

Vitamin D receptor FokI, BsmI, ApaI, and TaqI polymorphisms and the susceptibility to breast cancer: a meta-analysis

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The goal of this study is to examine whether vitamin D receptor (VDR) polymorphisms are associated with the susceptibility to breast cancer.

Meta-analysis was employed to investigate the association between the VDR FokI, BsmI, ApaI, and TaqI polymorphisms and the incidence of breast cancer.

A total of 32 comparative studies were evaluated in this meta-analysis, which included 17,067 patients and 20,843 controls. Meta-analysis of the VDR FokI polymorphism indicated an association between the incidence of breast cancer and the ff genotype in Europeans (OR = 1.126, 95% CI = 1.026–1.243, $p = 0.019$). Furthermore, an association between the incidence of breast cancer and the VDR FokI polymorphism was found in the Europeans using the allele contrast, as well as the homozygote contrast. However, the meta-analysis indicated no association between breast cancer and the BsmI polymorphism in all study subjects, including the Europeans (OR for the B allele = 0.996, 95% CI = 0.964–1.097, $p = 0.930$, 1.026, 95% CI = 0.929–1.134, $p = 0.610$). Moreover, breast cancer incidence was not associated with the ApaI and Taq polymorphisms (OR for the A allele = 0.908, 95% CI = 0.763–1.041, $p = 0.167$, OR for the T allele = 0.972, 95% CI = 0.929–1.017, $p = 0.221$).

This meta-analysis suggests that the VDR FokI polymorphism is associated with susceptibility to breast cancer in the European population.

Key words: breast cancer, vitamin D receptor, polymorphism, meta-analysis

Breast cancer, the most common cancer worldwide, accounts for 22.9% of the invasive cancers and is associated with the highest fatality rates in women. Although the etiology of breast cancer is unclear, both genetic and environmental factors are considered to contribute to its development [1].

Although the primary function of vitamin D involves the maintenance of bone mineral homeostasis, it is also involved in interleukin (IL)-2 inhibition, antibody production, and lymphocyte proliferation [2]. It has been reported that 1,25-dihydroxy vitamin D₃ (1,25(OH)₂ D₃) inhibits interferon secretion and negatively regulates IL-12 production by downregulating nuclear factor-kappaB [3]. In addition, vitamin D plays a critical regulatory role in the differentiation and proliferation of cancer cells by influencing cell cycle regulation [4]. Studies suggest that exposure to sunlight may reduce the risk of breast cancer in addition to increasing the production of vitamin D in the skin, as vitamin D inhibits

growth and induces apoptosis in the breast cancer cells [5]. Thus, vitamin D may play a pivotal role in the development of breast cancer.

The activity of vitamin D is dependent on the vitamin D receptor (VDR), a member of the nuclear hormone receptor superfamily. The VDR gene is one of the most frequently studied genes with respect to breast cancer. It is located on the chromosome 12q13.11 [6], and 3 polymorphisms, BsmI (rs1544410), ApaI (rs7975232) (both in intron 8), and TaqI (rs731236) (in exon 9), have been identified at the 3'-end of the gene, and shown to be in strong linkage of disequilibrium (LD) [7]. The other polymorphic region, FokI (rs2228570), is located in the start codon [6]. Although the functional significance of these 4 polymorphisms remains unknown, it is believed that LD and one or more functional polymorphisms elsewhere in the VDR gene contribute to the observed association between the polymorphisms of the VDR gene

and some cancers. Although these VDR polymorphisms have been linked to breast cancer development in several reports, failed to find an association [8-31]. This may be due to small sample sizes, low statistical power, and/or clinical heterogeneity [32-34] in these studies. In order to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we employed a meta-analysis. Therefore, the present study aims to determine whether the VDR FokI, BsmI, ApaI, and TaqI polymorphisms are associated with the susceptibility to breast cancer, using meta-analysis.

