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Meta Gene



Current evidence on the four polymorphisms of VDR and breast cancer risk in Caucasian women[☆]



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ABSTRACT

There have been a few epidemiological studies reporting VDR polymorphisms including Fok1, Bsm1, Apa1 and Taq1 with breast cancer incidence and therefore risk. The results however are controversial, often due to smaller sample size. Concerning most of the studies were performed on Caucasian women, we conducted this comprehensive meta-analysis encompassing 38,151 cases and 47,546 controls (Fok1: 13,152 cases, 17,443 controls; Bsm1: 14,755 cases, 18,633 controls; Apa1: 3080 cases, 3412 controls; Taq1: 7164 cases, 8068 controls) to better understand roles of the polymorphisms in breast cancer development among Caucasian population. We did not find any association of the most controversial genotype Fok1 with breast cancer risk in Caucasian women (ff vs. FF: OR = 1.05, 95% CI = 0.95–1.22, P = 0.32 for heterogeneity; ff vs. FF: OR = 1.05, 95% CI = 0.94–1.17, P = 0.40; ff vs. Ff + FF: OR = 1.07, 95% CI = 0.95–1.14, P = 0.37 and ff + Ff vs. FF: OR = 1.04, 95% CI = 0.99–1.09, P = 0.23). For Bsm1, Apa1 and Taq1, no significant association was also not found in the homozygote comparison, heterozygote comparison, recessive and dominant models

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respectively. In conclusion, the current analysis suggested that the four polymorphisms (Fok1, Bsm1, Apa1 and Taq1) of VDR may be not associated with breast cancer risk in Caucasian women.

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Introduction

Vitamin D was originally discovered by Edward Mellanby in 1919 (Mellanby, 1919, 2009). Over the past years, studies indicated that vitamin D not only has an important function in bones, but it also significantly affects cell proliferation and differentiation. In cancer cells, the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃) can suppress cell proliferation (Thorne and Campbell, 2008). Many studies suggested that serum concentrations of vitamin D metabolites have been inversely associated with risk for breast cancer development (Bertone-Johnson et al., 2005; Shin et al., 2002).

The effects of vitamin D for the most part are correlated with nuclear vitamin D receptor (VDR). It has been well established that the active hormone 1,25(OH)₂D₃ can induce a cascade of gene regulation and signaling molecules by binding to VDR (Welsh, 2011). However a series of polymorphisms in VDR gene have been reported. They include Bsm1, Apa1, Taq1 restriction sites, variable PolyA length and Fok1 restriction site (Köstner et al., 2009). Of these polymorphic sites Bsm1 and Apa1 are substitutions on intron 8 whereas Taq1 brings about substitution of cytosine to thymine on exon 9. The Fok1 restriction enzyme identifies a polymorphic site in exon 2 at the 50 end of the VDR gene.

Over the years, most of the molecular epidemiological studies were performed on Caucasian women to assess the associations of different VDR polymorphisms with breast cancer risk (Abbas et al., 2008; Anderson et al., 2011; Buyru et al., 2003; Chen et al., 2005b; Curran et al., 1999; Dalessandri et al., 2011; Dunning et al., 1999; Engel et al., 2012; Gapska et al., 2009; Guy et al., 2004; Hefler et al., 2004; Ingles et al., 2000; Lowe et al., 2005; Lundin et al., 1999; McCullough et al., 2007; McKay et al., 2009; Rollison et al., 2011; Ruggiero et al., 1998; Sillanpaa et al., 2004; Sinotte et al., 2008; Trabert et al., 2007). However, the results are inconsistent, which might be caused by the limitation of individual studies. Therefore we performed this meta-analysis which combines data from all published literatures to get a more precise evaluation of the association in Caucasian women.

Methods

Search strategy

In this meta-analysis, a comprehensive literature research of the US National Library of Medicine's PubMed database, ISI Web of Knowledge, Medline, Embase and Google Scholar Search (update to December, 2012) was conducted using the search terms including "breast cancer", "vitamin D receptor (VDR)", "polymorphism", "Fok1", "Apa1", "Bsm1", "Taq1", and the combined phrases in order to obtain all genetic studies on the relationship of the polymorphisms with breast cancer in Caucasian women. We also used a hand search of references of original studies or reviewed articles on this topic to identify additional studies.

Data extraction

Data extraction was carried out independently by two investigators. For each eligible study, the following information was recorded: the first author's name, the year of publication, country of origin, genotyping methods, racial descent of the study population, number of cases and controls with different genotypes.

