

Meta-analysis on Vitamin D Receptor TaqI Polymorphism and Breast Cancer Risk

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KEYWORDS

Vitamin D Receptor;
Polymorphism;
Breast Cancer;
Meta-Analysis

ABSTRACT

Vitamin D receptor (VDR) principally mediates the anticancer activities of vitamin D. Many studies investigated the association between VDR gene TaqI polymorphism and breast cancer, but the results were inconclusive. We performed this meta-analysis to evaluate the association between VDR gene TaqI polymorphism and breast cancer. 21 studies with a total of 10232 cancer cases and 11708 control subjects were identified from PubMed, Embase, Ovid Medline and CNKI databases. The pooled odds ratio (OR) and confidence intervals (95 % CI) were used to assess the association. The meta-analysis indicated that VDR gene TaqI polymorphism was associated with risk of breast cancer (T vs. t, OR = 0.94, 95 % CI 0.91–0.98, $p = 0.004$; TT vs. tt, OR = 0.88, 95 % CI 0.80–0.95, $p = 0.002$; TT vs. Tt, OR = 0.98, 95 % CI 0.92–1.04, $p = 0.445$; TT vs. Tt+tt OR = 0.95, 95 % CI 0.90–1.01, $p = 0.078$; TT+Tt vs. tt, OR = 0.89, 95% CI .82-0.96, $p = 0.002$). Subgroup analysis by ethnicity further showed the polymorphism of VDR TaqI was a potential risk factor for breast cancer in the Caucasian population (OR T vs. t = 0.94, 95 % CI 0.91–0.98, $p = 0.004$; OR TT vs. tt = 0.88, 95%CI 0.81–0.97, $p = 0.002$).

INTRODUCTION

Vitamin D (1,25-dihydroxyvitamin D₃, 1,25(OH)₂D₃) is a fat soluble secosteroid which is involved in a variety of biological processes like bone metabolism, immune response, cell proliferation and cell differentiation^[1-4]. Vitamin D has mainly been investigated for its role in the maintenance of calcium and phosphate homeostasis, and bone health^[2]. However, it is also involved in a wide range of other health issues, cardiovascular diseases, metabolic disorders, allergy and cancer^[5-8]. In several studies, vitamin D has been shown to promote cell differentiation and inhibit cell proliferation, potentially modifying cancer risk via binding to the VDR^[1]. The hormonal metabolite of vitamin D, 1 α ,25-dihydroxyvitamin D₃ (1,25D), initiates biological responses *via* binding to the vitamin D receptor (VDR). The mechanism of

vitamin D action is mediated by the nuclear VDR and the signaling cascade for its action is extensively reported. The vitamin D receptor (VDR) is a member of the nuclear receptor superfamily of transcriptional regulators, which is located in the long arm of chromosome 12 (12q12-14), and consists of 11 exons and 11 introns^[9], VDR is involved in inflammation, insulin-like growth factor signaling, and estrogen-related pathways beyond the activation and regulation of vitamin D and calcium^[8]. The VDR specifically binds to vitamin D and interacts with specific nucleotide sequences of target genes to produce a variety of biological effects. As vitamin D exerts its activity by binding to the VDR, the findings that normal breast epithelial cells and most breast cancer cells express VDR, suggest the possibility that VDR gene polymorphism may be involved in breast cancer risk. Breast can-

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cer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide. Breast cancer alone accounts for 25% of all cancer cases and 15% of all cancer deaths among females^[10]. There are three main factors regulating the VDR, namely environment, genetics and epigenetics^[11]. The VDR genotype is a significant determinant of VDR mRNA and VDR protein^[8]. VDR is expressed in many types of cancer including breast, cervix, ovary, and many others^[12]. The gene that encodes VDR harbors approximately 200 single nucleotide polymorphisms (SNPs). Over the years, there are a growing body of epidemiological studies shows that VDR polymorphisms including FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232) a polyadenosine (poly-A) repeat variant and TaqI (rs731236) with breast cancer incidence and therefore risk^[13–16]. BsmI located on intron 8, ApaI located on intron 9 have shown to influence gene transcription and mRNA stability. FokI located on exon 2 have been associated with a frameshift in the VDR protein. TaqI located on exon 9, The 3' TaqI SNP is located in a CpG site, VDR TaqI genotype influences regional DNA methylation of a 3' end CpG island^[17]. Its genotype has been found to influence not only methylation at this site, but also regional methylation of CGI 1060 at the 3' end of the VDR^[17]. SNPs such as FokI, G-1739A and A-1012G in the promoter appear to consistently influence VDR expression. However, functional findings on the commonly studied 3' UTR SNPs TaqI have been conflicting. To clarify the association between breast cancer risk and VDR TaqI polymorphisms, we performed a meta-analysis of 21 existing studies to clarify the relationship between genetic variations in VDR and the risk of breast cancer.