Materials and methods

Identification of eligible studies and data extraction. We performed a search for studies that examined the association between VDR polymorphisms and breast cancer. A literary search using the MEDLINE citation database was used to identify available articles in which VDR polymorphisms were analyzed in breast cancer patients (until June 2013). Combinations of keywords, such as 'vitamin D,' 'VDR,' 'polymorphism,' and 'breast cancer' were entered as Medical Subject Headings (MeSH) or text words. References in the identified studies were also investigated to identify additional studies not indexed by MEDLINE. No language or country restrictions were applied. Studies were included if (1) they were case-control studies, (2) the data were original (independent of other studies), (3) they provided enough data to calculate an odds ratio (OR), and (4) they showed a distribution of the VDR polymorphism in normal controls that was consistent with H-W equilibrium. Studies were excluded if: (1) they contained overlapping data; (2) the number of genotypes could not be ascertained; and (3) the family members were also included in the study, as these analyses are based on linkage considerations. Data were extracted from the original studies by 2 independent reviewers, following the specified selection criteria for the meta-analysis. Any discrepancies between the reviewer observations were resolved by a consultation with a third reviewer. The extracted information from each study included the author, year of publication, ethnicity of the study population, demographics, and the number of cases and controls for each of the FokI, BsmI, ApaI, and TaqI genotypes. Frequencies of the alleles were calculated from the corresponding distribution of the genotypes.

Evaluations of statistical associations. We performed meta-analyses using: 1) allelic contrast, 2) contrast of homozygotes, 3) recessive, and 4) dominant models. Point estimates of risk, ORs, and 95% confidence intervals (CI) were estimated for each study. In addition, within- and between-study variations or heterogeneities were assessed using Cochran's Q-statistic. This heterogeneity test assesses the null hypothesis that all studies evaluated have the same effect. The effect of heterogeneity was quantified using I^2 , which ranges between 0% and 100%, and represents the proportion of between-study

variability that can be attributed to heterogeneity rather than chance [35]. I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates. The fixed effects model assumes that the effect of genetic factors on breast cancer susceptibility across all studies investigated is similar, and that the observed variations among studies are caused by chance alone [36]. The random effects model assumes that different studies show substantial diversity and assesses both the within-study sampling error and between-study variance [37]. When study groups are homogeneous, the use of the fixed or random effect models generates similar results, and when this is not the case, the random effect model usually provides wider CIs than the fixed effect model. The random effect model is used in the presence of significant between-study heterogeneity [37]. The statistical analyses were done using a comprehensive meta-analysis computer program (Biosta, Englewood, NJ, USA).

Evaluation of publication bias. Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which requires a range of studies of varying sizes involving subjective judgments, publication bias was evaluated using Egger's linear regression test [38], which measures funnel plot asymmetry using a natural logarithm scale of the odds ratios (OR).

Results

Studies included in the meta-analysis. Sixty-seven studies were identified by electronic and manual searches and 30 were selected for a full-text review based on their title and abstract details [39-53]. Of these 30 studies, 6 studies were excluded as 4 were not in HWE [48-51] and 2 did not include the data on the VDR polymorphisms [52, 53]. Thus, 24 studies met the inclusion criteria [8-31] (Figure 1). Of the eligible studies, 4 contained data on 2 different groups [8, 16, 18, 30], and 1 had data on 5 different groups [17], and these were treated independently. Thus, a total of 32 separate comparisons were considered in the meta-analysis, which included 17,067 patients and 20,843 controls in total (Table 1). These 32 studies encompassed 20 Europeans, 2 Asians, 2 African Americans, 2 Hispanics, 2 mixed-race subjects, 1 Arab, 1 Indian, 1 Hawaiian, and one of unknown ethnicity. Thus, an ethnicity-specific meta-analysis was conducted for the European population. The VDR FokI polymorphism was examined by 18 studies, the BsmI polymorphism by 15, the ApaI polymorphism by 8, and the TaqI polymorphism by 15. Selected characteristics of these studies with respect to the association between the VDR polymorphisms and breast cancer are summarized in Table 1.