Statistical analysis

The strength of relationship between the four polymorphisms of VDR and breast cancer was assessed by using Crude OR with 95% CI. We examined the association using homozygote comparison, heterozygote comparison, dominant genetic model and recessive genetic model of the four polymorphisms. Between-study heterogeneity was evaluated by the χ^2 -based Q-test and the heterogeneity was considered significant when

Table 1

The main characteristics of all the studies in this meta-analysis.

Author	Year	Country	Ethnicity	Source of control	Matching criteria	Case/control	Genotyping methods	Studied polymorphism	HWE
Curran	1999	Australia	Caucasian	Population	Age	135/110	PCR-RFLP	Fok1, Apa1, Taq1	Y
Dunning1	1999	UK	Caucasian	Hospital	Age, residential area	211/268	PCR-RFLP	Taq1	Y
Dunning2	1999	UK	Caucasian	Hospital	Age, residential area	740/359	PCR-RFLP	Taq1	Y
Lundin	1999	Sweden	Caucasian	Population	Age	111/130	PCR-RFLP	Taq1	Y
Ingles	2000	America	Caucasian	Hospital	Residential area	143/300	PCR-RFLP	Bsm1	Y
Guy	2004	UK	Caucasian	Hospital	Age	398/427	PCR-RFLP	Fok1, Bsm1	Y
Sillanpaa	2004	Finnish	Caucasian	Hospital	Age, residential area	483/482	PCR-RFLP	Apa1, Taq1	Y
Hefler	2004	Germany	Caucasian	Population	Age	1699/1963	Microarray system	Bsm1	N
Chen	2005	Turkey	Caucasian	Hospital	Age and residential area	1234/1676	TaqMan	Fok1	Y
Lowe	2005	UK	Caucasian	Hospital	Age, residential area	179/179	PCR-RFLP	Bsm1	Y
McKay	2008	America	Caucasian	Population	Age, hormone status	4657/6578	TaqMan	Fok1, Bsm1	Y
Dana E. Rollison	2011	America	Caucasian	Population	Age, regional area	2318/2512	PCR	Bsm1, Fok1	Y
Ruggiero	1998	Italy	European	Population	Age, residential area	88/167	PCR-RFLP	Bsm1	N
Engel	2012	America	Caucasian	Population	Race, regional area	806/1650	MassARRAY system	Apa1, Fok1, Taq1	Y
McCullough	2007	America	Caucasian	Hospital	Age, residential area	500/500	TaqMan	Fok1, Apa1, Bsm1, Taq1	Y
Trabert	2007	America	Caucasian	Hospital	Age, residential area	1136/965	PCR-RFLP	Bsm1	Y
Abbas	2008	Germany	Caucasian	Population	Age	1408/2612	PCR-RFLP	Fok1, Taq1	Y
Buyru	2003	Turkey	Caucasian	Population	NA	27/78	PCR-RFLP	Bsm1, Taq1	N
Sinotte1	2008	Canada	Caucasian	Population	Regional match	225/463	Allele-specific PCR	Fok, Bsm1	Y
Scott	2008	Poland	Caucasian	Hospital	Age, regional match	960/800	RT-PCR	Apa1, Fok1	Y
Anderson	2011	Canada	Caucasian	Population	Age	6201/6509	MassARRAY system	Apa1, Fok1, Bsm1, Taq1	Y
Dalessandri,	2011	America	Caucasian	Population	Age, ethnicity	164/174	Allele-specific PCT	Apa1	Y
Sinotte2	2008	Canada	Caucasian	Population	Regional match	622/974	Allele-specific PCR	Fok1, Bsm1	Y

$P < 0.05$ (Lau et al., 1997). Fixed-effects model (the Mantel–Haenszel method) was used to pool the data when the P-value of Q-test ≥ 0.05 , otherwise, random-effects model (the DerSimonian and Laird method) was selected (DerSimonian and Laird, 1986; Mantel and Haenszel, 1959). These two models provided similar results when between-study heterogeneity was absent. Both funnel plot and Egger's test were used to assess the publication bias ($P < 0.05$ was considered representative of statistical significance) (Egger et al., 1997). All statistical analyses were performed using STATA11.0 software.

