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# Association of vitamin D receptor polymorphisms with colorectal cancer susceptibility

## A systematic meta-analysis

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**Abstract**

**Background:** Recent studies have reported an association between vitamin D receptor (VDR) polymorphisms and colorectal cancer (CRC) risk; however, the results are controversial. This meta-analysis was performed to investigate whether the Cdx-2, Tru9I, FokI, BsmI, TaqI, and ApaI polymorphisms were correlated with CRC susceptibility.

**Methods:** All potential studies were retrieved by searching the PubMed, EMBASE, and Cochrane Library databases through October 2, 2021. Odds ratios (ORs) with 95% confidence intervals were used to evaluate the correlation between VDR gene Cdx-2, Tru9I, FokI, BsmI, TaqI, and ApaI polymorphisms and CRC risk.

**Results:** In this meta-analysis, the BsmI variant was significantly correlated with a lower risk of CRC, especially in Caucasian population (B vs b: OR 0.94, 95%CI 0.90–0.99; BB vs bb: OR 0.88; 95%CI 0.79–0.97; BB vs Bb/bb: BB vs Bb/bb: OR 0.89; 95%CI 0.81–0.98). A statistically significant result from the FokI polymorphism was observed in colon cancer rather than rectal cancer (Ff vs FF: OR 0.86, 95%CI 0.84–0.93; ff/Ff vs FF: OR 0.88, 95%CI 0.79–0.98; ff vs Ff/FF: OR 0.90, 95%CI 0.82–0.99). Similarly, Cdx-2 polymorphism was found to be associated with decreased CRC risk among Africans (C vs c: OR 0.50, 95%CI 0.33–0.75; CC vs cc: OR 0.09, 95%CI 0.01–0.77; Cc vs cc: OR 0.49, 95%CI 0.30–0.81; CC/Cc vs cc: OR 0.45, 95%CI 0.28–0.74,).

**Conclusion:** Our findings indicate that VDR polymorphisms are significantly associated with CRC risk.

**Abbreviations:** CI = confidence interval, CRC = colorectal cancer, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle Ottawa Scale, OR = odds ratio, SNP = single nucleotide polymorphism, VDR = vitamin D receptor.

**Keywords:** CRC, meta-analysis, polymorphism, susceptibility, vitamin D receptor.

## 1. Introduction

Colorectal cancer (CRC) has been a major public health challenge and the third most frequent cause of cancer-related mortality with a rapidly increasing incidence around the world.[1] According to the latest statistics, there were 149,500 new cancer cases and 52,980 deaths in the world, and the mortality of CRC accounts for 8% of all cancer-related deaths.[2] However, the underlying pathogenesis of CRC remains poorly understood. Colorectal carcinogenesis is a complicated and multifactorial process that involves interactions among environmental, genetic, and lifestyle factors. It has been reported that several exogenous factors, including alcohol consumption, smoking, obesity, and deficiency of physical activity, may contribute to the development of CRC.[3–5] Accumulative evidence has shown that vitamin D status is negatively associated with the CRC incidence and recurrence, and lower serum vitamin D levels dramatically increased CRC risk.[6,7]

Vitamin D is an essential fat-soluble steroid hormone that is obtained from the diet and can be produced in the skin following exposure to ultraviolet irradiation.[8] The active metabolite of vitamin D, 1,25 $(OH)_2D_3$, regulates vitamin D-responsive downstream gene transcription by binding to the vitamin D receptor (VDR), ultimately participating in the immune response, cellular apoptosis, proliferation, differentiation, and oncogenesis.[9–11] As a member of the nuclear receptor superfamily, VDR is primarily expressed in the bone, liver, kidney, and intestine.[12] Other studies have provided strong evidence

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that VDR expression is downregulated in colon cancer cells, whereas high VDR expression is correlated with a favorable prognosis in CRC.[13,14]

The VDR gene is mapped on the long arm of chromosome 12 (12q13.11) and contains 2 promoter regions, 8 protein-coding exons, and 6 untranslated exons.[15] To date, more than 60 SNPs have been described in the VDR gene. At the 5' end of exon 2, the FokI polymorphism is a nonsynonymous SNP related to the VDR protein frameshift.[16–18] The FokI F allele has been reported to changes the location of the start codon later than the f allele, generating a smaller protein with higher transcription activity. BsmI, ApaI, Tru9I (intron 8), and TaqI (exon 9) are located near the 3′ untranslated region (UTR) of the FokI gene.[19,20] These polymorphisms do not change the amino acid sequence, but have a strong linkage disequilibrium, forming a haplotype block that affects mRNA stability and gene transcription. CDX-2 is an intestinal-specific transcription factor located in the 5′ region of the VDR, and its mutation results in G > A sequence diversification and regulates promoter activity in the exon 1. The transcriptional activity of the promoter with Cdx-2 G allele is 30% lower than that of the A allele.[21]

Several studies have investigated the potential association between VDR polymorphisms and CRC susceptibility, but the results remain inconsistent. Zhang et al[22] found no association between FokI, BsmI, ApaI, TaqI, and CRC risk; however, there was a significant interaction between dietary vitamin D intake and ApaI polymorphisms in relation to CRC risk. Al-Ghafari et al[23] demonstrated that the ApaI and TaqI polymorphisms were associated with increased CRC risk and that the BsmI polymorphism was related to decreased CRC risk in the Saudi population. VDR polymorphic sites, including FokI, BsmI, ApaI, TaqI, Tru9I, and Cdx2, have been evaluated in genetic association studies on CRC. Therefore, this meta-analysis included all eligible studies to evaluate the relationship between VDR polymorphisms and CRC risk comprehensively.