Meta-analysis of the association between the VDR FokI polymorphism and breast cancer. A summary of the meta-analysis, indicating the association between the VDR FokI and BsmI polymorphisms and breast cancer, is presented in Table 2. Meta-analysis of the VDR FokI polymorphism showed an association between the incidence of breast cancer and the ff

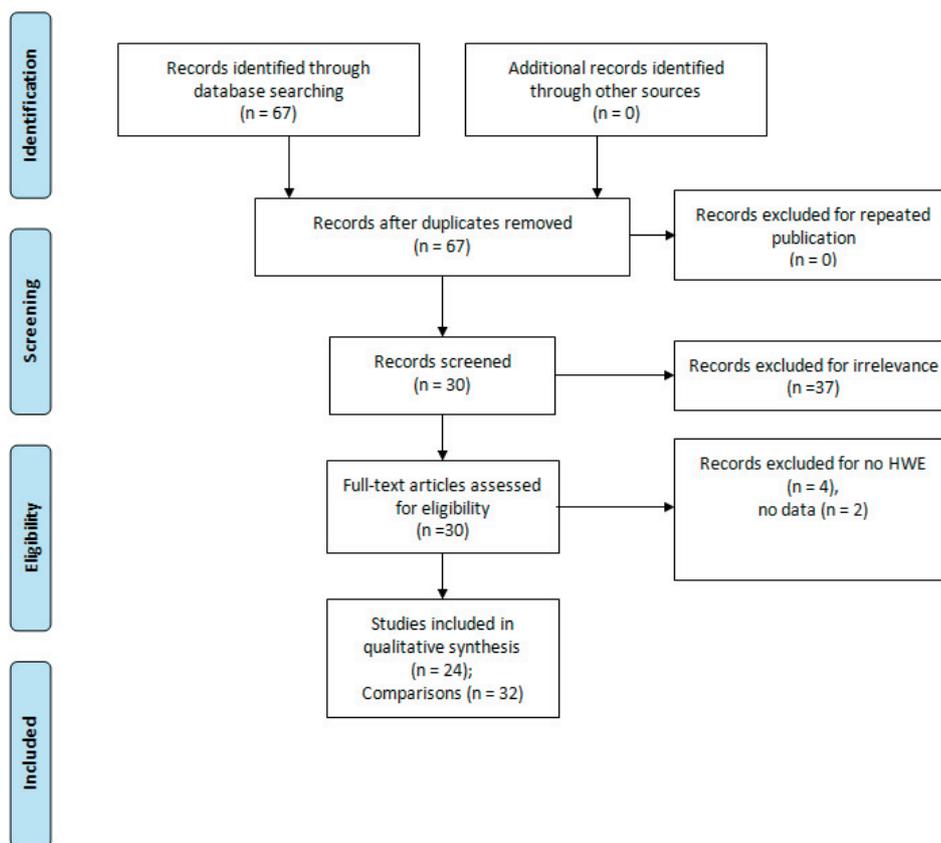


Figure 1. Flow chart illustrating the study design.

genotype in all study subjects (OR = 1.089, 95% CI = 1.010–1.175, $p = 0.026$) (Table 2, Figure 2). Stratification by ethnicity revealed a significant association between the VDR FokI ff genotype and breast cancer in Europeans (OR = 1.126, 95% CI = 1.026–1.243, $p = 0.019$) (Table 2). Furthermore, this association in the European cohort between breast cancer incidence and the VDR FokI polymorphism was revealed by the use of both the allele contrast, as well as homozygote contrast (Table 2).

Meta-analysis of the association between the VDR BsmI, ApaI and TaqI polymorphisms and breast cancer. Meta-analysis revealed no association between breast cancer and the BsmI B allele in all study subjects (OR = 0.996, 95% CI = 0.964–1.097, $p = 0.930$) (Table 3). Stratification by ethnicity revealed no association between the BsmI B allele and breast cancer in Europeans (OR = 1.026, 95% CI = 0.929–1.134, $p = 0.610$) (Table 3). The recessive and dominant models and homozygote contrast failed to reveal an association between the BsmI polymorphism and the incidence of breast cancer (Table 3, Figure 3). Meta-analysis of the VDR ApaI polymorphism showed no association be-

