Abstract  The vitamin D receptor (VDR) is a crucial mediator for the cellular effects of vitamin D. A great number of studies regarding the association between BsmI polymorphism in the VDR gene and breast cancer have been published. However, the results have been contradicting. Therefore, we conducted a meta-analysis to re-examine the controversy. Published literatures from PubMed, Embase, and Chinese Biomedical Literature Database (CBM) were searched (updated to July 10, 2013). The principal outcome measure was the odds ratio (OR) with 95% confidence interval (CI) for breast cancer risk associated with VDR BsmI polymorphism. With all studies involved, the meta-analysis results suggest no statistically significant association between VDR BsmI polymorphism and breast cancer risk (B vs. b, OR=0.922, 95% CI=0.836–1.018, P=0.108, I^2=80.0%); BB vs. bb, OR=0.843, 95% CI=0.697–1.021, P=1.75, I^2=75.5%; Bb vs. bb, OR=0.930, 95% CI=0.814–1.063, P=0.31, I^2=73.1%; BB+BB vs. bb, OR=0.906, 95% CI=0.787–1.043, P=1.37, I^2=78.7%; BB vs. bb+Bb, OR=0.899, 95% CI=0.786–1.028, P=1.56, I^2=61.0%). The results were not changed when studies were stratified by ethnicity or source of controls. This meta-analysis suggested that there were no associations between VDR BsmI polymorphism and breast cancer.

Keywords  Vitamin D receptor · Polymorphism · Breast cancer · Meta-analysis

Introduction

Breast cancer is one of the most common cancers and the second leading cause of cancer-related deaths among women in the world [1]. Despite the frequency and severity of breast cancer, the pathogenesis and progression of breast cancer are still not fully understood. Many researchers have concluded that breast cancer is the cumulative result of multiple environmental factors and genetic alterations [2]. Risk factors for breast cancer include estrogen stimulation [3], high birth weight [4], obesity [5], and family history of breast cancer [6, 7]. In addition, genome-wide association studies provide evidence that genetic factors are important in the pathogenesis of breast cancer [8].

Data are accumulating regarding the protective role of vitamin D in various types of cancers [9]. In vitro studies revealed that vitamin D enhanced the differentiation and apoptosis of cancer cells in culture [10] including mammary glands [11]. The effects of vitamin D are mediated via the vitamin D receptor (VDR) which is expressed in most cell types, including breast tissues [12]. The VDR gene is located on chromosome 12q12-q14, and several single-nucleotide polymorphisms (SNPs) have been identified that may influence cancer risk [13]. One of the most frequently studied SNPs is the restriction fragment length polymorphism BsmI (rs1544410). The BsmI is intronic and located at the 3’ end of the gene. BsmI is strongly linked with a poly (A) microsatellite repeat in the 3’ untranslated region, which may influence VDR messenger RNA stability [14]. Over the last two decades, a number of case–control studies were conducted to investigate the association of variants in the VDR gene BsmI polymorphism and the risk of breast cancer. However, the results of these studies are controversial. Therefore, we decided to...
perform a comprehensive meta-analysis of all published studies on the association between the most studied vitamin D receptor gene BsmI polymorphism and breast cancer.

Materials and methods

Publication search

We performed a comprehensive search of PubMed, Embase, and Chinese Biomedical Literature Database (CBM) to identify relevant articles on the association between the VDR BsmI polymorphism and breast cancer risk up to July 10, 2013. The search terms used were as follows: “VDR or vitamin D receptor,” “BsmI or rs1544410,” “cancer or tumor or carcinoma,” “breast,” and “polymorphism or polymorphisms.” Additional literature was collected from cross-references within both original and review articles. No language restrictions were applied. We also checked the references from retrieved articles and reviews to identify any additional relevant study.

Inclusion criteria

For inclusion, the studies must have met the following criteria: (1) assessing the VDR BsmI polymorphism and breast cancer risk, (2) applying case–control studies or nested case–control study, and (3) supplying the number of individual genotypes for the VDR BsmI polymorphism in breast cancer cases and controls, respectively. Reviews, case-only studies, or studies with overlapping data were all excluded.