Results

Eligible studies

The main characteristics of all the 21 studies are shown in Table 1. Genotype distribution of the studied polymorphisms among cancer cases and controls of the studies is shown in the supplementary material. The genotyping method contains the classic polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) assay, DNA sequencing, Affymetrix, TaqMan, MassARRAY system and Allele-specific PCR. All studies were case–control and Caucasian descent. Hospital based controls were carried out in ten studies, while population based controls were carried out in 11 studies. The distribution of genotypes in the controls was all in agreement with Hardy–Weinberg equilibrium except for five studies (Buyru et al., 2003; Hefler et al., 2004; Ruggiero et al., 1998; Sinotte et al., 2008; Trabert et al., 2007).

Meta-analysis

The main results of this meta-analysis and the heterogeneity tests were shown in Table 2. Overall, we did not find any association of all the studied polymorphisms with breast cancer risk in Caucasian women.

For Fok1, no association with breast cancer risk was found in all the models (ff vs. FF: OR = 1.05, 95% CI = 0.95–1.22, $P = 0.32$ for heterogeneity; ff vs. Ff: OR = 1.05, 95% CI = 0.94–1.17, $P = 0.40$; ff vs. Ff + FF: OR = 1.07, 95% CI = 0.95–1.14, $P = 0.37$ and ff + Ff vs. FF: OR = 1.04, 95% CI = 0.99–1.09, $P = 0.23$).

For Bsm1, Apa1 and Taq1, we also did not find any significant association in the homozygote comparison, heterozygote comparison, recessive and dominant models respectively.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis (Figs. 1–5). 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 (data not shown).

Table 2

The main results of this meta-analysis.

Polymorphisms	ORs and 95% CI	P ^a	ORs and 95% CI	P ^a	ORs and 95% CI	P ^a	ORs and 95% CI	P
Fok1	ff vs. FF 1.05(0.95–1.22)	0.32	ff vs. Ff 1.05(0.94–1.17)	0.40	ff vs. Ff + FF 1.07(0.95–1.14)	0.37	ff + Ff vs. FF 1.04(0.99–1.09)	0.23
Apa1	aa vs. AA 1.00(0.87–1.18)	0.34	aa vs. Aa 0.87(0.85–1.10)	0.11	aa vs. Aa + AA 0.88(0.86–1.12)	0.25	Aa + aa vs. AA 1.08(0.80–1.30) ^b	0.01
Bsm1	bb vs. BB 1.00(0.90–1.11) ^b	0.01	bb vs. Bb 1.02(0.9–1.22)	0.06	bb + Bb vs. BB 1.01(0.95–1.03) ^b	0.04	bb vs. BB + Bb 1.01(0.91–1.13) ^b	0.02
Taq1	tt vs. TT 1.05(0.95–1.16)	0.12	tt vs. Tt 1.00(0.91–1.10)	0.21	tt vs. TT + Tt 1.02(0.93–1.12)	0.06	tt + Tt vs. TT 1.04(0.97–1.11)	0.41

Abbreviations: CI, confidence interval; OR, odds ratio.

^a P-value of Q-test for heterogeneity test.

^b Random model was used.

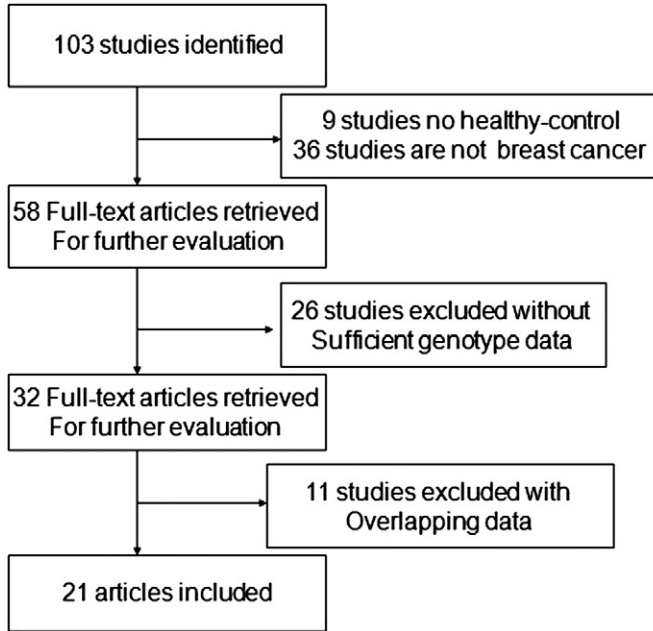


Fig. 1. Flow diagram of study identification.