## 2. Methods

### 2.1. Search strategy

This study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant literature was extracted through systematic retrieval of the PubMed, Embase, and Cochrane Library databases up to date to October 2, 2021. The search strategy included the following terms: ("colorectal cancer" or "CRC" or "colorectal tumor" or "colorectal carcinoma" or "colon cancer" or "rectal cancer") and ("1,25 $(OH)_2D_3$ receptor" or "receptor, vitamin D" or "vitamin D

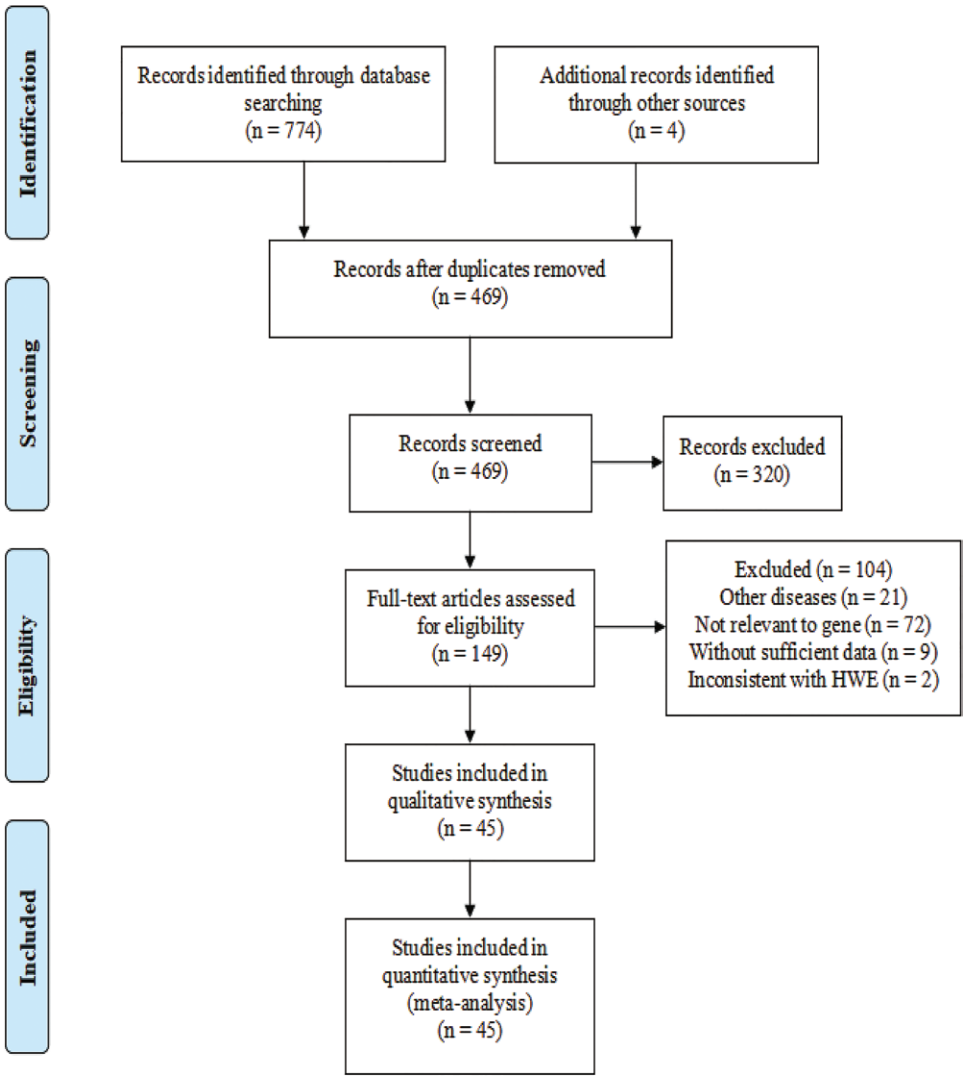


**Figure 1.** Flow chart of search strategy and study selection.

receptor" or "VDR"). In addition, the cited references in the selected articles were searched to identify potentially eligible studies. The above process was independently performed by 2 reviewers.

### 2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: case–control studies were designed to investigate the association between VDR gene polymorphisms and CRC. Sufficient data were available to calculate the odds ratio (OR) and 95% confidence interval (CI), and the study did not deviate from the Hardy–Weinberg equilibrium (HWE).

The exclusion criteria were as follows: insufficient data information was provided, such as reviews, case reports, meta-analyses, letters, conference abstracts, and conference papers; duplicate literature; studies that were not relevant to the gene; and in vitro experiments or animal studies.

### 2.3. Data extraction and quality assessment

Two participants (Yang and Ji) independently conducted the literature screening, data extraction, and quality assessment, and any differences were resolved through discussion. Information extracted from the included literature included the first author, year of publication, country of population, ethnicity, source of control, genotyping method, sample size, VDR gene subtypes, and Newcastle–Ottawa scale (NOS) score.

The NOS tool was applied to evaluate the quality of the included papers, which consisted of 3 parts: selection (4 items, 0–4 stars), comparability of queues (1 item, 0–2 stars), and evaluation of results ascertaining exposure or outcome (3 items, 0–3 stars).[24] The scores of at least 6 were considered high-quality literature.

