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Original Article

Menopausal status could modify breast cancer risk associated with the FokI polymorphism in vitamin D receptor gene: a meta-analysis

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Abstract: The FokI polymorphism in vitamin D receptor (VDR) gene has been reported to influence the risk of breast cancer among females. However, the association between the FokI polymorphism and breast cancer risk could probably be interfered by menopausal status. Actually, there is inconsistent evidence about the association among premenopausal and postmenopausal women. A meta-analysis was conducted to precisely estimate the association between the FokI polymorphism and breast cancer risk stratified by menopausal status. Two eligible case-control studies involving 1,526 cases and 2,058 control subjects among premenopausal women and five eligible studies involving 7,738 cases and 10,453 control subjects among postmenopausal women were identified through searching PubMed, Web of Science, CNKI and CBM. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by using a fixed-effect model or random-effect model based on the result of significant test for heterogeneity. The results showed that no overall significant breast cancer risk was found to be associated with any genetic contrast model of the FokI polymorphism among premenopausal women, while overall significant breast cancer risk was associated with the homozygous model (OR=1.106, 95% CI=1.011-1.211; P_Q=0.153, I^2=40.3% for ff vs. FF) and the dominant model (OR=1.105, 95% CI=1.017-1.200; P_Q=0.545, I^2=0.0% for ff vs. Ff+FF) of the FokI polymorphism among postmenopausal women, respectively. Begg's test and Egger's test for all genetic contrast models did not support the publication bias of the studies in postmenopausal women. Therefore, the VDR FokI polymorphism may represent a risk factor of breast cancer among postmenopausal women, whereas not among premenopausal women. More studies are warranted to evaluate the association of the FokI polymorphism with breast cancer risk stratified by menopausal status worldwide.

Keywords: FokI polymorphism, vitamin D receptor, breast cancer, menopausal status, meta-analysis

Introduction

Breast cancer is the most frequently diagnosed cancer, and accounts for 25% of all cancer cases and 15% of all cancer deaths among females worldwide. In 2012, there were an estimated 1.7 million cases and 521,900 deaths of breast cancer among females worldwide [1]. Although there are stable incidence rates in some Western countries due to changes in menopausal hormone therapy use and participation in mammographic screening [2, 3], the morbidity and mortality of breast cancer have been rising in many low-income and middle-income countries in Asia, South America, and Africa, most likely due to the delayed introduction of breast cancer screening programs and limited access to treatment [4].

The risk factors of breast cancer include the dysregulation of susceptibility genes (e.g. BRCA1, BRCA2, TP53, and PTEN) [5], menstrual and reproductive factors such as a long menstrual history, oral contraceptives use, menopausal hormone therapy use, and never having children [6]. Also, overweight or obesity, physical inactivity and alcohol intake are the potential risk factors of breast cancer [7]. Obviously, it is needed to explore additional risk factors constantly to provide a more complete understanding of the pathogenesis of breast cancer.

Epidemiologic studies have identified that vitamin D endocrine system is involved in the pathogenesis of breast cancer [8]. As an active regulator, vitamin D endocrine system has many important functions in several biological

processes including bone metabolism, immune response, and cell differentiation and proliferation [9]. Of course, vitamin D intake and high serum concentrations of vitamin D metabolites (1α,25-dihydroxyvitamin D3) are associated with a reduced risk of breast cancer [10-12]. In addition, most biological functions of 1α,25-dihydroxyvitamin D3 are mediated by nuclear vitamin D receptor (VDR), which regulates the transcription of target genes [13]. In a mouse model, the VDR gene dosage impacts on age-related changes in ductal morphology and oncogene-induced tumorigenesis in mammary gland [14]. Therefore, the VDR with normal molecular structure is the key to the functions of vitamin D endocrine system. Many studies have reported some possible associations between polymorphisms in the VDR gene and susceptibility to breast cancer across countries [15-18].

The VDR gene is located on chromosome 12q12-14 and comprises 11 exons and 11 introns. There are more than 600 single nucleotide polymorphisms that have been identified within the coding region of the VDR gene [19]. Among these VDR polymorphisms, FokI (rs2228570/rs10735810) in exon 2 at the 5' end of the VDR gene is one of the most frequently studied in the pathogenesis of breast cancer. However, a number of epidemiologic studies have reported largely inconsistent results with respect to the association between the FokI polymorphism and breast cancer risk, which have indicated some evidence of increased risk [20-23], deceased risk [18], and no association [11, 16, 17, 24-26]. Several meta-analyses have indicated that the FokI polymorphism may represent a risk factor based on many independent studies, especially in Caucasian population [27-30].