MATERIALS AND METHODS

Search Strategy

We performed a systemic search for all relevant literature. The literatures were obtained from the following databases using validated search strategies: PubMed, Ovid Medline, EMBASE, and CNKI (China National Knowledge Infrastructure) up to April 2015. We used the MeSH index terms 'VDR', 'Vitamin D receptor', or 'TaqI', and 'rs731236' in combination with 'breast cancer'.

Study Selection

The inclusion criteria to identify an eligible study were as follows: **1)** They were case-control or cohort studies; **2)** The studies had to be independent and not duplicate results published in another article; **3)** They showed sufficient information to estimate an odds ratios (OR) and 95% confidence intervals (95% CI) for the association between TaqI polymorphisms and breast cancer.

Data Abstraction

Data extraction was carried out independently by investigators. We screened titles, looked at abstracts and, if the abstract content was relevant, full copies of articles were retrieved and read by at least two coauthors. The following

information was recorded for each eligible study: the first author's name, the year of publication, country and ethnicity of the study population, source of controls (hospital or population), the number of genotypes and genotyping methods.

Statistical Analysis

The strength of the association between VDR TaqI polymorphism and the risk of breast cancer was assessed under the following genetic contrast models: T vs. t, TT vs. tt, TT vs. Tt, TT vs. Tt+tt and TT+Tt vs. tt by calculating the pooled OR and its 95% confidence interval (CI). The pooled ORs were obtained using either the fixed-effects (Mantel-Haenszel' method) model^[18] or the random-effect (DerSimonian and Laird method) model^[3], depending on the absence or presence of significant heterogeneity. The significance of pooled ORs was determined by the Z test. Heterogeneity among studies was assessed by the Chi-square test-based Q statistic and was quantified using the I² statistic^[19]. A significant Q statistic (p -value < 0.10) or I² statistic (I² > 50%) indicated significant heterogeneity existed across studies. Sensitivity analysis was performed to evaluate the key studies that had substantial impacts on between-study heterogeneity levels by removing the individual studies sequentially. All statistical analyses were performed using STATA statistical software (version 13.0; Stata Corporation, College Station, USA). The possibility of publication bias was assessed using funnel plots. An asymmetrical funnel plot suggested a possible publication bias.

RESULTS

Eligible Studies

A flow chart of the relevant studies is shown in **Figure 1**. According to the inclusion criteria, 21 studies were identified about the association between the TaqI polymorphism of *VDR* gene and breast cancer risk. A total of 10232 cancer cases and 11708 control subjects were included. The main characteristics of all the 21 studies are shown in **Table 1**. The 21 studies consisted of 12 Caucasian, 6 Asian, one African, two mixed ethnicity, which were enrolled from population-based controls (10 studies), hospital-based controls (9 studies), and mixed-based controls two studies. Moreover, the classical genotyping method PCR-RFLP was performed in the most studies.

Meta-Analysis

For the polymorphism of VDR TaqI, significant genetic association was identified in comparisons of T vs. t, TT vs. tt, TT vs. Tt, TT+Tt vs. tt, TT vs. Tt+tt (OR = 0.94, 95 % CI 0.91–0.98, p = 0.004; OR = 0.88, 95 % CI 0.80–0.95, p = 0.002; OR = 0.98, 95 % CI 0.92–1.04, p = 0.445; OR = 0.95, 95 % CI 0.90–1.01, P =0.078, OR = 0.89, 95% CI .82-0.96, p = 0.002). Overall, the polymorphism of VDR TaqI was a potential risk factor for breast cancer. In the subgroup analysis based on ethnicity, the pooled ORs revealed that the polymorphism of VDR TaqI was a potential risk factor for breast cancer in the Caucasian population (OR T vs. t = 0.94, 95 %

CI 0.91–0.98, $p = 0.004$; OR TT vs. tt = 0.88, 95%CI 0.81–0.97, $p = 0.002$). In addition, the VDR TaqI polymorphism seemed to exert no effect on breast cancer in Asians, Africa and mixed ethnicity. The heterogeneity analysis indicated that studies in Asians were the main source of between-study heterogeneity. The between-study heterogeneity was not significant under all genetic contrast models (Table 2).

Sensitivity Analysis and Publication Bias Evaluation

Sensitivity analysis further confirmed the pooled results. Both Begg's test and Egger's test were performed to assess the publication bias of the literature. Funnel plots were done to estimate the publication bias of literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis. Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not present any obvious evidence of publication bias.