### 2.4. Statistical analysis

Meta-analysis was performed using the Stata16.0 software (StataCorp, College Station, TX). The strength of the associations

**Table 1**

**Characteristics of the included studies in our meta-analysis.**

| Author | Year | Ethnicity | Sample size case/control | Genotyping methods | Source of control | NOS | VDR polymorphisms |
|---|---|---|---|---|---|---|---|
| Ingles[27] | 2001 | Mixed | 373/394 | PCR-RFLP | PB | 8 | FokI, BsmI |
| Peters[28] | 2001 | Caucasian | 208/184 | PCR-RFLP | HB | 7 | FokI |
| Slattery[29] | 2001 | Caucasian | 424/366 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI |
| Kim[30] | 2001 | Caucasian | 393/406 | Taqman | HB | 7 | BsmI |
| Speer[31] | 2001 | Caucasian | 56/112 | PCR-RFLP | HB | 6 | BsmI |
| Wong[32] | 2003 | Asian | 217/890 | PCR-RFLP | PB | 8 | FokI |
| Boyapati[33] | 2003 | Caucasian | 177/228 | PCR-RFLP | HB | 7 | BsmI |
| Slattery[34] | 2004 | Caucasian | 1936/2130 | PCR-RFLP | PB | 8 | FokI, BsmI |
| Peters[35] | 2004 | Caucasian | 763/774 | PCR-RFLP | PB | 7 | TaqI |
| Gong[36] | 2005 | Asian | 171/220 | PCR-RFLP | HB | 7 | Tru9I |
| Murtaugh[37] | 2006 | Mixed | 1820/2821 | PCR-RFLP | PB | 9 | FokI |
| Park[19] | 2006 | Asian | 190/318 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, ApaI |
| Kadiyska[38] | 2006 | Caucasian | 140/94 | PCR-RFLP | HB | 7 | BsmI |
| Flügge[20] | 2007 | Caucasian | 256/256 | PCR-RFLP | HB | 7 | Cdx-2, Tru9I, FokI, BsmI, TaqI, ApaI |
| Yaylim[39] | 2007 | Caucasian | 26/52 | PCR-RFLP | HB | 6 | FokI, TaqI |
| Slattery[40] | 2007 | Caucasian | 2380/2990 | Taqman | PB | 8 | FokI, BsmI |
| Grünhage[41] | 2008 | Caucasian | 194/220 | PCR-RFLP | HB | 7 | FokI |
| Balcom[42] | 2008 | Caucasian | 250/246 | Taqman | PB | 8 | Cdx-2, FokI, TaqI |
| Parasi[43] | 2008 | Caucasian | 50/32 | PCR-RFLP | HB | 6 | BsmI |
| Theodoratou[44] | 2008 | Caucasian | 3005/3072 | PCR-RFLP | PB | 9 | Cdx-2, FokI, BsmI, ApaI |
| Wang[45] | 2008 | Asian | 60/218 | PCR-RFLP | HB | 6 | FokI |
| Jenab[46] | 2009 | Caucasian | 1248/1248 | Taqman | PB | 8 | FokI, BsmI |
| Mahmoudi[47] | 2010 | Caucasian | 160/180 | PCR-RFLP | PB | 8 | ApaI, TaqI |
| Hughes[48] | 2011 | Caucasian | 754/627 | Taqman | HB | 7 | Cdx-2, BsmI, ApaI, TaqI |
| Mahmoudi[49] | 2011 | Caucasian | 452/452 | PCR-RFLP | PB | 8 | FokI, BsmI |
| Bentley[50] | 2012 | Caucasian | 200/200 | Taqman | HB | 6 | Cdx-2, FokI, TaqI |
| Gündüz[51] | 2012 | Caucasian | 43/42 | PCR-RFLP | HB | 6 | BsmI, TaqI |
| Yamaji[52] | 2012 | Asian | 684/641 | Taqman | PB | 8 | FokI, TaqI |
| Rasool[53] | 2013 | Asian | 312/305 | PCR-RFLP | HB | 7 | FokI |
| Atoum[54] | 2014 | Caucasian | 93/102 | PCR-RFLP | HB | 7 | TaqI |
| Mahmoudi[55] | 2014 | Caucasian | 303/354 | PCR-RFLP | PB | 8 | Cdx-2 |
| Laczmanska[56] | 2014 | Caucasian | 179/180 | PCR-RFLP | HB | 7 | FokI, BsmI, TaqI, AapI |
| Author | Year | Ethnicity | Sample size case/control | Genotyping methods | Source of control | NOS | VDR polymorphisms |
| Sarkissyan[57] | 2014 | Mixed | 78/230 | PCR-RFLP | HB | 7 | FokI, BsmI, TaqI, AapI |
| Takeshige[58] | 2015 | Asian | 685/778 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, AapI |
| Alkhayal[59] | 2016 | Caucasian | 100/100 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, AapI |
| Beckett[60] | 2016 | Caucasian | 57/201 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, AapI |
| Vidigal[61] | 2017 | Caucasian | 152/321 | PCR-RFLP | HB | 6 | BsmI, AapI |
| Ramadan[62] | 2017 | African | 145/130 | Taqman | HB | 6 | FokI, Cdx-2 |
| Moossavi[63] | 2018 | Caucasian | 100/100 | PCR-RFLP | PB | 7 | FokI, TaqI, |
| Al-Ghafari[64] | 2019 | Caucasian | 50/50 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, ApaI |
| Al-Ghafari[23] | 2020 | Caucasian | 132/124 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, ApaI |
| Sirinporn[65] | 2020 | Asian | 182/182 | PCR-RFLP | HB | 7 | Tru9I, FokI, BsmI, TaqI, ApaI |
| Latacz[66] | 2021 | Caucasian | 103/99 | PCR-RFLP | PB | 7 | FokI, BsmI, TaqI, ApaI |
| Zhang[67] | 2021 | Asian | 488/496 | PCR-RFLP | PB | 8 | FokI, BsmI, TaqI, ApaI |
| Rehman[68] | 2021 | Caucasian | 48/67 | ARMS-PCR | HB | 7 | Cdx-2 |