In fact, menopausal status can modify breast cancer risk associated with genotypes and some other risk factors, such as obesity, alcohol intake, and physical activity [31-35]. As a result, the association between vitamin D endocrine system and susceptibility to breast cancer could be interfered by menopausal status among females. A quantitative nonlinear dose-response meta-analysis of prospective studies evaluated the association between circulating 25-hydroxyvitamin D level and breast cancer risk, stratified by menopause [36]. The meta-analysis indicated that while no association was found among premenopausal women, dose-response modeling revealed a nonlinear inverse association among postmenopausal women. In addition, some inconsistent evidences suggest that the associations between the VDR genotypes and breast cancer risk may vary by menopausal status [17, 18, 22, 23, 37]. In particular, an inconsistent result has been reported with respect to the association between the FokI polymorphism and breast cancer risk among premenopausal and postmenopausal women, respectively [22]. However, the menopausal status of subjects was not considered in the previous meta-analyses that were performed to estimate the overall risk of breast cancer associated with the FokI polymorphism [27-30]. As a result, some vitamin D-related interventions that are developed based on those conclusions probably result in a confused outcome in reducing breast cancer risk among females with different menopausal status [38]. Therefore, we conducted this meta-analysis in order to get a precise estimation on the association between the FokI polymorphism and breast cancer susceptibility stratified by menopausal status.

Material and methods

Retrieval of relevant studies

To identify all epidemiological studies exploring the association between the FokI polymorphism and breast cancer risk among premenopausal and postmenopausal women, respectively, a comprehensive literature retrieval in databases including PubMed, Web of Science, China National Knowledge Infrastructure (CNKI) and China Biology Medicine (CBM) was conducted up until January 14th, 2016, using the following search terms: "FokI" or ''Fok1" or "rs2228570" or "rs10735810" in combination with "breast cancer". The published language was not restricted. Additional eligible studies that were not captured by the database retrieval were identified by reviewing the references of relevant literatures. In addition, the largest number of participants was included in this meta-analysis when there was an overlap among populations from several studies with the same design.

Inclusion and exclusion criteria

The following criteria were defined for eligible studies in this meta-analysis: first, case-control

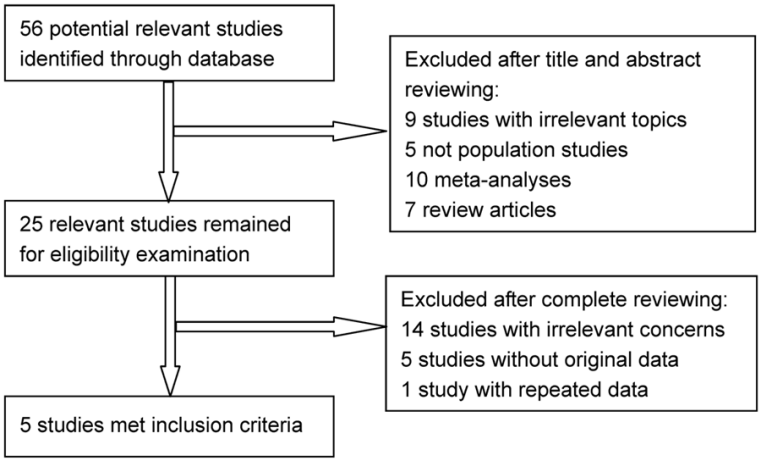

Figure 1. Working flow chart for identifying eligible studies.

study; second, concerning the association between the FokI polymorphism and breast cancer risk among premenopausal or postmenopausal women; third, available genotype distribution data for calculating odds ratios (ORs) and 95% confidence intervals (CIs). Articles were excluded for any of the following reasons: letters or editorial, review, articles with repeated data or insufficient data.

Quality assessment of eligible studies

The methodological qualities of included studies were assessed by two authors independently based on the Newcastle-Ottawa Scale (NOS) for quality of case-control studies in meta-analysis [39]. The NOS star system ranges from 0 to 9 stars for quality assessment. In this meta-analysis, studies awarded 7 or more, 4-6, and 3 or fewer stars were considered as high, moderate, and low quality, respectively. In addition, a senior researcher reviewed the included studies again and made final decisions on their qualities when there were disagreements between the two initial reviewers.