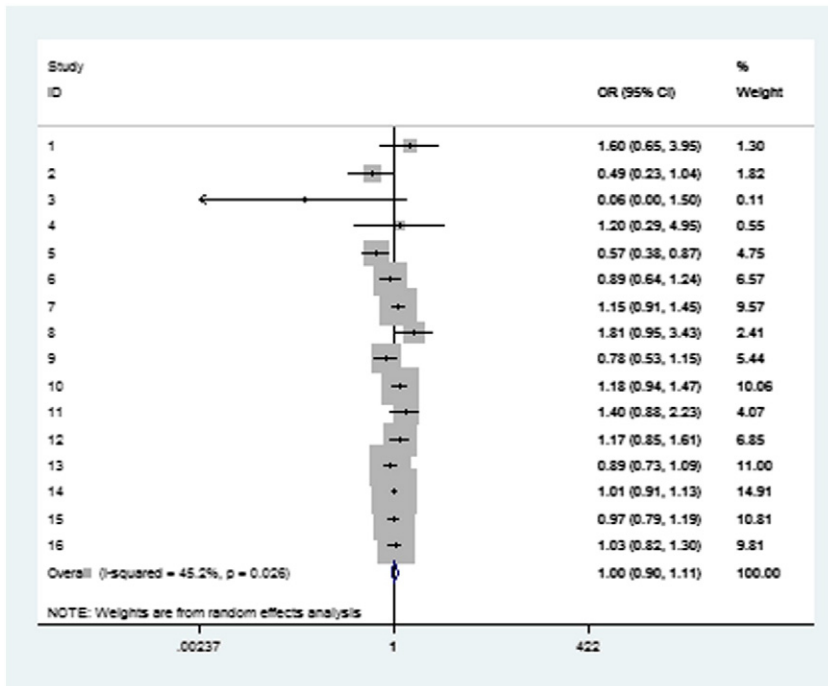


Fig. 2. OR on breast cancer not associated with Bsm1 for the bb genotype compared with the BB genotype.

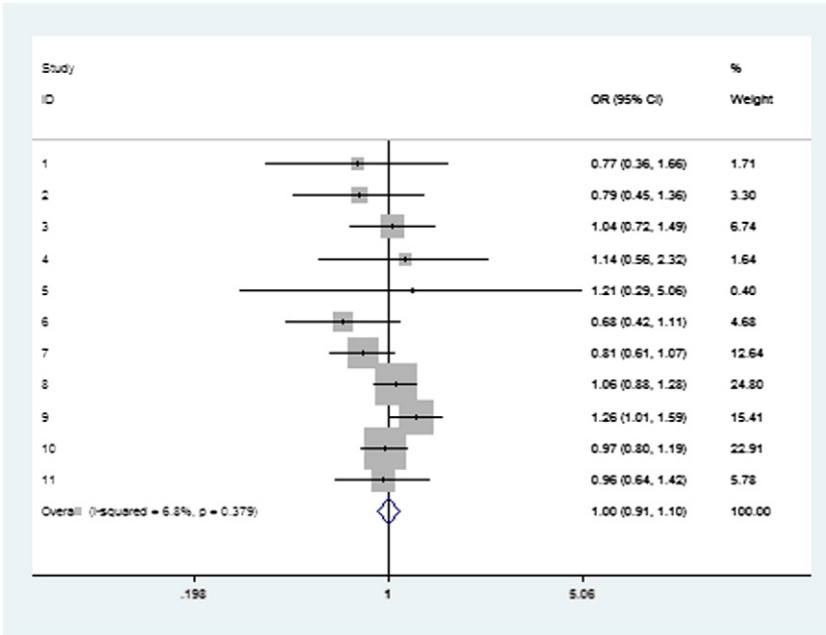


Fig. 3. OR on breast cancer not associated with Taq1 for the tt genotype compared with the TT genotype.

Discussion

This meta-analysis encompassing 21 studies involving 38,151 cases and 47,546 controls was conducted to investigate the potential association between four polymorphisms of VDR and breast cancer risk in Caucasian women. Overall, we did not find any association of all the studied four SNPs with breast cancer risk in Caucasian women.