DISCUSSION

The important roles between VDR polymorphisms and breast cancer have been investigated across the world. Many studies have been carried out to investigate the relationship between VDR gene polymorphisms and the risk of breast cancer. However the results have been conflicting and inconsistent. The role of VDR TaqI polymorphisms in the risk of cancer is controversial. To better define the possible clinical relevance, we carried out a comprehensive meta-analysis of VDR TaqI polymorphisms. The current meta-analysis based on 21 studies with 10232 cancer cases and 11708 control subjects suggested that the TaqI polymorphism was associated with the overall risk of breast cancer development. When we stratified the subgroups according to ethnicity, the results showed no statistical evidence for breast cancer risk among Asians, Africans and other ethnicities. We find that the polymorphism of VDR TaqI is a potential risk factor for breast cancer, the polymorphism of VDR TaqI is a potential risk factor for breast cancer in the Caucasian population (OR T vs. t = 0.94, 95 % CI 0.91–0.98, $p = 0.004$; OR TT vs. tt = 0.88, 95%CI 0.80–0.95, $p = 0.002$).

Numerous studies have investigated the association of VDR TaqI polymorphism with breast cancer. However, the association has been controversial. The conflicting results between these studies might be attributed to differences in sample size, ethnicity, genotyping methods and geographic variations. Some VDR meta-analyses have been published^[15,16,20-25], but the results are controversial, herein we investigated sources of heterogeneity, including ethnicity to conclude a comprehensive result.

As in all research, there are some limitations in the current meta-analysis. First, most of the patients were Caucasians and Asians, which limited the general application of the findings from the meta-analysis. Secondly, limited studies and the sample size of the included studies were relatively small, which could reduce the power of this analysis. Thirdly, the original data of the eligible studies are unavailable. Forth,

due to the deficient of age, environmental factors, meta-analysis was present unadjusted ORs.

CONCLUSION

Summary, this analysis suggested that the polymorphism TaqI of VDR may be associated with breast cancer risk in Caucasian women. Nevertheless, more studies with larger sample sizes are needed to obtain more reliable results.

