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Systematic Review / Meta-analysis

Vitamin D and breast cancer risk: A systematic review and meta-analysis in Iranian patients

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1. Introduction

Cancer is an extensive global health issue. Among various types of cancers, breast cancer (BC) is expected to have the highest incidence in women, counting for 29% of new cases. BC should be considered the most prevalent cancer in Iranian women, as 76% of cancerous Iranian women have this malignancy. As a heterogeneous disease, BC is influenced by genetic and environmental factors [1].

Vitamin D is essential in biological processes like immune response, bone metabolism, and cell growth regulation [2]. Several studies have shown an inverse association between vitamin D levels and BC risk. Vitamin D's protective effect on cancer development could be due to its participation in cell cycle regulation, apoptosis, cell differentiation, and anti-inflammatory factor within the tumor microenvironment [3]. Recent studies aimed to clarify the role of vitamin D serum level and its receptor function in BC. Dietary intake and sun exposure are risk factors; affecting vitamin D serum levels. They also directly affect vitamin D receptor (VDR) and genotype polymorphism status [4,5].

VDR, as a member of the nuclear receptor superfamily, is expressed in the breast tissue and intercedes the cellular effects of vitamin D. It is suggested that VDR gene polymorphisms could increase BC incidence. Recent evidence demonstrated that VDR expression is decreased in BC tissues compared to normal breast tissues [6]. The VDR gene has many single-nucleotide polymorphisms (SNPs), verified in the coding and non-coding regions. FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) variants are the most common studied SNPs within VDR gene. Recent studies showed that these polymorphisms dysregulate VDR expression and function in breast cells [5,7].

In addition to VDR polymorphism, many types of research have focused on the concentrations of vitamin D in the blood and the risk of BC [8]. High levels of circulating vitamin D ((25(OH) D)) may have a significant effect on the reduction of the postmenopausal incidence of BC, but still, there are controversies [9]. It has been shown that vitamin D deficiency is the most typical micronutrient deficiency in many regions of Iran [10].

Here, we perform a systematic review and meta-analysis to summarize the results of case-control studies on the association of VDR polymorphisms and vitamin D levels with the risk of BC in the Iranian population.

2. Methods

The methods section has been reported in line with the PRISMA criteri [11]. We state the level of compliance with AMSTAR 2 and we got high quality score according to AMSTAR 2 checklist [12].

2.1. Literature search

We systematically searched PubMed, Google Scholar, Scientific information database (SID) and Cochrane library databases for studies published in English and Persian (up to Jun 2021). Case-control studies of Iranian patients and healthy controls with a primary diagnosis of BC were included. The following search terms were used for polymorphism: vitamin D receptor polymorphism, polymorphism, vitamin D receptor, VDR, IRAN, cancer risk, breast cancer, breast neoplasms, malignant, or tumor. The following search terms were used for vitamin D level: "Breast Neoplasms, cancer, malignant or tumor", and "Vitamin D, Vitamin D3, 25-hydroxy vitamin D and 25(OH)D, Vitamin D Receptor or VDR," with or without "polymorphism or variant" and "Iranian woman, Iranian, Iran".

No restrictions were about the age, gender, tumor stage, or postmenopausal status of the patients. Studies that lacked useable data or had incomplete data were excluded [4,6,10,13–22].