Data extraction

All data in the eligible studies were extracted by two authors independently. The extracted data included the first author's name, year of publication, country, racial descent, and numbers of subjects in cases and controls, source of subjects, genotyping methods, and genotype frequencies of cases and controls. Once the genotype frequencies of cases and controls were missing, a data request was sent to the corresponding author by e-mail. In this meta-analysis, the FokI polymorphism was reported using restriction fragment length polymorphism (RFLP) nomenclature for the major and minor alleles (C=F and T=f), consistent with the previous studies. The allele frequencies were calculated from the genotype counts. Also, the accuracy of data extraction was examined by a senior researcher independently.

Statistical analysis

A chi-square test was adopted to determine if genotype frequencies in controls conformed to Hardy-Weinberg equilibrium (HWE), and $P<0.05$ was considered significant. The pooled ORs with 95% CIs were calculated to estimate the association between the FokI polymorphism and breast cancer risk among premenopausal and postmenopausal women, respectively, including the genetic contrast models of ff vs. FF (homozygous model), ff+Ff vs. FF (recessive model), ff vs. Ff+FF (dominant model), allele f vs. allele F (allelic model), and Ff vs. FF (additive model). Heterogeneity was assessed by the chi-square-based Q test and the I^2 index [40]. $P_Q>0.05$ and $I^2<50\%$ suggested that there was no statistically significant heterogeneity detected between studies, and the fixed-effect (the Mantel-Haenszel method) model was employed to estimate the pooled ORs [41]. Otherwise, the random-effect (the DerSimonian and Laird method) model was applied in this meta-analysis [42]. The pooled ORs assumption was checked by the Z test. The estimate of publication bias was performed by Begg's test and Egger's test, and $P<0.05$ for each test indicated significant publication bias [43]. All statistical data were analyzed with STATA software, version 11.0 (STATA Corp., College Station, TX, USA) and all tests were two-sided.

Results

Study characteristics

The working flow chart for identifying eligible studies is represented in **Figure 1**. According to the criteria eligibility, we identified five articles

Table 1. Basic characteristics of the eligible studies in this meta-analysis

First author	Year	Country	Racial descent	Cancer case	Control	Source	Genotyping method	NOS stars
Abbas	2008	Germany	European	1390	2596	Population-based	PCR-RFLP	8
Mckay	2009	Mixed	Mixed	5912	7691	Mixed	TaqMan	6
Rollison	2012	America	European	1737	2051	Population-based	PCR-RFLP	8
Nemenqani	2015	Saudi Arabia	Asian	95	100	Hospital-based	PCR-RFLP	5
Abd-Elsalam	2015	Egypt	African	130	100	Hospital-based	PCR-RFLP	4

PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, NOS = Newcastle-Ottawa Scale.

Table 2. The genotype distributions of the FokI polymorphism stratified by menopausal status in the eligible studies in this meta-analysis

Menopausal status	First author	Year	Case group						Control group						HWE
			n	F	f	FF	Ff	ff	n	F	f	FF	Ff	ff	
Premenopausal	Mckay	2009	880	1091	669	343	405	132	1405	1782	1028	562	658	185	0.94
	Rollison	2012	646	783	509	237	309	100	680	791	569	228	335	117	0.95
Postmenopausal	Abbas	2008	1390	1738	1042	566	606	218	2596	3199	1993	998	1203	395	0.58
	Mckay	2009	5032	6245	3819	1963	2319	750	6286	7990	4582	2556	2878	852	0.65
	Rollison	2012	1091	1348	834	425	498	168	1371	1696	1046	524	648	199	0.99
	Nemenqani	2015	95	98	92	24	50	21	100	126	74	39	48	13	0.96
	Abd-Elsalam	2015	130	138	122	43	52	35	100	116	84	37	42	21	0.39

HWE = Hardy-Weinberg equilibrium.

[11, 16, 21, 22, 26] reporting the association between the FokI polymorphism and breast cancer risk among premenopausal or postmenopausal women.

The basic characteristics and quality score of each included study are summarized in **Table 1**. The five eligible studies ranged from 2008 to 2015. The number of study populations varied from 95 to 5,912 in cases and from 100 to 7,691 in controls. A total of 9,264 cases and 12,538 control subjects were ultimately analyzed in this meta-analysis. The NOS stars of the five eligible articles ranged from 4 to 8, and the mean value of NOS stars was 6.2. Thus, they were defined as moderate and high-quality studies.