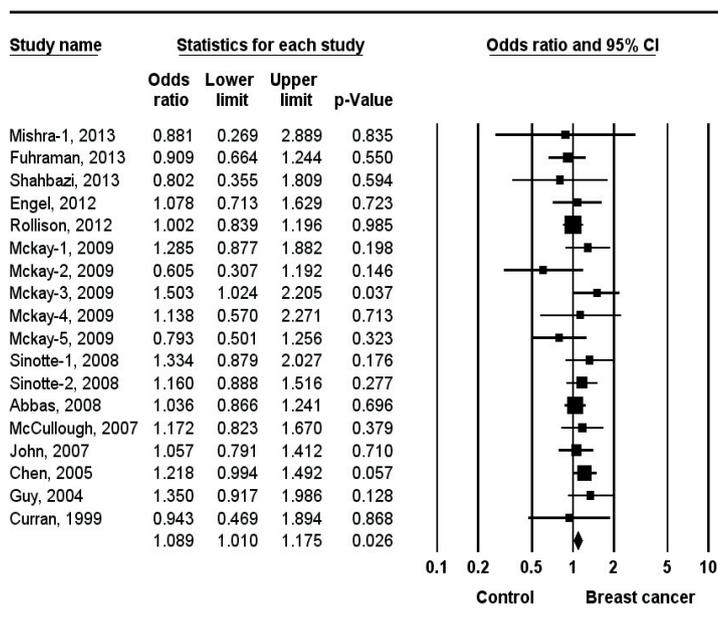


Figure 2. ORs and 95% CIs of individual studies and pooled data for the association between breast cancer incidence and the VDR FokI polymorphism, under the recessive model.

Table 1. Characteristics of individual studies included in the meta-analysis.

Study [Ref]	Country	Ethnicity	Numbers		Polymorphism(s)	Association findings
			Case	Control		
Mishra-1, 2013[8]	USA	African American	115	73	FokI, BsmI, ApaI, TaqI	NS
Mishra-2, 2013[8]	USA	Hispanic	117	276	FokI, BsmI, ApaI, TaqI	NS
Fuhrman, 2013[9]	USA	Unkonwn	484	845	FokI, BsmI	FokI (NS), BsmI (p = 0.02)
Shahbazi, 2013[10]	Iran	Arab	140	156	FokI, BsmI	FokI (NS), BsmI (p = 0.01)
Engel, 2012[11]	USA	European	270	554	FokI, ApaI, TaqI	NS
Dalessandri, 2012[12]	USA	European	164	174	ApaI	NS
Rollison, 2012[13]	USA	Mixed	2,318	2,521	FokI, BsmI	NS
Anderson, 2011[14]	Canada	European	1,777	1,839	FokI, BsmI, ApaI, TaqI	NS
Chakraborty, 2009[15]	Inida	Indian	160	140	ApaI, TaqI	NS
Gapska-1, 2009[16]	Poland	European	960	960	BsmI, TaqI	NS
Gapska-2, 2009[16]	Poland	European	800	550	BsmI, TaqI	NS
McKay-1, 2009[17]	USA	Hispanic	318	378	FokI	NS
McKay-2, 2009[17]	USA	African American	325	419	FokI	NS
McKay-3, 2009[17]	USA	Asian	401	405	FokI	NS
McKay-4, 2009[17]	USA	Hawaian	104	278	FokI	NS
McKay-5, 2009[17]	USA	European	378	421	FokI	NS
Sinotte-1, 2008[18]	Canada	European	225	463	FokI, BsmI	NS
Sinotte-2, 2008[18]	Canada	European	622	974	FokI, BsmI	NS
Abbas, 2008[19]	Germany	European	1,408	2,612	FokI, TaqI	NS
McCullough, 2007[20]	USA	European	500	500	FokI, BsmI, ApaI, TaqI	NS
John, 2007[21]	USA	Mixed	1,786	2,127	FokI, TaqI	NS
Lowe, 2005[22]	UK	European	179	179	BsmI	NS
Chen, 2005[23]	Turkey	European	1,234	1,676	FokI	NS
Sillanpaa, 2004[24]	Finland	European	483	482	ApaI, TaqI	NS
Guy, 2004[25]	UK	European	398	427	FokI, BsmI	NS
Buyru, 2003[26]	Turkey	European	27	78	BsmI, TaqI	NS
Hou, 2002[27]	Taiwan	Asian	34	169	BsmI, ApaI, TaqI	NS
Ingles, 2000[28]	USA	European	143	300	BsmI	NS
Lundin, 1999[29]	Sweden	European	111	130	TaqI	NS
Dunning-1, 1999[30]	UK	European	211	268	TaqI	NS
Dunning-2, 1999[30]	UK	European	740	359	TaqI	NS
Curran, 1999[31]	Australia	European	135	110	FokI, ApaI, TaqI	NS

Ref, reference; NS, not significant; UK, United Kingdom; USA, United States of America; *control genotypes not in Hardy-Weinberg equilibrium.