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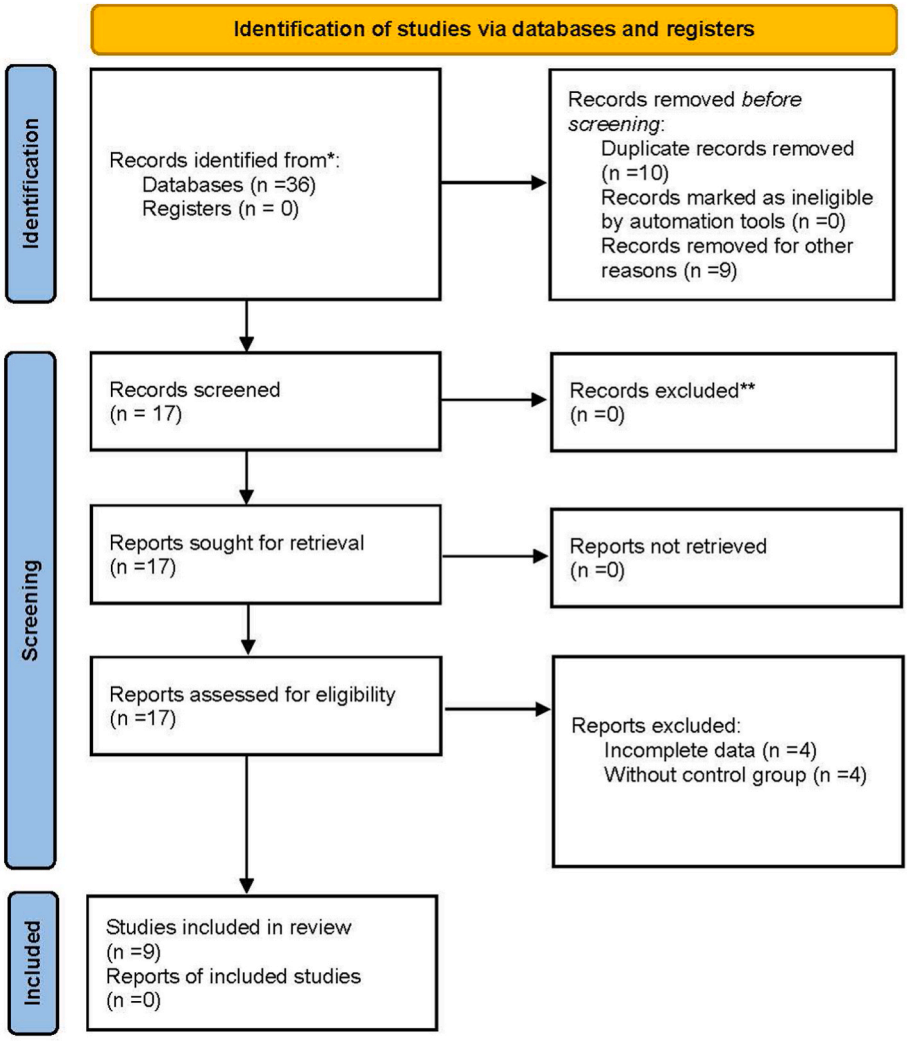

Fig. 1. The flow chart shows the detailed study selection process of meta-analysis.

2.2. Inclusion/exclusion criteria

The following criteria were considered as inclusion criteria: (1) BC cases that were pathologically confirmed; (2) Studies designed as case-control; (3) Provided data on VDR gene polymorphism, and (4) Provided data of vitamin D level.

The following criteria were considered as inclusion criteria: (1) Review articles, posters, thesis; (2) studies without control groups and (3) studies with incomplete data.

2.3. Data extraction

The following information was extracted from each study: authors' name, year of publication, province of patients, genotyping method, sample size (case and control), adjusted allele, and genotype frequencies of VDR gene polymorphisms. We took the homozygous genotype (TT for FokI, AA for BsmI, AA for ApaI, and TT for TaqI) as the reference genotype in this meta-analysis. Mean age, detected variables, vitamin D Level and its average level definitions, and vitamin D and BC association were also extracted.

2.4. Statistical analysis

The Hardy-Weinberg (HWE) of SNPs in the control group was calculated; using the Chi-square test for each study. The association of VDR polymorphisms (FokI, BsmI, TaqI, and ApaI) with BC's risk in 5 genetic models were evaluated; using pooled ORs with 95% CI. The $p < 0.05$ was considered statistically significant.

Since the cut-off range and unit of measurement were different in studies, we included vitamin D level as a categorical variable (sufficient and insufficient) in a meta-analysis of vitamin D levels.

Statistical heterogeneity among studies was tested with the Cochrane Q statistic, and statistical inconsistency was quantified with the I^2 statistic. The fixed-effects model was applied to combine the individual studies if the meta-analysis has no heterogeneity. Otherwise, the random-effects method was used.

Publication bias was assessed; using Egger's regression and Begg's and Egger's test. Sensitivity analysis was done to evaluate whether a single study could significantly affect the results by omitting each study to determine its effect on the pooled analysis. All statistical analyses were achieved; using STATA software (version 11.0; Stata-Corp, College Station, TX).