The genotype distributions of the FokI polymorphism are presented in **Table 2**. All the five articles reported the association between the FokI polymorphism and breast cancer risk among postmenopausal women, while only two studies reported the association among premenopausal women [11, 22]. A total of 1,526 and 7,738 cases and 2,058 and 10,453 control subjects were ultimately analyzed among premenopausal and postmenopausal women, respectively. In addition, the genotype distributions in the controls of all studies were in agreement with HWE.

Meta-analysis results

The pooled results on the association between the FokI polymorphism and breast cancer risk stratified by menopausal status are presented in **Table 3**. Among premenopausal women, no overall significant breast cancer risk was found to be associated with any genetic contrast model of the FokI polymorphism in this meta-analysis (OR=0.994, 95% CI=0.705-1.402; P_Q=0.096, I^2=63.8% for ff vs. FF; OR=0.976, 95% CI=0.851-1.119; P_Q=0.211, I^2=36.2% for ff+Ff vs. FF; OR=1.026, 95% CI=0.782-1.345; P_Q=0.150, I^2=51.7% for ff vs. Ff+FF; OR=0.987, 95% CI=0.842-1.157; P_Q=0.108, I^2=61.3% for allele f vs. allele F; OR=0.962, 95% CI=0.832-1.112; P_Q=0.404, I^2=0.0% for Ff vs. FF). Among postmenopausal women, overall significant breast cancer risk was found to be associated with the homozygous model and the dominant model of the FokI polymorphism, respectively (OR=1.106, 95% CI=1.011-1.211; P_Q=0.153, I^2=40.3% for ff vs. FF, **Figure 2**; OR=1.022, 95% CI=0.904-1.156; P_Q=0.062, I^2=55.5% for

Table 3. The pooled results on the association between the FokI polymorphism and breast cancer risk stratified by menopausal status

Menopausal status	Contrast models	OR (95% CI)	Z	P	P_Q	I^2	Begg's test		Egger's test		
							z	P	Coef.	t	P
Premenopausal	ff vs. FF	0.994 (0.705, 1.402)	0.04	0.971	0.096	63.8%	-	-	-	-	-
	ff+Ff vs. FF	0.976 (0.851, 1.119)	0.34	0.731	0.211	36.2%	-	-	-	-	-
	ff vs. Ff+FF	1.026 (0.782, 1.345)	0.18	0.855	0.150	51.7%	-	-	-	-	-
	allele f vs. allele F	0.987 (0.842, 1.157)	0.16	0.873	0.108	61.3%	-	-	-	-	-
	Ff vs. FF	0.962 (0.832, 1.112)	0.52	0.600	0.404	0.0%	-	-	-	-	-
Postmenopausal	ff vs. FF	1.106 (1.011, 1.211)	2.21	0.027	0.153	40.3%	0.73	0.462	0.982	0.93	0.421
	ff+Ff vs. FF	1.022 (0.904, 1.156)	0.35	0.726	0.062	55.5%	0.73	0.462	0.599	0.46	0.677
	ff vs. Ff+FF	1.105 (1.017, 1.200)	2.35	0.019	0.545	0.0%	1.22	0.221	0.909	1.44	0.246
	allele f vs. allele F	1.044 (0.958, 1.137)	0.98	0.329	0.066	54.6%	0.73	0.462	0.912	0.73	0.517
	Ff vs. FF	1.005 (0.943, 1.072)	0.16	0.876	0.136	42.9%	0.24	0.806	0.274	0.23	0.831

OR = odds ratio, CI = confidence interval, P_Q = *P*-value of heterogeneity Q test.