Table 2. Meta-analysis of the association between breast cancer incidence and the VDR FokI polymorphism.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-val	Model	p-val	I ²
FokI f vs. F	Overall	18	1.033	0.994-1.074	0.099	F	0.270	15.3
	European	9	1.057	1.004-1.114	0.034	F	0.186	29.0
ff vs. Ff + FF (recessive)	Overall	18	1.089	1.010-1.175	0.026	F	0.588	0
	European	9	1.126	1.020-1.243	0.019	F	0.704	0
ff + Ff vs. FF (dominant)	Overall	18	1.019	0.965-1.077	0.490	F	0.354	8.40
	European	9	1.048	0.974-1.128	0.212	F	0.138	34.9
ff vs. FF	Overall	18	1.086	1.000-1.178	0.049	F	0.305	12.4
	European	9	1.141	1.024-1.271	0.017	F	0.350	10.2

VDR, vitamin D receptor; OR, odds ratio; CI, confidence interval; R, Random effects model; F, Fixed effects model.

tween breast cancer and the A allele in all study subjects (OR = 0.908, 95% CI = 0.763–1.041, $p = 0.167$) (Table 3). Stratification by ethnicity revealed no association between the ApaI A allele and the incidence of breast cancer in Europeans (OR = 0.934, 95% CI = 0.818–1.067, $p = 0.317$) (Table 3). Furthermore, no association was found between breast cancer and VDR ApaI polymorphism using other genetic models (Table 3, Figure 3). Meta-analysis indicated no association between breast cancer and the TaqI T allele in either the overall study population or the European population (OR = 0.972, 95% CI = 0.929–1.017, $p = 0.221$ and OR = 0.974, 95% CI = 0.928–1.023, $p = 0.294$, respectively) (Table 3). The recessive and dominant models and homozygote contrast failed to reveal an association between the TaqI polymorphism and breast cancer incidence (Table 3, Figure 3).

Heterogeneity and publication bias. Some heterogeneity was observed in the meta-analysis of the VDR BsmI and ApaI polymorphisms, but between-study heterogeneity was not found during the meta-analysis of the VDR FokI and TaqI polymorphisms (Table 2, and 3). It was difficult to correlate the funnel plot, which is usually used to detect publication bias, as the number of studies included in the analysis was relatively small. However, Egger's regression test showed no evidence of publication bias (Egger's regression test p -values > 0.1) (Figure 4).

Discussion

Vitamin D regulates the processes of cellular proliferation, differentiation, and apoptosis, which influence cancer development. Since VDR polymorphisms have been reported to be associated with the development of several cancers [54], they could be considered as a risk factor for breast cancer development.

In this meta-analysis, we combined data from published studies to evaluate the genetic association between the most commonly studied polymorphisms of the VDR gene, namely, the FokI, BsmI, ApaI, and TaqI polymorphisms and the incidence of breast cancer. Our meta-analysis of the VDR BsmI, ApaI, and TaqI polymorphisms showed no association with breast cancer in all study subjects including the European sub-group. In contrast, the meta-analysis of the FokI polymorphism revealed a significant association between breast cancer and the f allele in the European population (OR = 1.057, 95% CI = 1.004–1.114, $p = 0.034$). In addition, the meta-analysis using the recessive model and the homozygote contrast found an association of this allele with breast cancer incidence in the European population. Our meta-analysis suggests that the VDR FokI f allele may be a risk factor for breast cancer development in Europeans.