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FIGURE LEGENTS

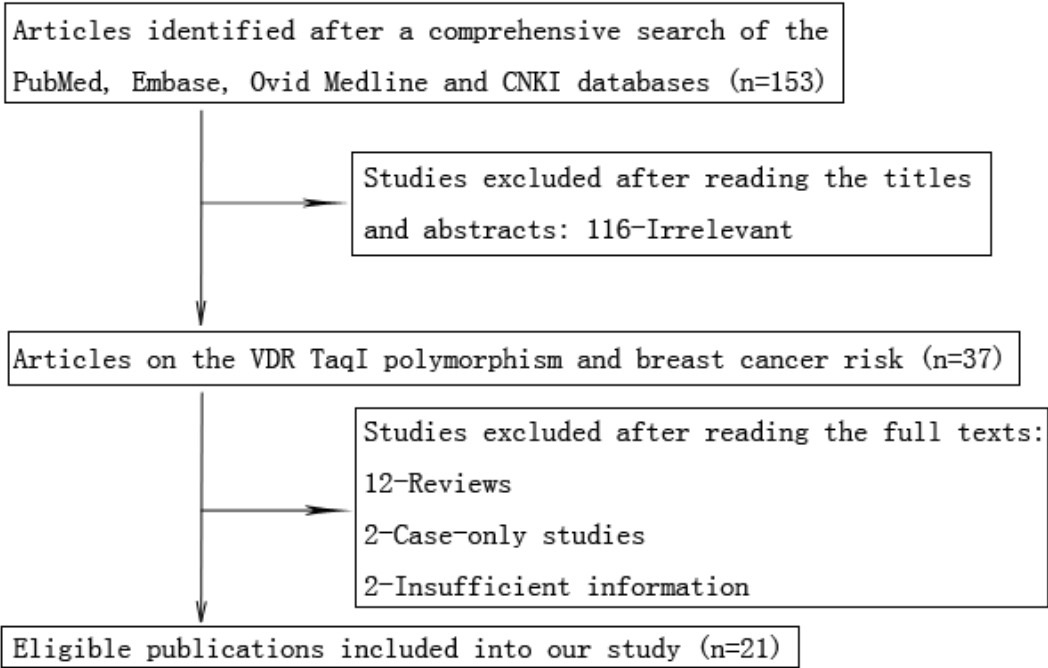


Figure 1 | Flowchart for relevant studies

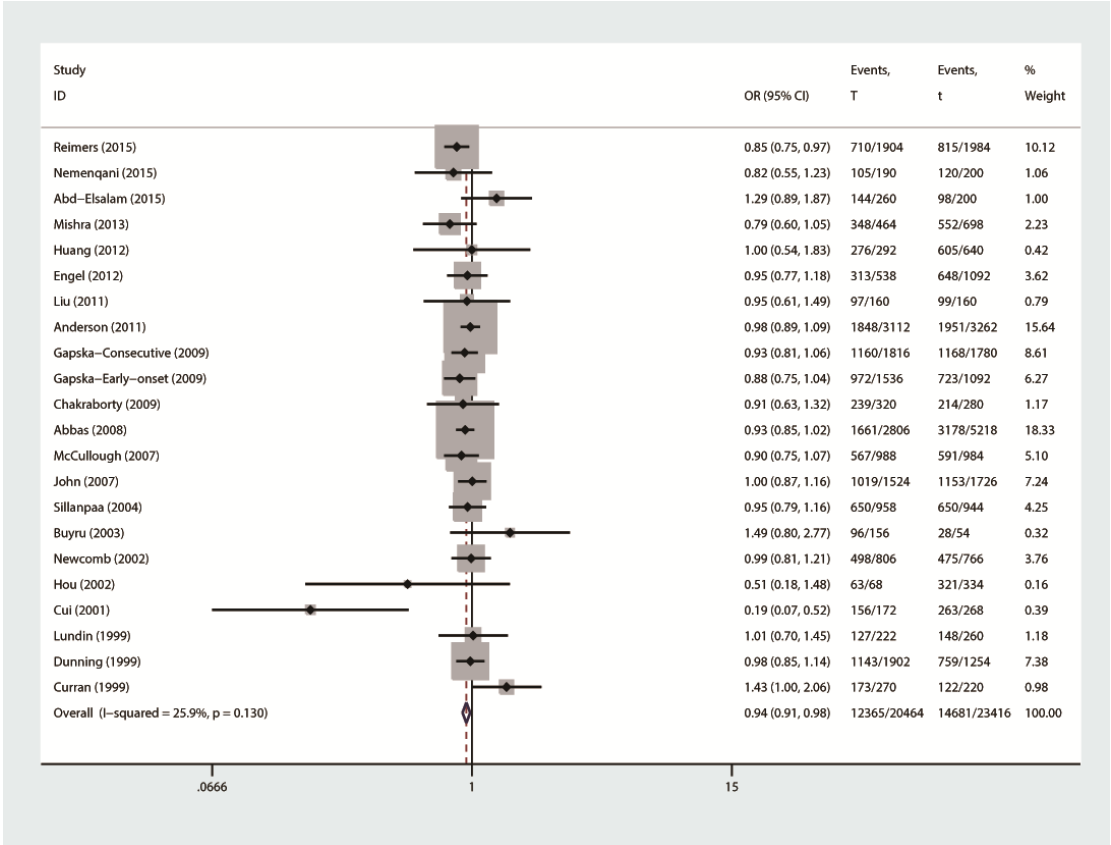


Figure 2 | Forest plots of association of TaqI polymorphism with breast cancer (T vs. t)