ARMS-PCR = Amplification refractory mutation system-polymerase chain reaction, CRC = colorectal cancer, VDR = vitamin D receptor, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

**Table 2**

**Results of meta-analysis in the VDR gene polymorphisms.**

| SNP | Model | OR (95% CI) | *P* | $I^2$ (%) | $P_{(H)}$ | Effect model |
|---|---|---|---|---|---|---|
| FokI | Allelic (f vs F) | 0.99 (0.94–1.05) | .815 | 58.2 | 0.000 | REM |
| | Homozygous (ff vs FF) | 0.99 (0.88–1.11) | .858 | 51.3 | 0.001 | REM |
| | Heterozygous (ff vs Ff) | 0.99 (0.92–1.06) | .760 | 37.5 | 0.023 | REM |
| | Dominant (ff/Ff vs FF) | 0.99 (0.92–1.06) | .806 | 50.9 | 0.001 | REM |
| | Recessive (ff vs FF/Ff) | 0.98 (0.89–1.07) | .604 | 39.5 | 0.016 | REM |
| BsmI | Allelic (B vs b) | 0.94 (0.90–0.99) | .013* | 29.9 | 0.108 | FEM |
| | Homozygous (BB vs bb) | 0.88 (0.79–0.97) | .010* | 26.9 | 0.135 | FEM |
| | Heterozygous (Bb vs bb) | 0.97 (0.90–1.04) | .351 | 0.0 | 0.702 | FEM |
| | Dominant (BB/Bb vs bb) | 0.94 (0.88–1.01) | .089 | 0.0 | 0.531 | FEM |
| | Recessive (BB vs bb/Bb) | 0.89 (0.81–0.98) | .014* | 34.8 | 0.068 | FEM |
| TaqI | Allelic (t vs T) | 1.04 (0.94–1.15) | .419 | 46.6 | 0.016 | REM |
| | Homozygous (tt vs TT) | 1.11 (0.89–1.37) | .360 | 39.9 | 0.046 | REM |
| | Heterozygous (Tt vs TT) | 1.00 (0.92–1.10) | .963 | 24.8 | 0.162 | FEM |
| | Dominant (tt/Tt vs TT) | 1.01 (0.93–1.10) | .779 | 37.3 | 0.056 | FEM |
| | Recessive (tt vs TT/Tt) | 1.06 (0.93–1.20) | .426 | 30.1 | 0.116 | FME |
| ApaI | Allelic (A vs a) | 0.94 (0.89–1.00) | .040* | 42.5 | 0.066 | FEM |
| | Homozygous (AA vs aa) | 0.89 (0.79–1.01) | .066 | 35.1 | 0.118 | FEM |
| | Heterozygous (Aa vs aa) | 1.05 (0.95–1.17) | .347 | 20.6 | 0.247 | FEM |
| | Dominant (AA/Aa vs aa) | 0.92 (0.84–1.01) | .074 | 22.9 | 0.226 | FEM |
| | Recessive (AA vs aa/Aa) | 0.93 (0.84–1.02) | .125 | 33.8 | 0.128 | RME |
| Cdx-2 | Allelic (C vs c) | 1.01 (0.87–1.17) | .894 | 63.7 | 0.007 | REM |
| | Homozygous (CC vs cc) | 1.15 (0.95–1.39) | .157 | 46.0 | 0.073 | FEM |
| | Heterozygous (Cc vs cc) | 1.05 (0.95–1.15) | .359 | 40.3 | 0.110 | FEM |
| | Dominant (CC/Cc vs cc) | 1.00 (0.85–1.18) | .963 | 55.3 | 0.028 | REM |
| | Recessive (CC vs cc/Cc) | 1.13 (0.94–1.26) | .207 | 40.6 | 0.108 | FME |
| Tru9I | Allelic (A vs G) | 0.88 (0.70–1.10) | .264 | 0.0 | 0.429 | FEM |
| | Homozygous (AA vs GG) | 1.33 (0.68–2.61) | .491 | 0.0 | 0.960 | FEM |
| | Heterozygous (GA vs GG) | 0.75 (0.57–0.99) | .041* | 0.0 | 0.490 | FEM |
| | Dominant (AA/GA vs GG) | 0.80 (0.62–1.04) | .092 | 0.0 | 0.508 | FEM |
| | Recessive (AA vs GG/GA) | 1.41 (0.72–2.74) | .315 | 0.0 | 0.962 | FME |

VDR = vitamin D receptor.

P: *P*-value of Z-test for statistical significance, $P_H$: *P*-value of Q-test for heterogeneity test.

between the VDR polymorphisms and CRC risk was appraised by the OR and relevant 95% CI under various genetic models. Statistical significance was set at $P < .05$. A heterogeneity test was conducted using the Q-statistic and $I^2$ statistics. Studies with $P < .05$ or $I^2 \geq 50\%$ were considered to have obvious heterogeneity, and the random-effects model (REM) should be applied for a merger. Otherwise, a fixed-effects model (FEM) was used in the absence of heterogeneity. Potential sources of heterogeneity were identified through subgroup analysis based on ethnicity and tumor site. Publication bias was assessed using the Begg rank correlation test and Egger linear regression test. If $P < .05$, there was an obvious publication bias.

