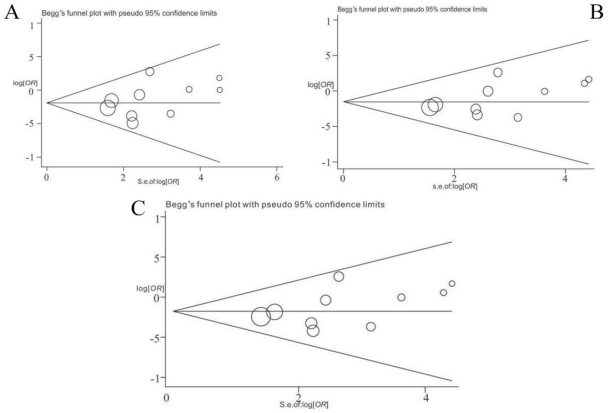

Figure 3. A Funnel-plot Analysis of Relation Between Taq I Polymorphism and Prostatic Cancer Susceptibility. A: C vs T; B: CT vs TT; C:CC+CT vs TT

Publication bias

Draw a funnel plot of each genotype based on the OR value and sample size, all funnel plot are symmetrical (Figures 3A-C). Egger test showed that C vs. T (t=1.27, P=0.239), CT vs. TT (t=1.66, P=0.135), CC+CT vs. TT (t=1.39, P=0.201), suggesting that there was no significant publication bias of VDR gene TaqI, the results are credible.

Discussion

The mechanism of Vitamin D inhibiting tumor is that its main active form 1,25 (OH_2) D_3 play biological role via VDR, after the combination of 1,25(OH_2)D_3 and VDR, VDR and retinoid X receptor (RXR) form a dimeric complex, which bind the specific DNA sequences in promoter regulatory regions of target gene upstream, to regulate downstream transcription of a series of target genes, such as cell cycle dependence kinase (CCDK) inhibitory protein P16, P21 and P27, etc. The inhibitory protein can inhibit the activation of CCDK complexes, then the cells are arrested in G0/G1 phase; therefore, the proliferation of tumor cells is inhibited (Campbell et al., 1997; Ylikomi et al., 2002).

The relationship of VDR gene TaqIpolymorphism and genetic susceptibility to prostate cancer has been extensively reported (Cariati et al., 2012), however, these studies were small-sample researches, and the results are incredibility and inconsistent; therefore, these studies should be combined analyzed to evaluate the relationship VDR gene TaqI polymorphism and genetic susceptibility to prostate cancer in Asian men. We combined analyzed 10 case-control studies through a rigorous screening with Meta-analysis (1141 cases of prostate cancer, 1685 cases of control). The results showed that C vs. T (OR=0.81, 95%CI: 0.70- 0.94, $P_{heterogeneity}$=0.578, P=0.006); CC+CT vs. TT (OR=0.84, 95%CI: 0.73-0.97, $P_{heterogeneity}$=0.702, P=0.020), suggesting individuals carried the mutant allele C have less risk of suffering from prostate cancer, allele C is a protective mutant.

This study has some limitations: 1) the number of cases and control is not much enough; 2) the confounding factors failed to control, such as occupation, diet, smoking and mental, which will affect the results; 3) the interaction between gene and gene, gene and environment, VDR and other locus can adjust the risk of prostate cancer; 4) the study included a small-sample study, its representative is not strong (Chaimuangraj et al., 2006); 5) the pathogenesis of sporadic and hereditary prostate is different, and we didn't classify according to it; 6) there are four literatures which included group prostate care, group prostatic hyperplasia and control group, we combined the latter two groups as the control group, it is not the normal control group in strict terms. However, this study has three advantages: 1) the included studies are from different samples, which have a widely representation; 2) all case-control studies met the inclusion criteria; 3) there was no significant publication bias through qualitative funnel plot and quantitative Egger linear regression.

In summary, we analyzed the VDR gene TaqIpolymorphism and genetic susceptibility to prostate cancer in Asian men with Meta-analysis, and confirmed that VDR gene TaqI allele C is a protective mutant, which could reduce the risk of suffering from prostate cancer, and might be a new marker of prostate cancer screening. However, the sample size is small in our study, it needs further multi-center and large sample studies to confirm the results. In addition, we only analyzed the VDR gene TaqI locus, without considering the interaction between genes, genes and environment. In future study, we will further explore the other interaction, to facilitate the discovery of the pathogenesis of prostate cancer.

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