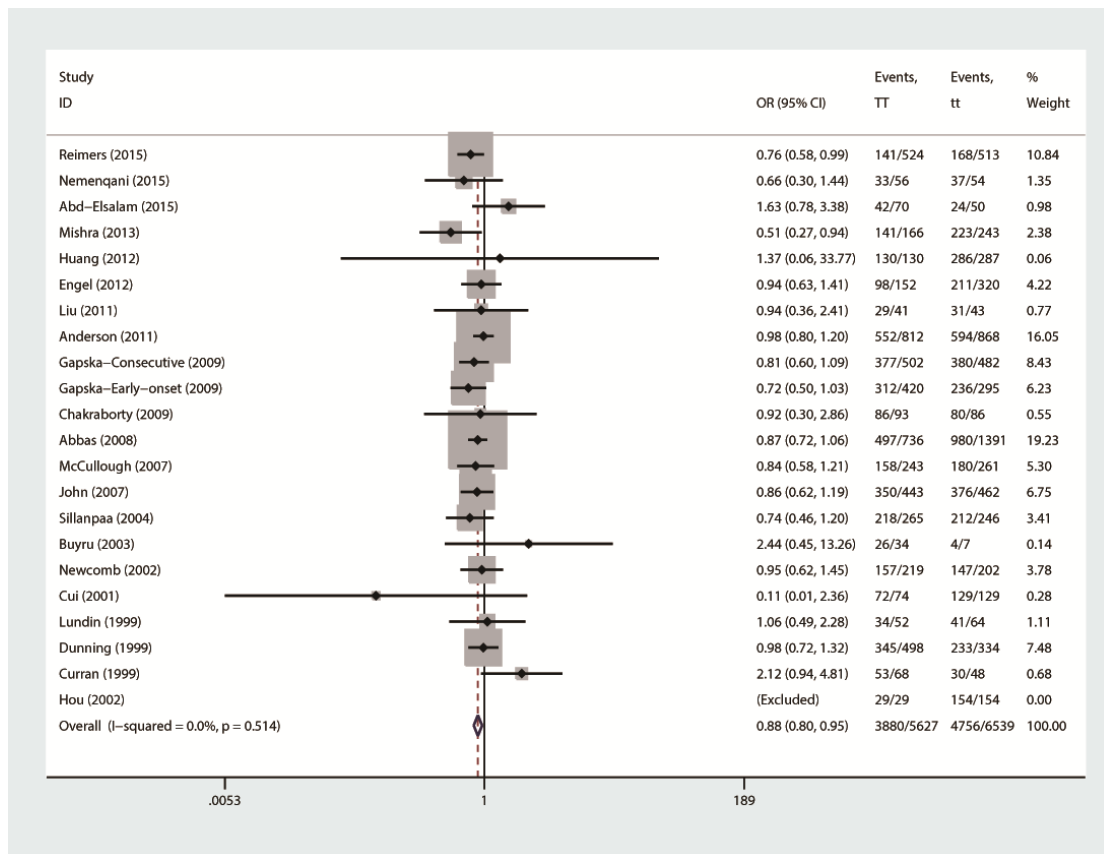


Figure 3 | Forest plots of association of TaqI polymorphism with breast cancer (TT vs. tt)

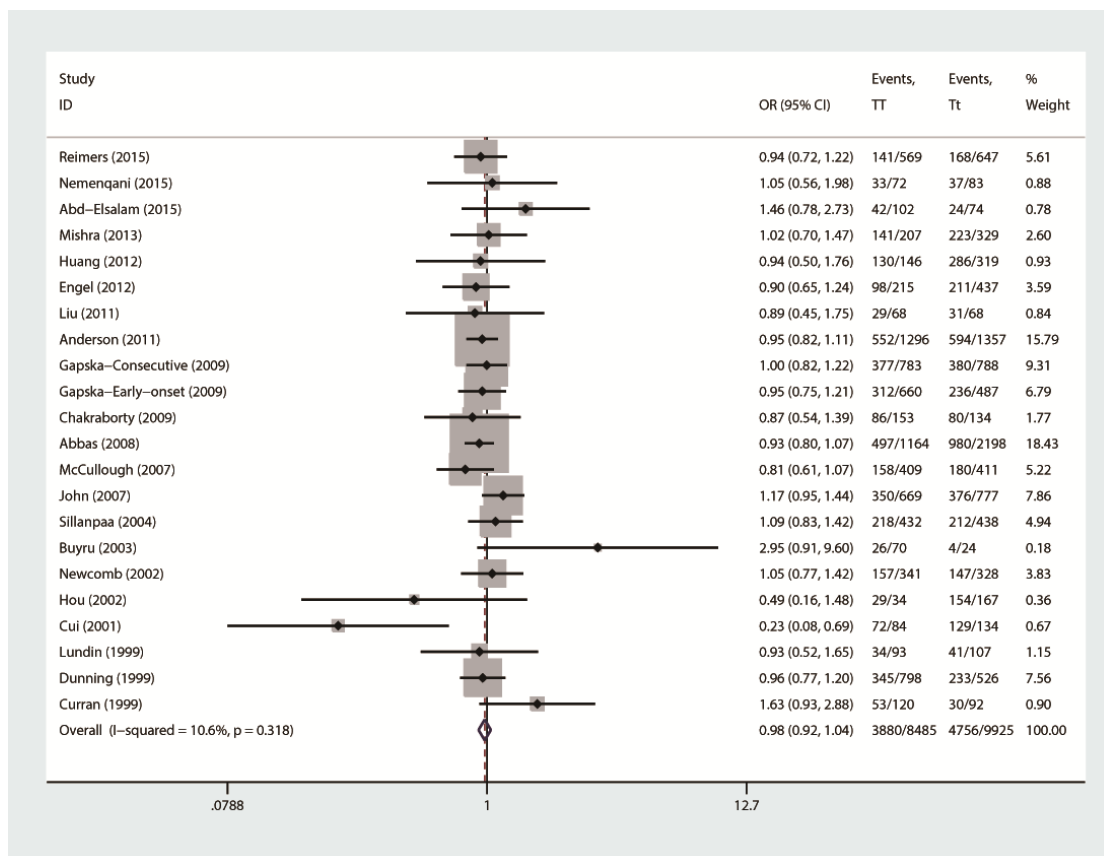


Figure 4 | Forest plots of association of TaqI polymorphism with breast cancer (TT vs. Tt)