## 3. Results

### 3.1. Literature search and screening

The flow diagram shows the detailed steps of the literature search (Fig. 1). The literature search identified 774 articles through the PubMed (n = 317), Embase (n = 425), and Cochrane Library (n = 32) databases, and 4 additional records were retrieved from other sources. After excluding 309 repeated studies, 320 additional publications were removed by screening titles and abstracts. Among these papers, 174 were reviews, letters, conference abstracts, meta-analyses, editorials, conference papers, short surveys, and notes and 146 were animal or in vitro studies. After full-text review, 104 articles were excluded for the following reasons: other diseases were studied (n = 21), studies were not pertinent to the gene (n = 72), and insufficient data (n = 9). In addition, 2 studies that did not comply with HWE were excluded from our study (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/MD/I268).[25,26] As listed in Table 1, 45 eligible studies were included in our meta-analysis to investigate potential associations between VDR gene polymorphisms and CRC risk. With regard to tumor location, we explored the correlations between the VDR FokI, BsmI, and ApaI polymorphisms and CRC risk.

### 3.2. Characteristics of the included studies

A total of 19,673 CRC cases and 24,029 healthy controls were included in this meta-analysis. Thirty-two studies on Caucasians, 10 studies on Asians and 1 study on Africans were conducted. However, 3 studies were related to multiple races. In addition, the sources of the 22 control groups were based on the hospital, and those of 23 control groups were based on the population. Regarding genotyping detection methods, 36 studies used the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Among the remaining studies, 8 focused on the TaqMan method and 1 on the polymerase chain reaction amplification refectory system (PCR-ARMS). Subgroup analyses were conducted based on ethnicity and anatomical sites of CRC. The NOS score of the eligible articles ranged from 6 to 9, indicating that all the included studies were of high quality. (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/MD/I269).

### 3.3. Relationship between VDR gene polymorphisms and CRC susceptibility

Apart from 2 studies[39,41] deviating from HWE, 29 eligible studies with 16,303 patients and 18,924 controls have investigated the association between FokI polymorphism and CRC risk.[19,20,23,27–29,32,34,37,40,42,44–46,49,50,52,53,56–60,62–67] The overall analyses of 5 genetic models did not have any significant correlation

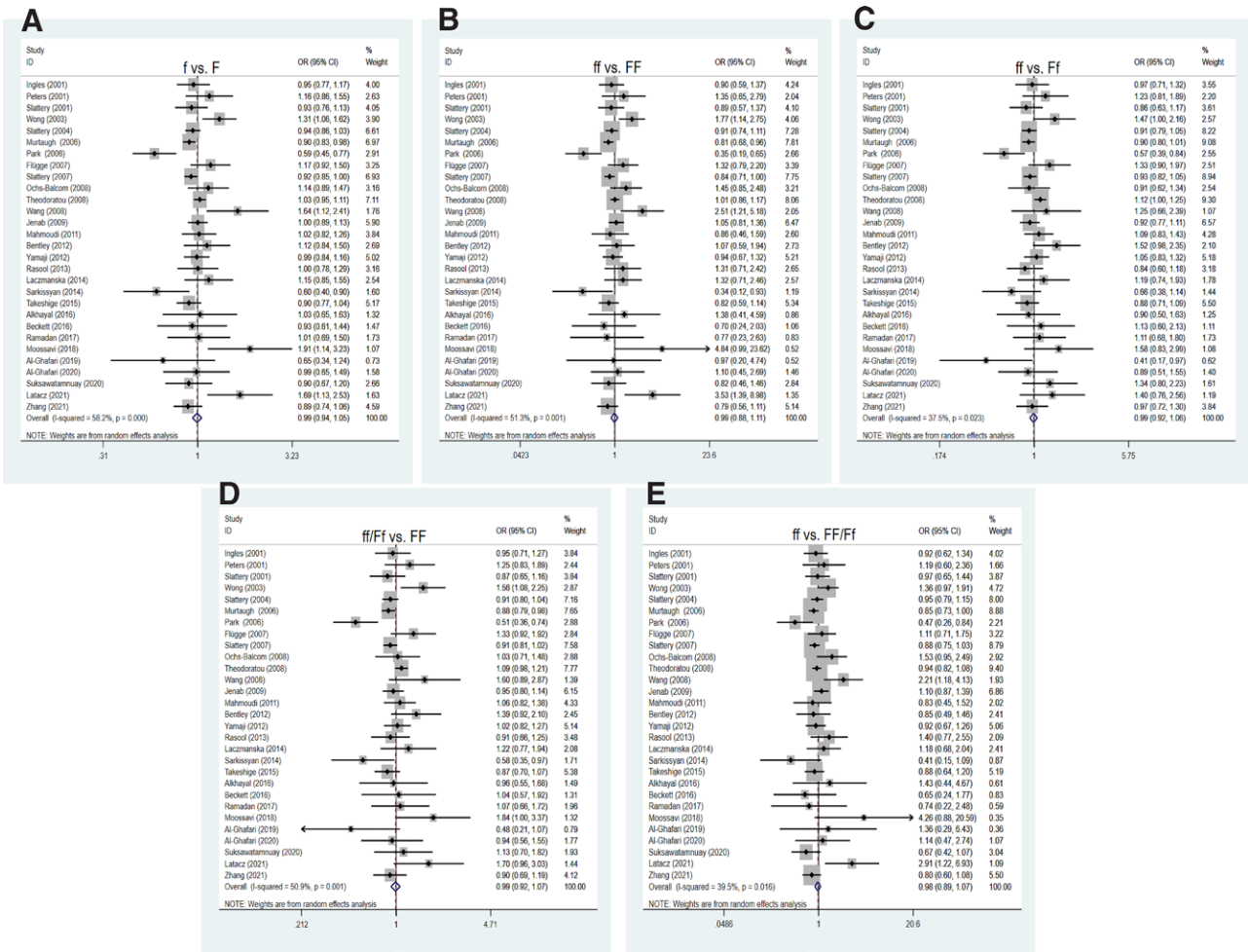


**Figure 2.** Association between VDR FokI gene polymorphism and CRC susceptibility in 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CRC = colorectal cancer, VDR = vitamin D receptor.