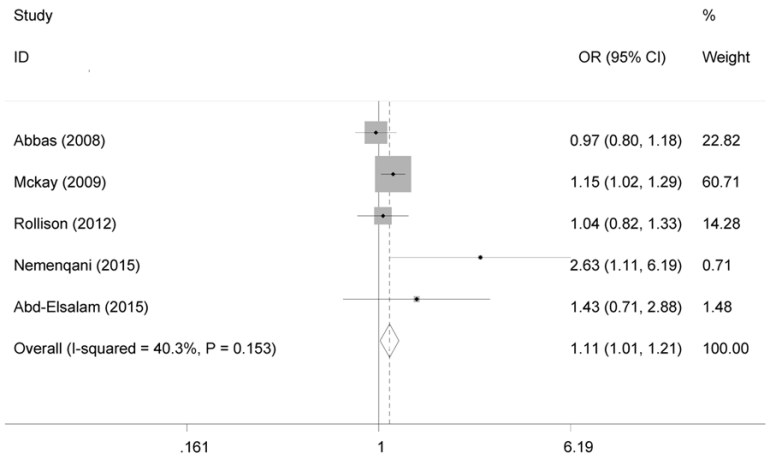

Figure 2. Meta-analysis of the association between the FokI polymorphism and breast cancer risk under the homozygous model (ff vs. FF) among postmenopausal women.

ff+Ff vs. FF; OR=1.105, 95% CI=1.017-1.200; P_Q=0.545, I^2=0.0% for ff vs. Ff+FF, **Figure 3**; OR=1.044, 95% CI=0.958-1.137; P_Q=0.066, I^2=54.6% for allele f vs. allele F; OR=1.005, 95% CI=0.943-1.072; P_Q=0.136, I^2=42.9% for Ff vs. FF).

Publication bias

Begg's test and Egger's test were performed to evaluate the publication bias of the studies included in the meta-analysis of postmenopausal women. The outcomes of Begg's test and Egger's test from all genetic contrast models did not support the existence of publication bias (**Table 3**). However, publication bias was not investigated because there were only two studies reported the association among premenopausal women.

Discussion

This is the first meta-analysis to estimate the association of the VDR FokI polymorphism with breast cancer risk stratified by menopausal status. Although the association has also been investigated in several meta-analyses, the moderating role of menopausal status must be considered precisely. The current meta-analysis based on five case-control studies with 7,738 breast cancer cases and 10,453 control subjects suggested that the FokI polymorphism was associated with the risk of breast cancer among postmenopausal women, while not among premenopausal women based on two case-control studies with 1,526 breast cancer cases and 2,058 control subjects.

As a nuclear receptor, the VDR binds to 1α,25-dihydroxyvitamin D3 with high affinity and regulates the expression of target genes through zinc finger-mediated DNA binding and protein-protein interactions [44]. The signaling pathways downstream of the VDR are involved with the regulation of cell proliferation, differentiation, and apoptosis [9]. There is no linkage disequilibrium between the FokI polymorphism and some other VDR gene polymorphisms, such as BsmI, ApaI, and TaqI [45]. Therefore, the FokI polymorphism can be thought of as an independent marker within the VDR gene. F to f

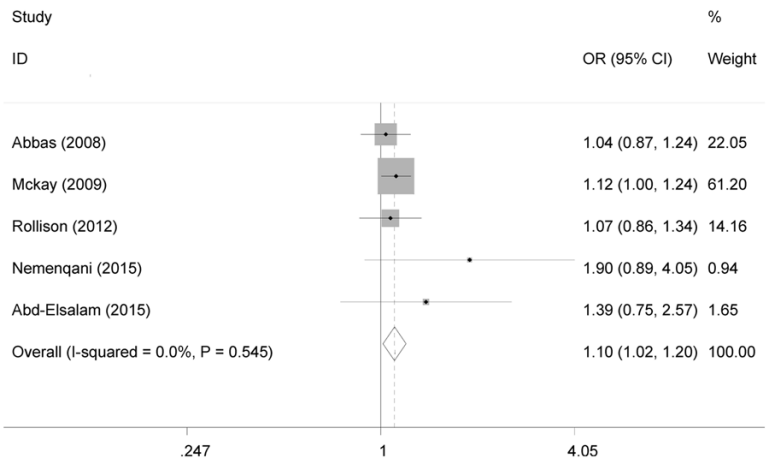

Figure 3. Meta-analysis of the association between the FokI polymorphism and breast cancer risk under the dominant model (ff vs. Ff+FF) among postmenopausal women.

transition makes the f allele three amino acids longer because the transition alters the translation start site for the VDR protein. The larger VDR molecule encoded by the f allele is less active than the regular-sized receptor [46]. Moreover, the VDR protein encoded by the F allele has a higher stability than the f isoform. The regular-sized VDR is more effective in suppressing the estrogen receptor (ER) signaling pathway and other pro-inflammatory pathways in breast cancer cells [47]. It has been reported that the FokI polymorphism affects immune system regulation, and the regular-sized VDR molecule enhances NF-κB and NFAT-driven transcription and stimulates a higher IL-12p40 promoter driven transcription activity in the absence of 1α,25-dihydroxyvitamin D3 compared with the f VDR isoform [48]. Plausibly, the FokI polymorphism of the VDR gene could have a significant association with the risk of breast cancer.