3. Results

3.1. Study characteristics

Through the literature search, a total of 36 studies were found. After removing duplicates (10 articles) and selection by the inclusion criteria, we found 9 relevant articles that described the association between the

Table 1
The main characteristics of studies included in the **VDR gene polymorphism meta-analysis.**

ID	First Author	Year	Province	Case/Control)N)	Mean Age (Y)	Genotyping methods	Studied SNPs (p-value HWE**)
1	Shirin Shahbazi [2]	2013	Tehran	140/156	cases: 45.44 controls: 42.64	RFLP-PCR*	BsmI (0.3723) FokI (0.2531)
2	Sasan Talaneh [23]	2016	West Azerbaijan	90/90	cases: 42 controls: 42	RFLP-PCR	FokI (0.0004)
3	Seyed Mehdi Hashemi [7]	2017	Cistan va Balochestan	180/178	cases: 47.93 controls: 48.28	RFLP-PCR	BsmI (0.0163) FokI (0.0082) TaqI (0.9818) ApaI
4	Hengameh Mozaffarizadeh [5]	2017	Isfahan	50/50	cases: 49.61 controls: 42.7	RFLP-PCR	BsmI (0.6283) FokI (0.7683) TaqI (0.9818)
5	Ahmad Shahabi [6]	2017	Mazandaran	203/214	cases: controls:	RFLP-PCR	BsmI (0) FokI (0.5887)
6	Sasan Talaneh [24]	2017	West Azerbaijan	95/71	cases: 42 controls: 42	RFLP-PCR	BsmI (0.2402) FokI (0)
7	Ahmad Hamta [25]	2017	Markazi	140/160	cases: 51 controls: 45.8	RFLP-PCR	ApaI

* RFLP-PCR: Restriction fragment length polymorphism-PCR.
**P value $>$ 0.05 is in HWE.

Table 2
The main characteristics of studies included in the Vitamin D level meta-analysis.

ID	First Author	Year	Province	Case/ Control (N)	Mean Age (Y)	Detected Variables	Vitamin D Level	Vitamin D normal level Definitions	Vitamin D and Breast cancer association
8	Sepideh Arbabi Bidgoli [27]	2014	Khorasan	60/116	cases:36.45 ± 7.02 controls:34.2 ± 5.7	serum 25-hydroxi vitamin D	Cases = 15.17 ± 8.15 ng/ml Controls = 15.47 ± 7/45 ng/ml	10–20 ng/ml	No
9	Seyed Mostafa Shiryazdi [29]	2015	Yazd	57/85	cases:49.14 ± 12 controls:46.25 ± 9.2	serum 25-hydroxy vitamin D and calcium	Cases = 45.18 ng/ml Controls = 41.18 ng/ml	>75 nmol/L	No

Table 3
Meta-analysis and publication bias between VDR gene polymorphisms and breast cancer (BC).