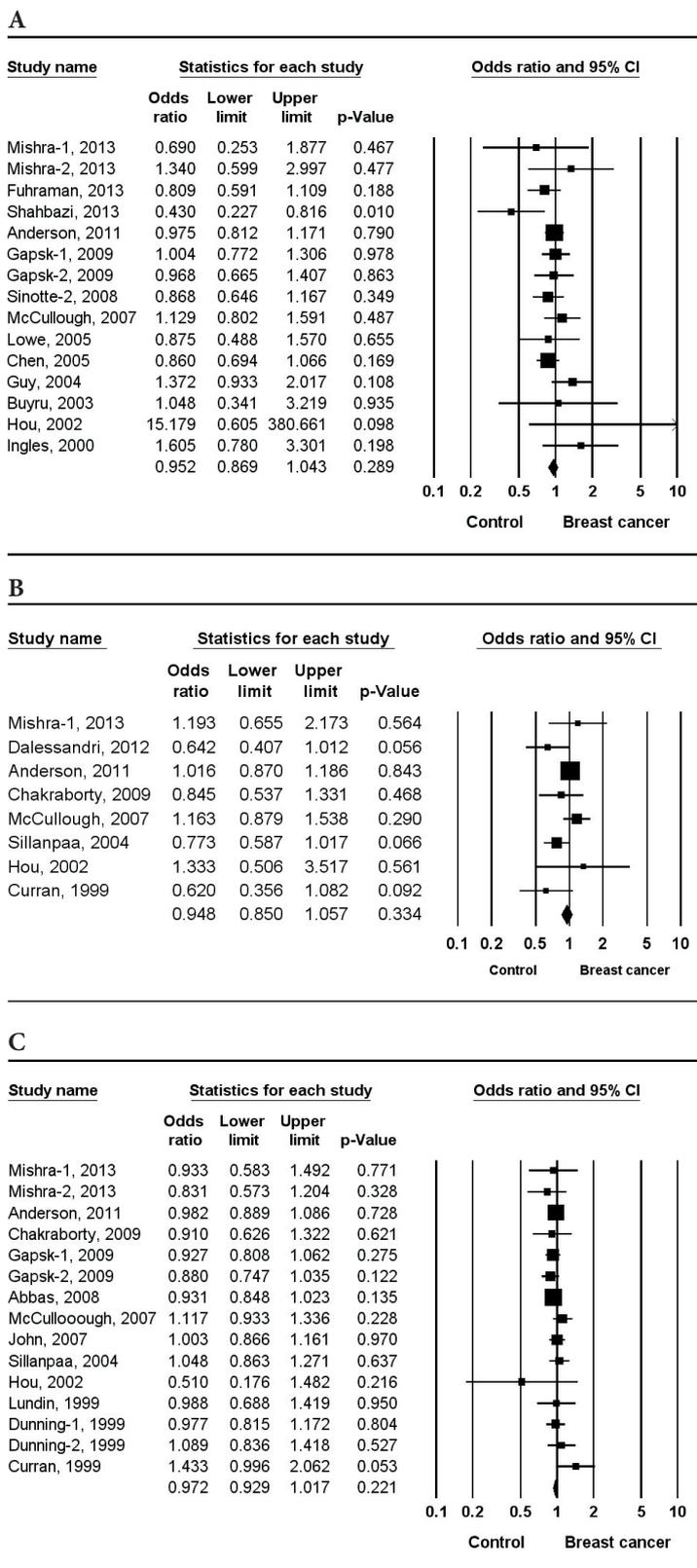


Figure 3. ORs and 95% CIs of individual studies and pooled data for the association between breast cancer incidence and the VDR BsmI (A), ApaI (B) and TaqI (C) polymorphisms, under the recessive model.