Data extraction

The following information was collected from each study: the first author’s name, the year of publication, sources of controls, sample size of cases and controls, genotyping method, number of breast cancer cases, controls with different genotypes, and the Hardy–Weinberg equilibrium (HWE) of controls, respectively. Different ethnicity descents were categorized as Asians, Caucasians, African-Americans, or Hispanics. Study design was stratified into hospital-based studies or population-based studies. Data were extracted independently by two investigators, and the disagreements during the data extraction were resolved by discussion among all reviewers.

Quality score assessment

The quality of the studies was also independently assessed by the same two reviewers according to the predefined scale for quality assessment. These scores were based on both

| Table 1 | Characteristics of case–control studies included in a meta-analysis of the relation between the BsmI polymorphism in the vitamin D receptor gene and breast cancer |
|---|---|---|---|---|---|---|---|---|
| ID | First author | Year | Ethnicity | Source of controls | Cases/controls | Genotyping method | Case | Control | HWE | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ingle [20] | 2000 | Caucasian | Population | 143/300 | TaqMan | 61 68 14 169 112 19 | 0.939 | 13 |
| 2 | Bretherton-Watt [21] | 2001 | Caucasian | Hospital | 181/241 | QiAamp | 78 84 19 39 133 69 | 0.06 10 |
| 3 | Hou [22] | 2002 | Asian | Hospital | 34/169 | PCR-RFLP | 27 6 1 153 16 0 | 0.518 | 10 |
| 4 | Buyru [23] | 2003 | Caucasian | Hospital | 78/27 | PCR-RFLP | 18 45 15 5 17 5 | 0.178 | 10 |
| 5 | Guy [24] | 2004 | Caucasian | Hospital | 398/427 | PCR-RFLP | 173 173 52 139 215 73 | 0.513 | 9 |
| 6 | Chen [25] | 2005 | Caucasian | Population | 1,180/1,547 | TaqMan | 431 586 163 565 737 245 | 0.857 | 11 |
| 7 | Lowe [26] | 2005 | Caucasian | Population | 179/179 | PCR-RFLP | 84 70 25 52 99 28 | 0.091 | 10 |
| 8 | McCullough [27] | 2007 | Caucasian | Population | 472/460 | TaqMan | 151 237 84 170 216 74 | 0.698 | 14 |
| 9 | Sinottte2 [28] | 2008 | Caucasian | Population | 617/956 | TaqMan | 237 300 80 355 461 140 | 0.625 | 15 |
| 10 | McKay1 [29] | 2009 | Caucasian | Mixed | 1,596/2,620 | TaqMan | 573 767 256 951 1,219 | 450 0.08 | 9 |
| 11 | McKay2 [29] | 2009 | Caucasian | Population | 1,065/1,097 | TaqMan | 405 468 192 407 533 | 157 0.408 | 13 |
| 12 | McKay3 [29] | 2009 | Caucasian | Population | 604/604 | TaqMan | 201 303 100 200 298 | 106 0.782 | 13 |
| 13 | Anderson [30] | 2011 | Caucasian | Population | 1,553/1,629 | PCR-RFLP | 538 746 269 592 749 | 288 0.057 | 15 |
| 14 | Rollison [31] | 2011 | Mixed | Population | 1,740/2,047 | PCR-RFLP | 247 809 684 278 905 | 864 0.095 | 12 |
| 15 | Shahbazi [32] | 2013 | Asian | Population | 140/156 | QiAamp | 51 73 16 48 72 36 | 0.372 | 12 |
| 16 | Mishra1 [33] | 2013 | African-American | Hospital | 115/73 | PCR-RFLP | 66 40 9 34 31 | 8 0.816 | 9 |
| 17 | Mishra2 [33] | 2013 | Hispanic | Hospital | 117/276 | PCR-RFLP | 57 50 10 148 110 | 18 0.686 | 10 |

HWE: Hardy–Weinberg equilibrium, PCR-RFLP: polymerase chain reaction restriction fragment length polymorphism

a: Hospital: hospital-based case–control study; population: population-based case–control study
traditional epidemiological considerations and cancer genetic issues. Any disagreement was resolved by discussion between the two reviewers. Total scores ranged from 0 (worst) to 15 (best). Reports scoring <10 were classified as “low quality” and those ≥10 as “high quality.”