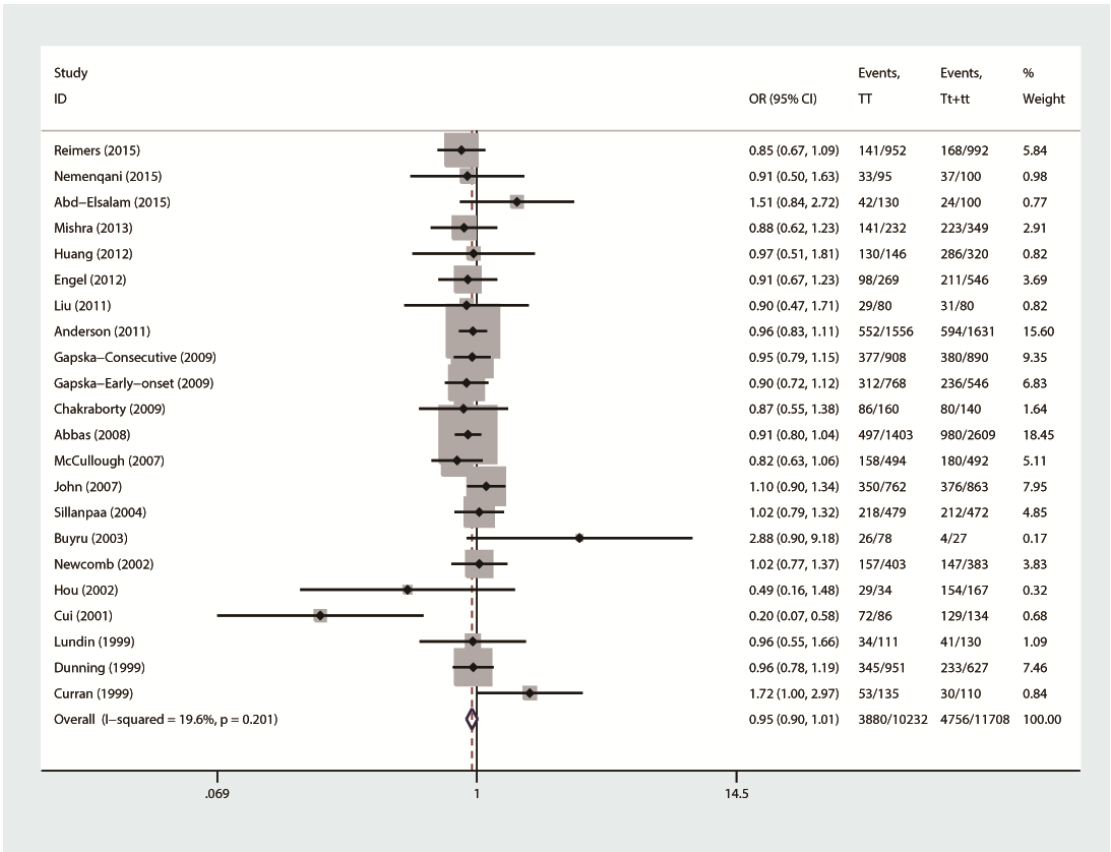


Figure 5 | Forest plots of association of TaqI polymorphism with breast cancer (TT vs. Tt+tt)