Table 3. Meta-analysis of the association between breast cancer incidence and the VDR and BsmI, ApaI and TaqI polymorphisms.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	<i>p</i> -val	Model	<i>p</i> -val	<i>I</i> ²
BsmI B vs. b	Overall	15	0.996	0.964-1.097	0.930	R	0.000	68.8
	European	10	1.026	0.929-1.134	0.610	R	0.001	68.3
BB vs. Bb + bb (recessive)	Overall	15	0.952	0.869-1.043	0.289	F	0.170	25.7
	European	10	0.980	0.889-1.081	0.690	F	0.570	0
BB + Bb vs. bb (dominant)	Overall	15	1.016	0.950-1.086	0.643	R	0.000	69.2
	European	10	1.042	0.893-1.217	0.600	R	0.000	73.4
BB vs. bb	Overall	15	0.967	0.813-1.149	0.700	R	0.005	55.1
	European	10	1.028	0.870-1.215	0.748	R	0.037	49.5
ApaI A vs. a	Overall	8	0.908	0.763-1.041	0.167	R	0.018	58.5
	European	5	0.934	0.818-1.067	0.317	R	0.055	56.8
AA vs. Aa + aa (recessive)	Overall	8	0.948	0.850-1.057	0.334	F	0.127	37.9
	European	5	0.877	0.708-1.086	0.229	R	0.041	59.9
AA + Aa vs. aa (dominant)	Overall	8	0.860	0.659-1.121	0.264	R	0.076	64.2
	European	5	1.001	0.881-1.138	0.985	F	0.371	6.20
AA vs. aa	Overall	8	0.964	0.834-1.114	0.619	F	0.143	35.8
	European	5	0.898	0.697-1.158	0.407	R	0.085	51.1
TaqI T vs. t	Overall	15	0.972	0.929-1.017	0.221	F	0.515	0
	European	10	0.974	0.928-1.023	0.294	F	0.296	16.0
TT vs. Tt + tt (recessive)	Overall	15	0.970	0.910-1.034	0.354	F	0.788	0
	European	10	0.959	0.895-1.029	0.247	F	0.740	0
TT + Tt vs. tt (dominant)	Overall	15	0.953	0.873-1.039	0.276	F	0.185	24.9
	European	10	0.979	0.893-1.073	0.645	F	0.171	29.8
TT vs. tt	Overall	15	0.929	0.844-1.023	0.136	F	0.320	12.1
	European	10	0.947	0.855-1.050	0.303	F	0.196	26.9

VDR, vitamin D receptor; OR, odds ratio; CI, confidence interval; R, Random effects model; F, Fixed effects model.

Our findings are consistent with the functional analysis of the VDR FokI polymorphism. The FokI polymorphism is located in a start codon that creates an alternative start site resulting in the synthesis of a protein of an alternate length [55]. The long variant f allele is transcriptionally less active and is associated with a lower transactivation of the VDR gene than the short F allele (29). The variant protein may have a decreased capacity to inhibit cellular growth after the administration of vitamin D (29). Thus, the VDR FokI f allele may increase the risk of breast cancer.

The functional effects of the VDR BsmI, ApaI, and TaqI polymorphisms, which are all located near the 3'-UTR region, are not clear. However, some studies suggest that these polymorphisms may alter the polyadenylation of the VDR mRNA transcript, and thus affect mRNA stability [56]. The VDR BsmI, ApaI, and TaqI polymorphisms are in regions of strong LD. Our study did not identify any association between breast cancer and the BsmI, ApaI, and TaqI polymorphisms. The reason for this lack of association could be explained with further haplotype studies.

Our results should be interpreted with caution, as the full purpose of this analysis for each ethnic group could not be achieved due to the limited number of studies included in this meta-analysis. The importance of the VDR polymorphisms during the development of breast cancer may be dependent on specific ethnicity. However, we were able to perform an ethnicity specific meta-analysis of the VDR polymorphisms only for Europeans. It is very important to substantially increase this number so that subgroup analysis for various ethnic populations can be performed. This information will increase the depth of meta-analysis and add new information to the existing field. Furthermore, meta-analysis ORs for FokI polymorphism were very modest, ranging from 1.057 to 1.141.

The study differs in scope from a previous meta-analysis performed by Tang et al. [57], which examined the association between the VDR polymorphism and breast cancer. In the present analysis, 10 more studies, 8,831 more patients, and 9,989 more controls were included [8-17]. Nevertheless, the findings of this meta-analysis, indicating the contribution of