Statistical analysis

For each case–control study, the HWE of genotypes in the control group was assessed by using the chi-square test in the control groups [15]. The pooled odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated to assess the strength of the association between VDR BsmI polymorphism and breast cancer risk. To estimate associations with breast cancer risk, five genetic models were selected, including the allelic (B vs. b), homozygous (BB vs. bb), additive (Bb vs. bb), recessive (BB vs. Bb+bb), and dominant (BB+Bb vs. bb) models. Subgroup analyses based on ethnicity and source of controls were also performed.

Heterogeneity among studies was assessed by the chi-square test-based $Q$ statistic and $I^2$ statistic [16]. A significant $Q$ statistic ($P<0.10$) indicated heterogeneity across studies. In case a significant heterogeneity was detected, the random effects model (the DerSimonian Laird method) [16] was applied; otherwise, the fixed effects model (Mantel–Haenszel method) [17] was chosen.

The possibility of publication bias was assessed by using a funnel plot [18] and Egger’s linear regression test [19]. An asymmetric funnel plot suggests a possible publication bias. Then, the funnel plot asymmetry was assessed by Egger’s linear regression test, and the significance of the intercept was determined by the $t$ test suggested by Egger ($P<0.05$ indicates significant publication bias).

Analyses were performed using the software Stata version 12.0 (Stata Corporation, College Station, TX, USA). A $P$ value of less than 0.05 was considered statistically significant.

Results

Characteristics of included studies

A total of 17 eligible studies met the inclusion criteria [20–33]. All of the included studies were case–control or cohort

Table 2: Summary ORs and 95% CI for various contrasts in VDR BsmI polymorphism

| Total studies | Test of association | Test of heterogeneity | Model |
|---------------|---------------------|-----------------------|-------|
|               | OR (95% CI)         | Z         | P     | $\chi^2$ | $P$ | $I^2$ |
| All studies (17) |                      |           |       |          |     |       |
| B vs. b       | 0.922 (0.836–1.018) | 1.61     | 0.108 | 80.19   | 0.000 | 80.0 R |
| BB vs. bb     | 0.843 (0.697–1.021) | 1.75     | 0.080 | 65.29   | 0.000 | 75.5 R |
| BB vs. bb     | 0.930 (0.814–1.063) | 0.31     | 0.759 | 59.41   | 0.000 | 73.1 R |
| BB vs. bb+Bb  | 0.906 (0.787–1.043) | 1.37     | 0.170 | 75.22   | 0.000 | 78.7 R |
| BB vs. bb+Bb  | 0.899 (0.786–1.028) | 1.56     | 0.119 | 41.93   | 0.000 | 61.0 R |
| Hospital-based (6) |                  |           |       |          |     |       |
| B vs. b       | 0.838 (0.559–1.255) | 0.86     | 0.390 | 34.63   | 0.000 | 85.6 R |
| BB vs. bb     | 0.644 (0.275–1.509) | 1.01     | 0.311 | 27.52   | 0.000 | 81.8 R |
| BB vs. bb+Bb  | 0.737 (0.462–1.175) | 1.28     | 0.200 | 20.75   | 0.001 | 61.8 R |
| BB vs. bb+Bb  | 0.736 (0.426–1.271) | 1.10     | 0.271 | 31.89   | 0.000 | 84.3 R |
| BB vs. bb+Bb  | 0.757 (0.419–1.366) | 0.92     | 0.356 | 15.92   | 0.007 | 68.6 R |
| Population-based (12) |          |           |       |          |     |       |
| B vs. b       | 0.838 (0.559–1.255) | 0.45     | 0.655 | 25.38   | 0.003 | 25.38 R |
| BB vs. bb     | 0.959 (0.823–1.118) | 0.53     | 0.595 | 19.98   | 0.018 | 55.0 R |
| BB vs. bb+Bb  | 1.007 (0.889–1.141) | 0.11     | 0.915 | 23.53   | 0.005 | 61.8 R |
| BB vs. bb+Bb  | 0.992 (0.880–1.120) | 0.12     | 0.902 | 24.51   | 0.004 | 63.3 R |
| BB vs. bb+Bb  | 0.957 (0.840–1.089) | 0.67     | 0.504 | 19.22   | 0.023 | 53.2 R |
| Caucasian (12) |                      |           |       |          |     |       |
| B vs. b       | 0.918 (0.817–1.031) | 1.44     | 0.150 | 67.73   | 0.000 | 83.8 R |
| BB vs. bb     | 0.845 (0.675–1.058) | 1.47     | 0.142 | 55.38   | 0.000 | 80.1 R |
| BB vs. bb+Bb  | 0.902 (0.767–1.060) | 1.26     | 0.209 | 55.01   | 0.000 | 80.0 R |
| BB vs. bb+Bb  | 0.883 (0.745–1.046) | 1.44     | 0.150 | 67.69   | 0.000 | 83.8 R |
| BB vs. bb+Bb  | 0.915 (0.783–1.069) | 1.12     | 0.261 | 31.78   | 0.001 | 65.4 R |