SNPs	N[a]	Model	Test of Association			Test of Heterogeneity			Publication bias
			OR[b]	95% CI[c]	p-value ****	Model	p-value	I^2	p-value (Egger's test)
BsmI		GG vs. AA + AG	1.0995	[0.5786; 2.0892]	0.77	Random	3e-04	80%	0.8349
		AA vs. AG + GG	2.2469	[1.3568; 3.7211]	0.001	Random	0.0425	59%	0.4291
		GG vs. AA	1.9102	[0.9020; 4.0453]	0.09	Random	0.0057	72%	0.7196
	5	GG vs. AG	0.8913	[0.5174; 1.5352]	0.67	Random	0.0127	68%	0.4569
		A vs. G	1.3103	[0.8429; 2.0366]	0.22	Random	0	84%	0.7975
ApaI		CC vs. CA + AA	0.8542	[0.4099; 1.7799]	0.67	Random	0.0297	78%	–
		AA vs. CC + CA	1.4388	[0.7113; 2.9103]	0.31	Fixed	0.282	13%	–
	2	CC vs. AA	1.3081	[0.3788; 4.5171]	0.67	Random	0.0979	63%	–
		CA vs. CC	0.8274	[0.4062; 1.6850]	0.60	Random	0.0376	76%	–
		C vs. A	0.9626	[0.6465; 1.4334]	0.85	Random	0.0763	68%	–
FokI		CC vs. CT + TT	1.057	[0.718; 1.558]	0.777	Fixed	0.522	0%	0.011
		CC + CT vs. TT	1.168	[0.732; 1.863]	0.515	Random	0.001	74%	0.082
	6	CC vs. TT	1.021	[0.678; 1.539]	0.921	Fixed	0.387	4.6%	0.007
		CT vs. TT	1.107	[0.677; 1.809]	0.686	Random	0.003	72.2%	0.194
		T vs. C	1.156	[0.802; 1.667]	0.515	Random	0.002	73.7%	0.052
		CC vs. CT + TT	0.0913	[0.0488; 0.1708]	0	Fixed	0.1213	58%	–
		TT vs. CC + CT	0.5568	[0.0378; 8.1927]	0.669	Random	0	96%	–
TaqI	2	CC vs. TT	0.1174	[0.0067; 2.0537]	0.142	Random	0.0028	88%	–
		CT vs. TT	0.1241	[0.0651; 0.2366]	0.00001	Fixed	0.5098	0	–
		C vs. T	0.5019	[0.0880; 2.8614]	0.437	Random	0	96%	–

****P-value of Q-test for heterogeneity test.
[a] N: Number of studies included in the meta-analysis.
[b] OR: odds ratio.
[c] 95%CI: 95% confidence interval.

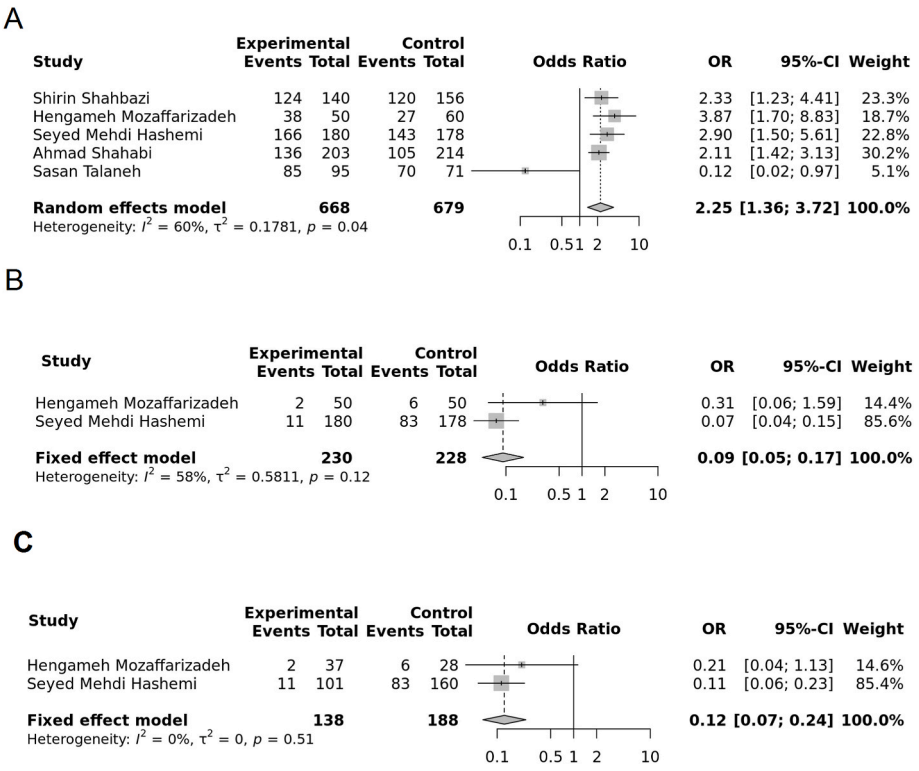

Fig. 2. The forest plots for the association between the BsmI and TaqI polymorphisms and BC risk. BsmI: AA vs. AG + GG (A), TaqI: CC vs. CT + TT (B), CT vs. TT (C).

VDR gene polymorphism or vitamin D level and BC. The flow diagram of the literature search is shown in Fig. 1.