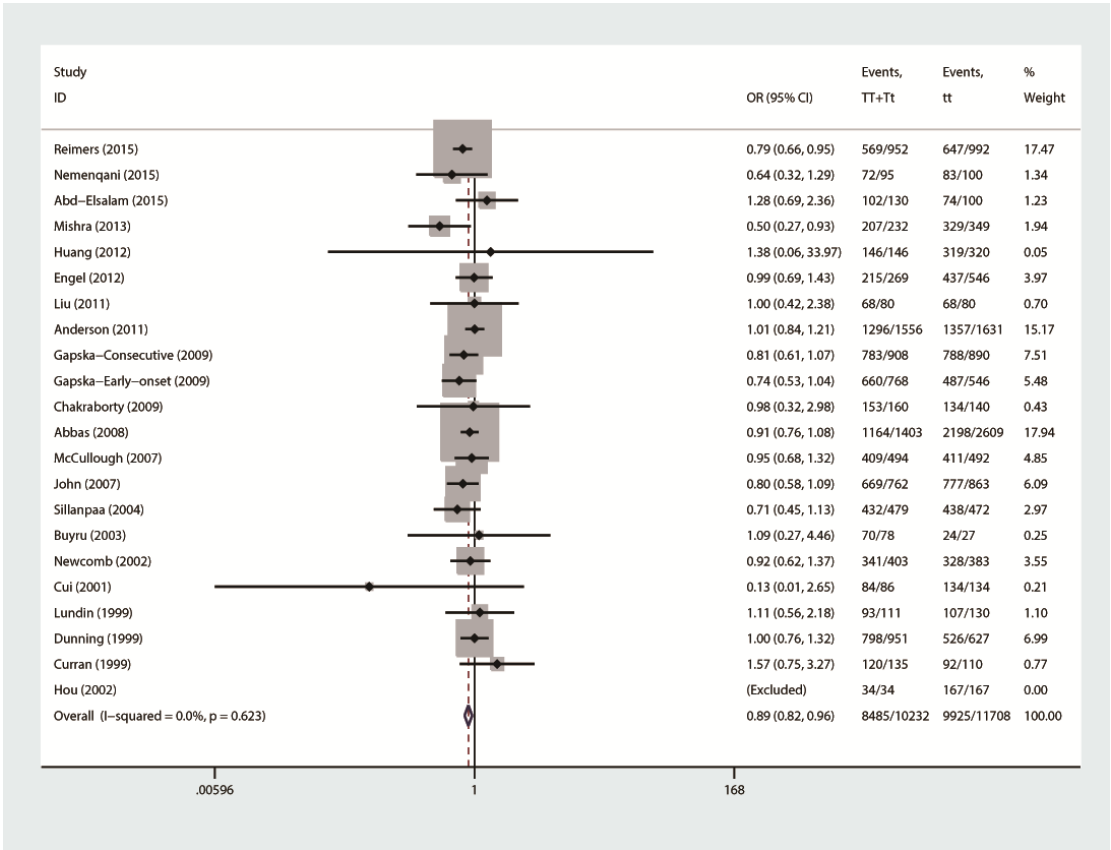


Figure 6 | Forest plots of association of TaqI polymorphism with breast cancer (TT+Tt vs. tt)

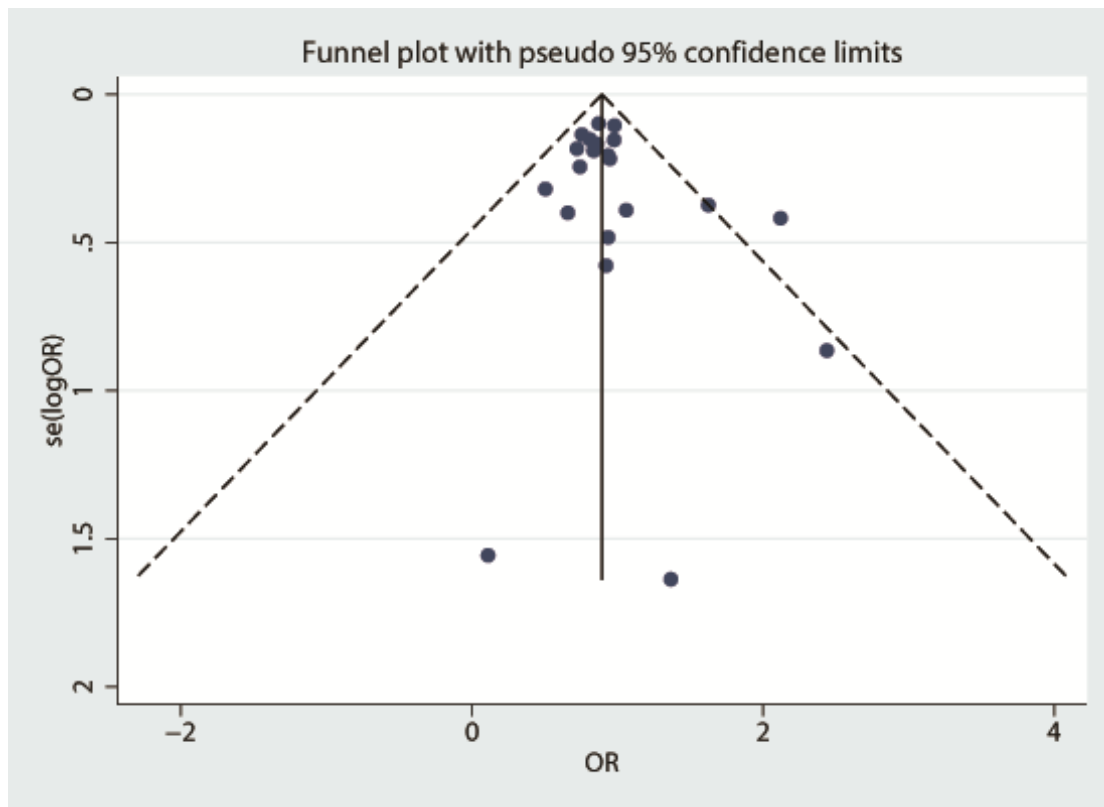


Figure 7 | Funnel plots of association of TaqI polymorphism with breast cancer (TT vs. tt)

TABLES

Table 1 | Characteristics of studies included in this meta-analysis between the TaqI polymorphism in the vitamin D receptor gene and breast cancer