between the FokI gene polymorphism and CRC risk (f vs F: OR 0.99, 95%CI 0.94–1.05, *P* = .815; ff vs FF: OR 0.99, 95%CI 0.88–1.11, *P* = .858; Ff vs FF: OR 0.99, 95%CI 0.92–1.06, *P* = .760; ff/Ff vs FF: OR 0.99, 95%CI 0.92–1.06, *P* = .806; ff vs Ff/FF: OR 0.98, 95%CI 0.89–1.07, *P* = .604; Table 2, Fig. 2). As shown in Table 3, no association between FokI polymorphism and CRC risk was detected in the ethnicity subgroup analyses. Meanwhile, there was no heterogeneity in Caucasian studies (f vs F: OR 1.02, 95%CI 0.96–1.09, *P* = .477; ff vs FF: OR 1.02, 95%CI 0.91–1.15, *P* = .704; Ff vs FF: OR 1.02, 95%CI 0.94–1.11, *P* = .695; ff/Ff vs FF: OR 1.03, 95%CI 0.94–1.12, *P* = .23; ff vs Ff/FF: OR 1.00, 95%CI 0.91–1.10, *P* = .993). Through cancer site stratification analyses, the FokI polymorphism was remarkably linked to decreased colon cancer risk (Ff vs FF: OR 0.86, 95%CI 0.84–0.93, *P* = .000; ff/Ff vs FF: OR 0.88, 95%CI 0.79–0.98, *P* = .022; ff vs Ff/FF: OR 0.90, 95%CI 0.82–0.99, *P* = .033; Table 4). Heterogeneity results revealed that heterogeneity existed in the allelic, homozygote and dominant models of the overall group. Sensitivity analysis revealed that the pooled ORs of the FokI polymorphism were not materially altered by excluding studies individually. The Begg rank correlation test and Egger linear regression test were used to estimate potential publication bias, and no publication bias was found (Table 5).

Nineteen studies on BsmI polymorphism and CRC risk consisting 11,254 patients and 12,640 controls were qualified for inclusion criteria.[19,20,29–31,38,40,43,46–48,57,58,60,61,64–68] The pooled results indicated that BsmI polymorphism was notably associated with a lower CRC risk in the allele (B vs b: OR 0.94; 95%CI 0.90–0.99, *P* = .013), homozygote (BB vs bb: OR 0.88; 95%CI 0.79–0.96, *P* = .010) and recessive comparison (BB vs Bb/bb: OR 0.89; 95%CI 0.81–0.98, *P* = .014, Fig. 3, Table 2). When subgroup analysis was conducted according to ethnicity, a significantly decreased risk of CRC was found in the Caucasian population under the allele (B vs b: OR 0.94, 95%CI 0.90–0.99, *P* = .015), homozygous (BB vs bb: OR 0.88; 95%CI 0.79–0.97, *P* = .010) and recessive models (BB vs Bb/bb: OR 0.89; 95%CI 0.81–0.98, *P* = .016, Table 3), indicating that the BsmI site might serve as a crucial protective role among Caucasians. Interestingly, BsmI polymorphism in the allelic, homozygous, and recessive models (B vs b: OR 0.91, 95%CI 0.86–0.97, *P* = .004; BB vs bb: OR 0.80; 95%CI 0.71–0.91, *P* = .001; BB vs Bb/bb: OR 0.88; 95%CI 0.85–0.95, *P* = .005, Table 4) was significantly correlated with decreased colon cancer susceptibility. The pooled ORs and its 95%CI of BsmI polymorphism were not materially altered by dropping any individual study, indicating that our results are robust (Fig. 4). In addition, the results of the Begg test and Egger test revealed no obvious publication bias (Table 5, Fig. 5).

Eighteen eligible studies with 5093 cases and 5368 controls were included in this meta-analysis.[19,20,35,39,42,48,50–52,54,56,58–60,63,66–68] The pooled analysis showed no significant correlation between TaqI polymorphism and CRC risk (Table 2). In ethnicity subgroup analysis, no significant association was observed among the 5 genetic models (Fig. 6, Table 3). This suggests that the heterogeneity consisted of allelic and homozygous models of the overall and Caucasian subgroups. The sensitivity analysis results