The characteristics of seven eligible studies for VDR gene polymorphism meta-analysis are summarized in Table 1. This meta-analysis included two articles on vitamin D levels (Table 2).

3.2. VDR gene polymorphism and BC

The associations between the FokI, BsmI, TaqI, and ApaI polymorphisms and the BC risk are discussed below. All the results are summarized in Table 3.

3.2.1. BsmI

The association between BsmI polymorphism and the risk of BC was investigated in 5 studies (668 cases/669 controls) [2,6,7,23–26]. Four studies' genotype distributions in the control groups were fitted into the HWE [2,6,24,26]. The meta-analysis of the studies suggested that there was an association between the dominant model (AA vs. AG + GG) (OR: 2.2469, 95%CI: 1.3568 to 3.7211, p = 0.001) and BC risk (Fig. 2a). There were heterogeneities in all examined models. The Begg's and Egger's tests discovered no publication bias in our overall analysis of any genetic models (Fig. 3a). The sensitivity analysis results indicated that articles did not significantly affect the pooled ORs (Table 3, Fig. 4).

3.2.2. ApaI

Only two studies (320 cases/338 controls) were about ApaI polymorphisms and BC [7,25]. In the meta-analysis, the summary estimated for VDR polymorphism showed no significant association between ApaI polymorphisms and BC risk in the Iranian population. There were heterogeneities in all examined models except for the dominant models. According to Begg's and Egger's tests, there was no evidence of bias (Table 3).

3.2.3. FokI

Six articles (758 cases/759 controls) were finally included in the quantitative analysis for FokI polymorphisms and BC development risk [2,6,7,23,24,26]. The genotype distributions in the four studies were fitted into the HWE [2,6,24,26]. The meta-analysis of the studies suggested no association between all genetic models for FokI and BC risk. Except for recessive model and homozygote contrast, there were heterogeneities in other genetic models. Begg's and Egger's tests showed no apparent publication bias in our overall analysis in any genetic models except for the recessive model and homozygote contrast. A sensitivity analysis was done to inspect the impact of an individual study on the pooled ORs. The results indicated that the pooled ORs were not significantly affected by a single research, suggesting that the pooled results are reliable (Table 3).

3.2.4. TaqI

Based on the inclusion criteria, two articles (230 cases/228 controls) were included in the quantitative analysis related to TaqI polymorphism [7,26]. The genotype distribution in the two groups of controls followed HWE [7,26]. As shown in Table 3, a correlation was found between the TaqI polymorphism and BC risk. The meta-analysis revealed an association between recessive model CC versus CT + TT (OR: 0.514, 95% CI: 0.290 to 0.912), CT vs. TT (OR: 0.1241, 95% CI: 0.0651; 0.2366, p = 0.00001), and BC risk (Fig. 2b and c). Significant heterogeneities were found in all genetic models analyzed except for the heterozygote contrast (CT vs. TT). According to Begg's and Egger's test, there is no evidence of bias (Table 3, Fig. 3b and c).

3.3. Vitamin D level and BC

A few studies were conducted on the correlation between BC and vitamin D serum levels among Iranian women. We have found seven related articles about vitamin D levels and BC [8,21,27–31]. Two articles were selected for meta-analysis (117 case/201 controls) [27,29]. There was no association between vitamin D level and BC (OR: 0.780, 95% CI: 0.472 to 1.289, p = 0.332).