OR odds ratio, CI confidence interval, R random effects model
studies. In total, 10,212 cases and 12,808 controls were included in the pooled analyses. Of the 17 studies for polymorphisms, there were 12 with Caucasian ethnicity, 2 with Asian ethnicity, 1 with Hispanic ethnicity, 1 with mixed ethnicity, and 1 with American-African populations. The characteristics of the selected studies are summarized in Table 1.

Meta-analysis

The results on the association between VDR \textit{BsmI} polymorphism and susceptibility to breast cancer are shown in Table 2. Meta-analysis of the 17 studies suggested that there was no association between VDR \textit{BsmI} polymorphism and susceptibility to breast cancer (B vs. b, OR=0.922, 95% CI=0.836–1.018, \(P=0.108\), \(I^2=80.0\%\); BB vs. bb, OR=0.843, 95% CI=0.697–1.021, \(P=1.75\), \(I^2=75.5\%\); Bb vs. bb, OR=0.930, 95% CI=0.814–1.063, \(P=0.31\), \(I^2=73.1\%\); BB+ Bb vs. bb, OR=0.906, 95% CI=0.787–1.043, \(P=1.37\), \(I^2=78.7\%\); BB vs. bb+Bb, OR=0.899, 95% CI=0.756–1.028, \(P=1.56\), \(I^2=61.0\%\)) (Table 2, Figs. 1 and 2). When stratifying for source of controls and for ethnicity, no significant association between \textit{BsmI} polymorphism and breast cancer risk was observed.

Publication bias

Funnel plot and Egger’s test were performed to assess the publication bias. The shape of the funnel plot did not reveal obvious evidence of asymmetry (Fig. 3), and Egger’s test provided statistical evidence of funnel plot symmetry (\(P>0.05\), Table 3). Therefore, the results above did not suggest any evidence of publication bias in the meta-analysis.

Discussion

As with other malignancies, the pathogenesis of breast cancer involves environmental factors, molecular signaling pathways, and host genetic factors. In order to provide the most comprehensive and reliable conclusion, we performed the present meta-analysis of 17 independent case-control studies, including 10,212 cases and 12,808 controls. We explored the association between \textit{BsmI} polymorphism in the VDR gene region and breast cancer risk. The results of our meta-analysis do not provide evidence for an association between the VDR \textit{BsmI} polymorphism and