**Table 3**

**The correlation between VDR gene polymorphisms and CRC risk under ethnicity stratification.**

| SNP | Model | Caucasian | | Asian | | African | |
|---|---|---|---|---|---|---|---|
| | | OR (95% CI) $P_a$ | $I^2$ | OR (95% CI) $P_a$ | $I^2$ | OR (95% CI) | $I^2$ |
| FokI | Allelic (f vs F) | 1.02 (0.96–1.09) 0.477 | 37.8 | 0.97 (0.83–1.14) 0.719 | 77.1 | 1.01 (0.69–1.50) 0.945 | _ |
| | Homozygous (ff vs FF) | 1.02 (0.91–1.15) 0.704 | 24.3 | 0.98 (0.71–1.36) 0.911 | 75.1 | 0.77 (0.23–2.63) 0.677 | _ |
| | Heterozygous (ff vs Ff) | 1.02 (0.94–1.11) 0.659 | 33.7 | 0.98 (0.82–1.17) 0.778 | 54.8 | 1.11 (0.68–1.80) 0.689 | _ |
| | Dominant (ff/Ff vs FF) | 1.03 (0.94–1.12) 0.523 | 38.3 | 0.97 (0.79–1.19) 0.789 | 68.9 | 1.07 (0.67–1.72) 0.781 | _ |
| | Recessive (ff vs FF/Ff) | 1.00 (0.91–1.10) 0.993 | 14.4 | 0.96 (0.74–1.24) 0.765 | 68.6 | 0.74 (0.22–2.48) 0.623 | _ |
| BsmI | Allelic (B vs b) | 0.94 (0.90–0.99) 0.015* | 41.7 | 0.94 (0.79–1.12) 0.487 | 3.5 | _ | _ |
| | Homozygous (BB vs bb) | 0.88 (0.79–0.97) 0.010* | 42.4 | 0.67 (0.31–1.44) 0.304 | 0.0 | _ | _ |
| | Heterozygous (Bb vs bb) | 0.97 (0.90–1.04) 0.369 | 0.0 | 0.98 (0.80–1.19) 0.803 | 0.0 | _ | _ |
| | Dominant (BB/Bb vs bb) | 0.94 (0.88–1.01) 0.098 | 7.4 | 0.96 (0.79–1.16) 0.635 | 0.0 | _ | _ |
| | Recessive (BB vs bb/Bb) | 0.89 (0.81–0.98) 0.016* | 49.1 | 0.67 (0.31–1.45) 0.314 | 0.0 | _ | _ |
| TaqI | Allelic (t vs T) | 1.07 (0.93–1.22) 0.336 | 59.5 | 0.99 (0.88–1.12) 1.921 | 0.0 | _ | _ |
| | Homozygous (tt vs TT) | 1.14 (0.89–1.47) 0.292 | 48.7 | 1.02 (0.66–1.55) 0.955 | 6.1 | _ | _ |
| | Heterozygous (Tt vs TT) | 1.07 (0.95–1.19) 0.260 | 30.5 | 0.96 (0.72–1.28) 0.758 | 14.6 | _ | _ |
| | Dominant (tt/Tt vs TT) | 1.03 (0.93–1.15) 0.593 | 51.4 | 0.98 (0.86–1.13) 0.815 | 0.0 | _ | _ |
| | Recessive (tt vs TT/Tt) | 1.06 (0.92–1.22) 0.460 | 38.2 | 1.06 (0.73–1.52) 0.767 | 13.7 | _ | _ |
| ApaI | Allelic (A vs a) | 0.93 (0.87–0.99) 0.029 | 24.0 | 0.98 (0.87–1.11) 0.761 | 66.1 | _ | _ |
| | Homozygous (AA vs aa) | 0.87 (0.76–0.99) 0.038 | 16.9 | 0.87 (0.76–0.99) 0.930 | 58.6 | _ | _ |
| ApaI | Heterozygous (Aa vs aa) | 1.09 (0.97–1.21) 0.143 | 14.6 | 0.96 (0.72–1.28) 0.758 | 54.9 | | |
| | Dominant (AA/Aa vs aa) | 0.90 (0.80–1.01) 0.062 | 0.0 | 0.96 (0.83–1.12) 0.629 | 56.3 | | |
| | Recessive (AA vs aa/Aa) | 0.91 (0.82–1.01) 0.087 | 32.8 | 1.03 (0.78–1.35) 0.654 | 46.2 | | |
| Cdx-2 | Allelic (C vs c) | 1.09 (1.01–1.17) 0.029* | 0.0 | _ | _ | 0.50 (0.33–0.75) 0.001* | _ |
| | Homozygous (CC vs cc) | 1.19 (0.98–1.45) 0.073 | 18.6 | _ | _ | 0.09 (0.01–0.77) 0.028* | _ |
| | Heterozygous (Cc vs cc) | 1.08 (0.98–1.19) 0.138 | 0.0 | _ | _ | 0.49 (0.30–0.81) 0.006* | _ |
| | Dominant (CC/Cc vs cc) | 1.10 (1.00–1.20) 0.055 | 0.0 | _ | _ | 0.45 (0.28–0.74) 0.001* | _ |
| | Recessive (CC vs cc/Cc) | 1.16 (0.96–1.40) 0.114 | 18.9 | _ | _ | 0.12 (0.02–1.01) 0.051 | _ |
| Tru9I | Allelic (A vs G) | 0.83 (0.55–1.24) 0.354 | _ | 0.90 (0.69–1.19) 0.469 | 21.9 | _ | _ |
| | Homozygous (AA vs GG) | 1.58 (0.37–6.70) 0.537 | _ | 1.27 (0.59–2.72) 0.534 | 0.0 | _ | _ |
| | Heterozygous (GA vs GG) | 0.71 (0.45–1.12) 0.141 | _ | 0.78 (0.56–1.09) 0.145 | 23.7 | _ | _ |
| | Dominant (AA/GA vs GG) | 0.76 (0.48–1.18) 0.216 | _ | 0.82 (0.60–1.14) 0.237 | 20.3 | _ | _ |
| | Recessive (AA vs GG/GA) | 1.68 (0.40–7.10) 0.481 | _ | 1.34 (0.63–2.84) 0.447 | 0.0 | _ | _ |

CRC = colorectal cancer, VDR = vitamin D receptor.

$P_a$: *P*-value in Caucasians population.

*$P < .05$. $P_b$: *P*-value in Asian population. $P < .05$. $P_c$: *P*-value in African population. $P < .05$.