However, the association between the FokI polymorphism and breast cancer risk was found among postmenopausal women, but not among premenopausal women in this meta-analysis. In fact, epidemiologic studies have reported that the serum concentrations of vitamin D metabolites of postmenopausal women are normally lower than that of premenopausal women [49, 50]. The likelihood of vitamin D deficiency increases with age probably due to the decline of cutaneous vitamin D production. Therefore, the serum levels of vitamin D metabolites could be a moderator of the association between the FokI polymorphism and breast cancer risk. In addition, the altered breast cancer risk observed by menopausal status may be partly attributed to the difference in estrogen level between premenopausal and postmenopausal women. Vitamin D and estrogen deficiencies seem to reduce the activation of vitamin D and the expression of VDR protein [51]. The level of estrogen of postmenopausal women is significant lower than that of premenopausal women [52]. Estrogen can modify the activity of VDR by influencing its gene expression. E2 (17beta-estradiol) binds to receptor compartmentalized to membrana caveolar domains in MCF-7 breast cancer cells, inducing extracellular regulated kinase1/2 (ERK1/2) activation and transcriptional activity, which finally results in upregulation of the expression of VDR gene [53]. Thus, the level of VDR gene expression that can be regulated by estrogen has a moderating role on the association between the FokI polymorphism and breast cancer risk. More importantly, ER was positive in more than 60% breast cancer cases, increasing with rising age [54, 55]. Pervez et al. reported that 78% of all negative ERs were in breast cancer cases younger than 50 years of age (premenopausal), while 52% of strong ER positivity was observed in cases older than 50 years (postmenopausal) [56]. However, in response to 1α,25-dihydroxyvitamin D3 treatments, ER protein expression was downregulated by 62% in VDRFF cells compared to 25% in VDRff cells that were established from parental MCF-7 cells as single-cell clones [47]. Also, ER expression seems to have a certain degree of influence on the association between the FokI polymorphism and breast cancer risk.

Deviation from HWE is usually considered as an existence of potential bias from genetic or methodological factors, resulting in false-positive conclusions [57]. Therefore, HWE test is essential for determining genetic associations in meta-analysis. In this meta-analysis, none of the included studies was detected to be deviated from HWE. Moreover, the eligible articles

were identified as moderate and high-quality studies based on their high quality scores. Among postmenopausal women, the outcomes of Begg's test and Egger's test did not support the existence of publication bias in all genetic contrast models. Thus, the results suggested that the association between the FokI polymorphism and breast cancer risk among postmenopausal women is statistically reliable. However, there were only two studies exploring the association among premenopausal women, which decreased the statistical power of this meta-analysis. Some excluded studies due to without original data have reported a consistent finding that the FokI polymorphism is not associated with the risk of breast cancer among premenopausal women [17, 18, 24]. However, Chen et al. reported a positive association between the FokI ff genotype and breast cancer risk among premenopausal women, but not among postmenopausal women [20]. Therefore, more studies are needed to further assess the association in premenopausal women worldwide.

There are several limitations to this meta-analysis. First, the sample size used to determine the association between the FokI polymorphism and breast cancer risk was relatively small among premenopausal women. The lack of significant association may result from low statistical power. Second, the most study subjects came from Western countries. Therefore, additional studies are warranted to further assess the association in Asians and Africans or different ethnic groups. Sensitivity analysis and assessment on the effects of population stratification were not conducted due to the limited number of the eligible studies. Third, some co-factors were not fully taken into account in this meta-analysis, such as age, sun exposure, the levels of vitamin D metabolites, reproductive and hormonal factors, all of which could modify the association between the FokI polymorphism and breast cancer risk.

The meta-analysis identified that the VDR FokI polymorphism may represent a risk factor of breast cancer among postmenopausal women, whereas not among premenopausal women. Nevertheless, more studies are warranted to evaluate the association of the FokI polymorphism with breast cancer risk stratified by menopausal status worldwide and further understand the mechanism underlying the association.

Disclosure of conflict of interest

None.

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