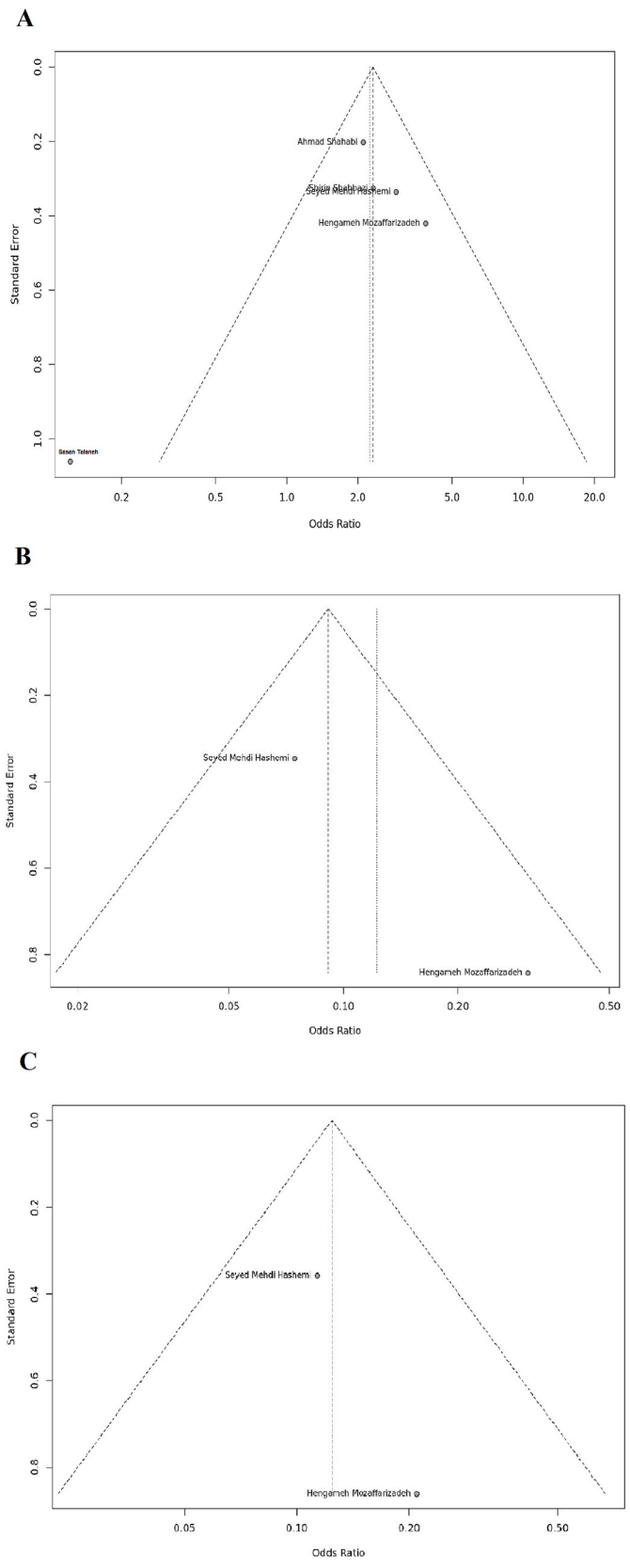

Fig. 3. Egger's funnel plot on publication bias for the association between the BsmI and TaqI polymorphisms and BC risk. BsmI: AA vs. AG + GG (A), TaqI: CC vs. CT + TT (B), CT vs. TT (C).

4. Discussion

It is shown that an increment in vitamin D intake could decrease the risk of some cancers, especially BC. The active metabolite form of vitamin D (1, 25-dihydroxy vitamin D) applies to the cells through binding to VDR. The influence of VDR gene polymorphisms on BC's risk and prognosis has been noticed recently. Accordingly, researchers have investigated vitamin D-related genetic variants, especially VDR polymorphisms. Among all of the VDR polymorphisms, FokI, BsmI, ApaI, and TaqI have more essential effects on VDR function. Studies on different populations have investigated the role of these SNPs in the BC. However, the results of these studies are controvertible. More reliable studies with higher quality and larger sample sizes must be done amongst Iranian women [7,26].

In the current meta-analysis, we assessed BsmI, ApaI, TaqI, and FokI polymorphisms of the VDR gene and the correlation between BC and vitamin D serum levels for their association with BC risk among Iranian women. There is some meta-analysis on VDR polymorphism and BC [32–34]. Our meta-analysis results revealed that the rs1544410 (BsmI) and rs731236 (TaqI) polymorphisms significantly increased BC risk compared to healthy controls. BsmI polymorphisms at the third end of the VDR gene are an intronic variant. It does not directly affect the structure or function of the VDR protein; however, it may influence the amount of VDR protein by modulating its mRNA stability [35]. These results were consistent with previous meta-analyses, which showed a positive association between BsmI SNP and BC risk [32,36]. However, Lihua Song et al. did not prove any significant correlation between BsmI, polymorphisms, and BC risk in their study [37].