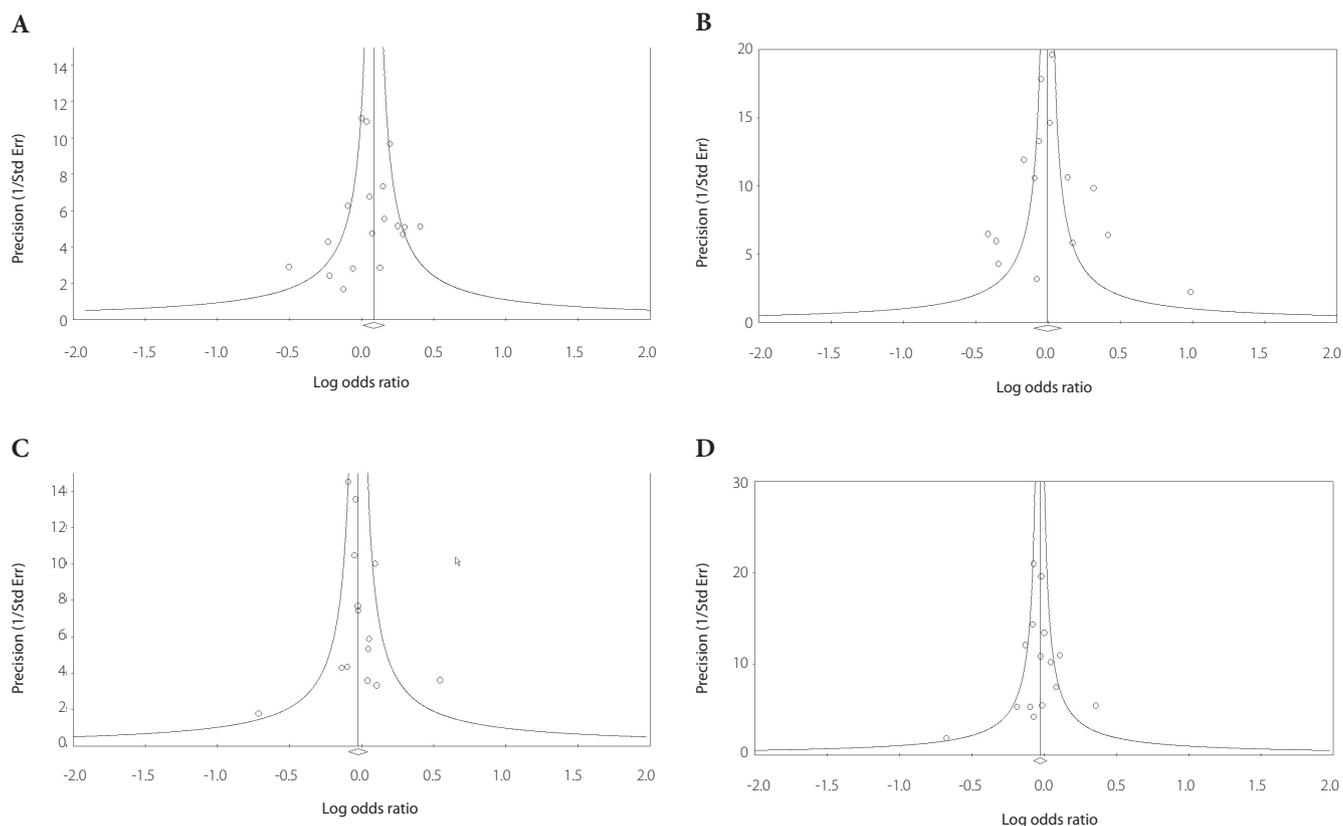


Figure 4. Funnel plot of studies analyzed for the association between breast cancer incidence and the VDR FokI (A), BsmI (B), ApaI (C) and TaqI (D) polymorphisms (Egger's regression p -values = 0.657, 0.891, 0.484, and 0.740, respectively).

VDR FokI f allele to the development of breast cancer, are in agreement with the previous study.

The present study has some limitations that needs to be taken into account while interpreting its findings. First, patient heterogeneity and confounding factors may have distorted the analysis. Second, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. Furthermore, LD was found for the BsmI, TaqI, and ApaI polymorphisms [7], however, no meta-analysis of haplotypes was possible due to inadequate haplotype data. Third, the VDR polymorphisms may be associated with breast cancer severity, but the limited amount of available data did not allow us to investigate this association.

In conclusion, this meta-analysis demonstrates that the VDR FokI polymorphism is associated with the susceptibility to breast cancer in the European population, suggesting that the VDR polymorphisms may play an important role in breast carcinogenesis. However, a similar association was not found between the VDR BsmI, ApaI, and TaqI polymorphisms and the incidence of breast cancer in the Europeans. Large-scale studies in populations that include different ethnicities are necessary to explore the roles of the VDR gene polymorphisms in the pathogenesis of breast cancer.

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