Up to now, Fok1 is the most controversial SNP concerning its relationship with breast cancer risk, VDR FF allele in combination with long-Poly A was reported to be a risk factor in the UK (Guy et al., 2004), whereas in another report Chen (Chen et al., 2005a) found VDR ff to be a risk factor in the Nurses' Health

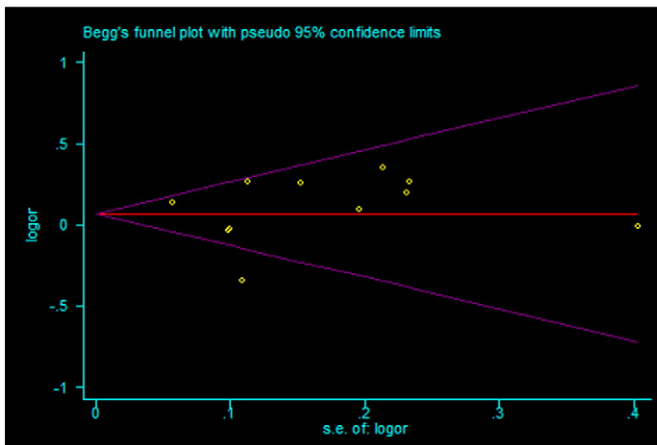


Fig. 4. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association (ff vs. FF).

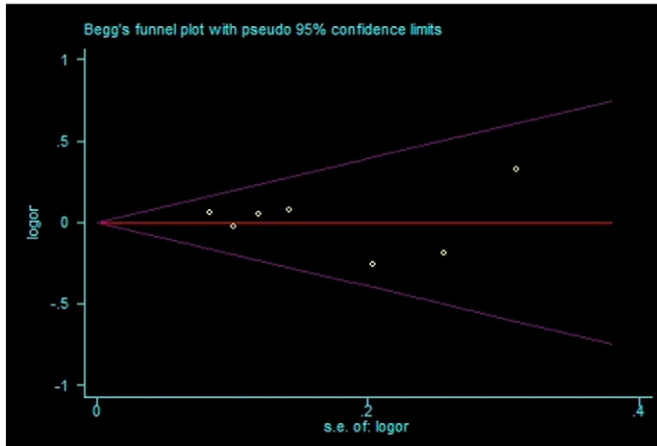


Fig. 5. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association (aa vs. AA).

study in the USA. In 2009, the meta-analysis conducted by Tang et al. indicated a positive association between VDR ff and augmented risk for breast cancer in European women (Tang et al., 2009). Yet other reports did not find any correlation between Fok1 polymorphism and breast cancer incidence. Most recently, Shahbazi et al. found no statistically significant association between Fok1 genotypes and breast cancer risk in Iranian breast cancer patients (Shahbazi et al., 2013). Our analysis involving 13,152 cases and 17,443 controls confirmed that Fok1 was not overall significantly associated with breast cancer risk in Caucasian women.

Compared to Fok1, the Bsm1 exhibits strong linkage disequilibrium with Apa1 and Taq1, located at the 30 untranslated region (30 UTR) of the VDR gene. This haplotype may affect mRNA stability and processing as well as regulation of VDR transcription and translation (Gapska et al., 2009; Trabert et al., 2007). Among all the studies, only four studies which were performed on Caucasian women reported an increased risk of breast cancer with the Bsm1 bb genotype (Buyru et al., 2003; Lundin et al., 1999; Ogunkolade et al., 2002; Whitfield et al., 2001). Curran et al. claimed that allele frequencies of the Apa1 polymorphism showed a significant association with breast cancer risk, other studies found no association (Curran et al., 1999). Comparing t allele carriers with non-carriers, Abbas et al. conducted one study suggesting that the Taq1 polymorphism was associated with a significantly increased breast cancer risk in estrogen receptor positive patients (Abbas et al., 2008). Other studies did not find significant overall association in Caucasian women. Concerning the strong linkage disequilibrium of the three polymorphisms, combinations of the three variants may be more discriminating as risk factors than a single one.

As in all research, our study has limitations. Firstly, the controls were not uniformly defined. Secondly, since there is a lack of detailed individual information on genotypes of Bsm1, Apa1 and Taq1, we could not perform the pooled analysis of linkage disequilibrium and the combined genotypes of these three SNPs. Thirdly, due to the original data of the eligible studies are unavailable. We did not perform the analysis adjusted for some covariates such as: age, dietary vitamin D, sun exposure, intake and steroid hormone receptor status.

In conclusion, this analysis suggested that the four polymorphisms (Fok1, Bsm1, Apa1 and Taq1) of VDR may be not associated with breast cancer risk in Caucasian women.

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