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Ingles(2000) | 1.52 (1.11, 2.06) | 4.83 |
| Bretherton-Watt(2001) | 0.40 (0.30, 0.53) | 5.21 |
| Hou(2002) | 2.68 (1.10, 6.55) | 1.07 |
| Buyru(2003) | 0.93 (0.50, 1.72) | 1.98 |
| Guy(2004) | 0.73 (0.60, 0.89) | 6.65 |
| Chen(2005) | 0.96 (0.86, 1.07) | 8.21 |
| Lowe(2005) | 0.66 (0.49, 0.89) | 4.90 |
| McCullough(2007) | 1.15 (0.95, 1.38) | 6.92 |
| Sinotte(2008) | 0.94 (0.81, 1.09) | 7.58 |
| McKay1(2009) | 0.98 (0.90, 1.08) | 8.50 |
| McKay2(2009) | 1.06 (0.94, 1.20) | 8.02 |
| McKay2(2009) | 0.98 (0.83, 1.15) | 7.33 |
| Anderson(2011) | 1.03 (0.93, 1.14) | 8.36 |
| Rollison(2011) | 0.93 (0.84, 1.02) | 8.44 |
| Shahbazi(2013) | 0.70 (0.50, 0.97) | 4.52 |
| Mishra1(2013) | 0.71 (0.45, 1.12) | 3.07 |
| Mishra2(2013) | 1.19 (0.85, 1.66) | 4.40 |
| Overall (I-squared = 80.0%, p = 0.000) | 0.92 (0.84, 1.02) | 100.00 |

**Fig. 1** Overall meta-analysis for VDR \textit{BsmI} polymorphism (B vs. b) and breast cancer risk.
the risk of breast cancer. It is consistent with the result of a previous meta-analysis, which was conducted by Tang et al. in 2009 [34]. However, we included 10,212 cases and 12,808 controls from 17 studies in the present meta-analysis. Hence, a more stringent and comprehensive result has been obtained.

When stratifying for ethnicity, this present meta-analysis failed to identify the association between VDR BsmI polymorphism and susceptibility to breast cancer in Caucasians. However, there were only two from Asians, one from African-Americans, and one from Hispanics, and we were unable to get a precise estimation on the association between VDR BsmI polymorphism and susceptibility to breast cancer in Asians, African-Americans, and Hispanics. Therefore, future studies on Asians, African-Americans, or Hispanics are needed to further assess the above association.

Some limitations of our study should be acknowledged. First, in the subgroup analyses, the number of Asians, Africans, and Hispanics is small, which may lead to a lack of statistical power. Second, the study populations are from different countries and may have different genetic backgrounds, which may affect the results.

Table 3 Tests for publication bias (Egger’s test) in overall population

| Polymorphism | Comparison          | Egger’s test (P) |
|--------------|---------------------|------------------|
| BsmI         | B vs. b             | 0.491            |
|              | BB vs. bb           | 0.441            |
|              | Bb vs. bb           | 0.272            |
|              | BB+Bb vs. bb        | 0.289            |
|              | BB vs. bb+Bb        | 0.838            |

Fig. 2 Overall meta-analysis for VDR BsmI polymorphism (BB vs. bb) and breast cancer

Fig. 3 Begg’s funnel plot with pseudo 95% confidence limits
African-Americans, and Hispanics was relatively small. In order to have enough statistical power to explore real association, it is necessary to collect more samples from Asians, African-Americans, and Hispanics. Second, significant heterogeneity was observed in overall comparisons and also subgroup analyses. Third, meta-analysis is just a statistical test that is subject to the methodological limitations.

Although some limitations were listed previously, there were also some advantages in our meta-analysis. First, all studies are in Hardy–Weinberg equilibrium, which indicated that the samples could better represent the expected distribution of the genotypes. Second, studies included in our meta-analysis were satisfactory and definitely met our inclusion criteria. Third, publication bias was not detected in the present study, indicating that our findings seemed not to be due to biased publications.

In summary, this meta-analysis suggests that there is no association between VDR BsmI polymorphism and susceptibility to breast cancer in Caucasians. Future studies from Asians, African-Americans, or Hispanics are needed to further assess the above association.

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Conflict of interest None

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