TaqI is another polymorphism near the third end of the VDR gene, like BsmI and ApaI polymorphisms. Our meta-analysis revealed that the TaqI genotype was associated with increased BC risk in the recessive model. This result was consistent with a previous meta-analysis; reporting an association between TaqI polymorphism and BC. However, further studies are needed to confirm these findings.

Our results revealed no association between the ApaI variant genotypes and BC risk in the Iranian population.

In FokI polymorphism, a translocation of thymine to cytosine converts the code ATG to ACG at the beginning of two possible translation sites. Thus, resulting in a short three amino acid VDR protein on the N-terminal [38]. However, some studies revealed that the FokI polymorphism of the VDR gene was associated with an increased risk of BC; especially in the European population and Caucasian population [39], but not in the Asian population. Our results were consistent with a previous meta-analysis, which revealed no association between FokI SNP and BC risk in the general, Caucasian, and Asian populations [40].

However, this study may have some limitations. The low number of included studies in our meta-analysis was one of our study limitations. Low sample size of included studies could be considered as another important limitation. We have only found seven studies about BC and VDR genes in Iranian women, which mainly had small sample sizes. Furthermore, in the present meta-analysis, four studies were in HWE as an essential part of genotyping. However, the deviation from HWE may have some reasons, including non-randomized matching of case and control groups, bias in participant selection, and errors in genotyping. None of the studies include the same sets of patients for both polymorphisms and vitamin D level investigation. So, it is unclear if the increased risk is due to the association of polymorphism and possible cellular defects in vitamin D uptake or insufficient vitamin D level in blood.

So, there is a severe requirement to design studies with an accurate methodology to have a clear conclusion in this field. Moreover, menopausal status, dietary factors, and other gene variants that influence vitamin D pathways, such as the enzymes included in vitamin D activation, like CYP2R1 and vitamin D-binding protein (DBP), should also be taken into consideration.

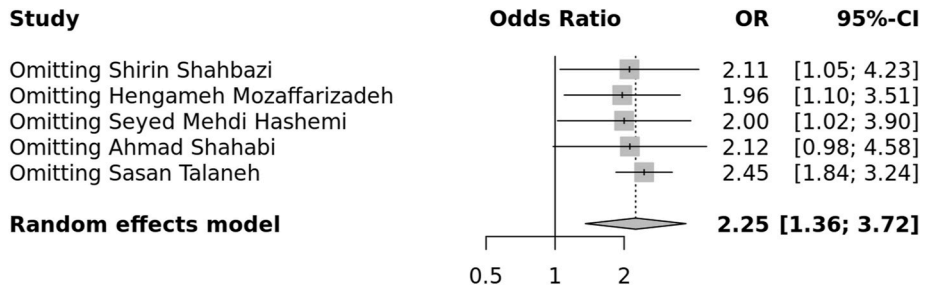

Fig. 4. Sensitivity analysis for studies on BsmI polymorphism and BC risk.

5. Conclusions

In conclusion, our results show that BsmI and TaqI polymorphisms are associated with an increased risk of BC. Consequently, genetic monitoring of BsmI and TaqI polymorphisms could be used to predict and identify the group of people with the highest risk of BC incidence.

Our review and meta-analysis indicated that although the studies on vitamin D serum levels were insufficient, serum 25(OH) D deficiency was not associated with BC occurrence in the Iranian population. Based on the present study's findings, more research should be done to investigate the link between breast cancer and vitamin D to have a definite conclusion about VitD polymorphism/concentration and breast cancer.

Ethical approval

NA.

Sources of funding

Motamed Cancer Institute, ACECR has provided the fund of the study.

Author contribution

All authors are participated in the literature search. RE managed the group, manuscript categorization, data extraction, writing manuscript. TO be responsible for data extraction and analysis, preparing tables, writing the manuscript. EN was responsible for data extraction and analysis, preparing tables. NI was responsible for data extraction and analysis. All authors have participated in providing the first draft of the manuscript and they have approved the final version.

Registration of research studies

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Consent

NA.

Guarantor

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Declaration of competing interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104162.

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