Study	Year	Country	Ethnicity	Source of control	Genotyping method	Case TT/Tt/tt	Control TT/Tt/tt	HWE
Reimers[26]	2015	USA	Caucasian	Hospital	TaqMan	141/428/33	168479/345	0.9368
Nemenqani[27]	2015	Saudi	Asian	Not reported	PCR-RFLP	33/39/23	37/46/17	0.6772
Abd-El salam[28]	2015	Egyptian	Africa	Population	PCR-RFLP	42/60/28	24/50/26	0.9968
Mishra[29]	2013	USA	Mixed	Hospital	PCR-RFLP	141/66/25	223/106/20	0.1351
Huang[30]	2012	China	Asian	Hospital	PCR-RFLP	130/16/0	286/33/1	0.9632
Engel[31]	2012	USA	Caucasian	Population	MassARRAY system	98/117/54	211/226/109	0.0009
Liu[32]	2011	China	Asian	Hospital	PCR-RFLP	29/39/12	31/37/12	0.8602
Anderson[33]	2011	Canada	Caucasian	Population	MassARRAY system	552/744/260	594/763/274	0.2773
Gapska-Consecutive[34]	2009	Poland	Caucasian	Population	TaqMan	377/406/125	380/408/102	0.6331
Gapska-Early-onset[34]	2009	Poland	Caucasian	Population	TaqMan	312/348/108	236/251/59	0.5213
Chakraborty[35]	2009	Indian	Asian	Hospital	PCR-RFLP	86/67/7	80/54/6	0.3942
Abbas[36]	2008	Germany	Caucasian	Population	PCR-RFLP	497/667/239	980/1218/411	0.3151
McCullough[37]	2007	USA	Caucasian	Population	TaqMan	158/251/85	180/231/81	0.636
John[38]	2007	USA	Mixed	Population	TaqMan	350/319/93	376/401/86	0.16
Sillanpaa[39]	2004	Finland	Caucasian	Population	PCR-RFLP	218/214/47	212/226/34	0.0102
Buyru[40]	2003	Turkey	Caucasian	Not reported	PCR-RFLP	26/44/8	4/20/3	0.0102
Newcomb[41]	2002	USA	Caucasian	Population	TaqMan	157/184/62	147/181/55	0.9525
Hou[42]	2002	china	Asian	Hospital	PCR-RFLP	29/5/0	154/13/0	-
Cui[43]	2001	china	Asian	Hospital	PCR-RFLP	72/12/2	129/5/0	-
Lundin[44]	1999	Sweden	Caucasian	Hospital	PCR-RFLP	34/59/18	41/66/23	0.6877
Dunning[45]	1999	UK	Caucasian	Population	PCR-RFLP	345/453/153	233/293/101	0.5812
Curran[46]	1999	Australia	Caucasian	Hospital	PCR-RFLP	53/67/15	30/62/18	0.1384

Table 2 | The main results of this meta-analysis

Models	OR	95%CI	P(OR)	I ² (%)	P(I ²)
Caucasians					
T vs. t	0.94	0.90-0.98	0.008	0.0	0.451
TT vs. tt	0.88	0.81-0.97	0.007	0.0	0.528
TT vs. Tt	0.96	0.90-1.03	0.277	0.0	0.604
TT vs. Tt+tt	0.94	0.89-1.00	0.069	0.0	0.495
TT+Tt vs. tt	0.90	0.83-0.97	0.009	0.0	0.649
Asians					
T vs. t	0.82	0.66-1.01	0.057	49.9	0.076
TT vs. tt	0.74	0.45-1.23	0.250	0.0	0.722
TT vs. Tt	0.81	0.62-1.06	0.125	27.6	0.227
TT vs. Tt+tt	0.79	0.61-1.02	0.071	38.5	0.149
TT+Tt vs. tt	0.76	0.47-1.22	0.253	0.0	0.685
Africa					
T vs. t	1.29	0.89-1.87	0.174	-	-
TT vs. tt	1.63	0.78-3.38	0.194	-	-
TT vs. Tt	1.46	0.78-2.73	0.238	-	-
TT vs. Tt+tt	1.51	0.84-2.72	0.169	-	-
TT+Tt vs. tt	1.28	0.69-2.36	0.429	-	-
Mixed					
T vs. t	0.95	0.84-1.09	0.472	53.1	0.144
TT vs. tt	0.77	0.58-1.03	0.074	54.2	0.140
TT vs. Tt	1.13	0.94-1.36	0.180	0.0	0.515
TT vs. Tt+tt	1.04	0.88-1.23	0.651	22.5	0.256
TT+Tt vs. tt	0.73	0.55-0.96	0.023	41.5	0.191
Overall					
T vs. t	0.94	0.91-0.98	0.004	25.9	0.130
TT vs. tt	0.88	0.80-0.95	0.002	0.0	0.514
TT vs. Tt	0.98	0.92-1.04	0.445	10.6	0.318
TT vs. Tt+tt	0.95	0.90-1.01	0.078	19.6	0.201
TT+Tt vs. tt	0.89	0.82-0.96	0.002	0.0	0.623