**Table 4**

**Stratified analyses of 3 VDR gene polymorphisms by tumor site, including FokI, BsmI and AapI.**

| SNP | Tumor site | n | Allelic OR (95% CI) P | Homozygous OR (95% CI) P | Heterozygous OR (95% CI) P | Dominant OR (95% CI) P | Recessive OR (95% CI) P |
|---|---|---|---|---|---|---|---|
| FokI | CC | 11 | 0.93 (0.85–1.01) 0.095 | 0.89 (0.74–1.08) 0.241 | 0.86 (0.84–0.93) 0.000* | 0.88 (0.79–0.98) 0.022* | 0.90 (0.82–0.99) 0.033* |
| | RC | 7 | 1.03 (0.96–1.10) 0.447 | 1.04 (0.90–1.20) 0.604 | 1.04 (0.94–1.15) 0.411 | 1.04 (0.95–1.14) 0.397 | 1.02 (0.90–1.15) 0.760 |
| BsmI | CC | 6 | 0.91 (0.86–0.97) 0.004* | 0.80 (0.71–0.91) 0.001* | 0.80 (0.60–1.09) 0.154 | 0.75 (0.48–1.17) 0.206 | 0.85 (0.75–0.95) 0.005* |
| | RC | 6 | 0.93 (0.86–1.01) 0.072 | 0.87 (0.74–1.03) 0.105 | 0.84 (0.64–1.12) 0.231 | 0.76 (0.46–1.24) 0.284 | 0.94 (0.81–1.09) 0.409 |
| ApaI | CC | 5 | 1.14 (0.88–1.49) 0.328 | 1.10 (0.60–2.03) 0.750 | 0.85 (0.66–1.10) 0.214 | 1.01 (0.64–1.60) 0.953 | 1.14 (0.89–1.45) 0.301 |
| | RC | 3 | 0.98 (0.82–1.16) 0.787 | 1.00 (0.74–1.54) 0.997 | 0.74 (053–1.02) 0.068 | 0.86 (0.72–1.26) 0.435 | 1.20 (0.88–1.64) 0.243 |

CC = colon cancer, OR = odds ratios, VDR = vitamin D receptor, RC = rectal cancer.

*$P<0.05$.

demonstrated no substantial alterations when individual studies were sequentially eliminated in all genetic models, indicating the robustness of the pooled results. As shown in Table 5, no publication bias was confirmed by Begg test and Egger test.

Correlations between VDR ApaI, Cdx-2 and Tru9I polymorphisms and CRC risk were investigated in 11 studies with 4968 cases and 5489 controls,[19,20,44,47,48,58,60,61,66–68] 8 studies with 3929 cases and 3890 controls,[20,42,44,48,50,55,62,68] and 3 studies with 609 cases and 658 controls,[20,36,65] respectively. The ApaI gene polymorphism was associated with decreased CRC risk in allelic model (A vs a: OR 0.94, 95%CI 0.89–1.00, *P* = .040, Fig. 7, Table 2). After the analysis, it was found that the Tru9I polymorphism and reduced CRC risk were significantly associated (AA vs GA: OR 0.75, 95%CI 0.57–0.99, *P* = .041, Fig. 8, Table 2). Subsequently, we found a significant correlation between Cdx-2 polymorphism and decreased CRC risk in African population (C vs c: OR 0.50, 95%CI 0.33–0.75, *P* = .001; CC vs cc: OR 0.09, 95%CI 0.01–0.77, *P* = .028; Cc vs cc: OR 0.49, 95%CI 0.30–0.81, *P* = .006; CC/Cc vs cc: OR 0.45, 95%CI 0.28–0.74, *P* = .001, Fig. 9, Table 3). As for the Cdx-2 polymorphism, heterogeneity was showed to exist in allelic and dominant models of overall group. No substantial alterations were found when sequentially excluding any of the studies on these 3 polymorphisms. Additionally, visual inspection of funnel plots showed a symmetrical distribution, and Egger tests demonstrated no publication bias (Table 5).

**Table 5**

**Publication bias of the 5 genetic models for various VDR polymorphisms.**

| SNP | Allelic | | Homozygous | | Heterozygous | | Dominant | | Recessive | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $P_B$ | $P_E$ | $P_B$ | $P_E$ | $P_B$ | $P_E$ | $P_B$ | $P_E$ | $P_B$ | $P_E$ |
| FokI | 0.302 | 0.207 | 0.399 | 0.241 | 0.183 | 0.188 | 0.183 | 0.188 | 0.399 | 0.281 |
| BsmI | 0.373 | 0.945 | 0.631 | 0.625 | 0.537 | 0.825 | 0.631 | 0.832 | 0.537 | 0.581 |
| TaqI | 0.449 | 0.174 | 0.434 | 0.308 | 0.198 | 0.156 | 0.225 | 0.151 | 0.266 | 0.297 |
| ApaI | 0.640 | 0.582 | 0.436 | 0.560 | 0.436 | 0.574 | 1.000 | 0.634 | 0.436 | 0.572 |
| Cdx-2 | 0.174 | 0.206 | 0.266 | 0.231 | 0.174 | 0.224 | 0.174 | 0.218 | 0.266 | 0.242 |
| Tru9I | 0.296 | 0.067 | 1.000 | 0.227 | 0.296 | 0.273 | 0.296 | 0.250 | 1.000 | 0.225 |

VDR = vitamin D receptor.

$P_B$: *P*-value of Begg rank correlation test.

*$P < .05$. $P_E$: *P*-value of Egger linear regression test.

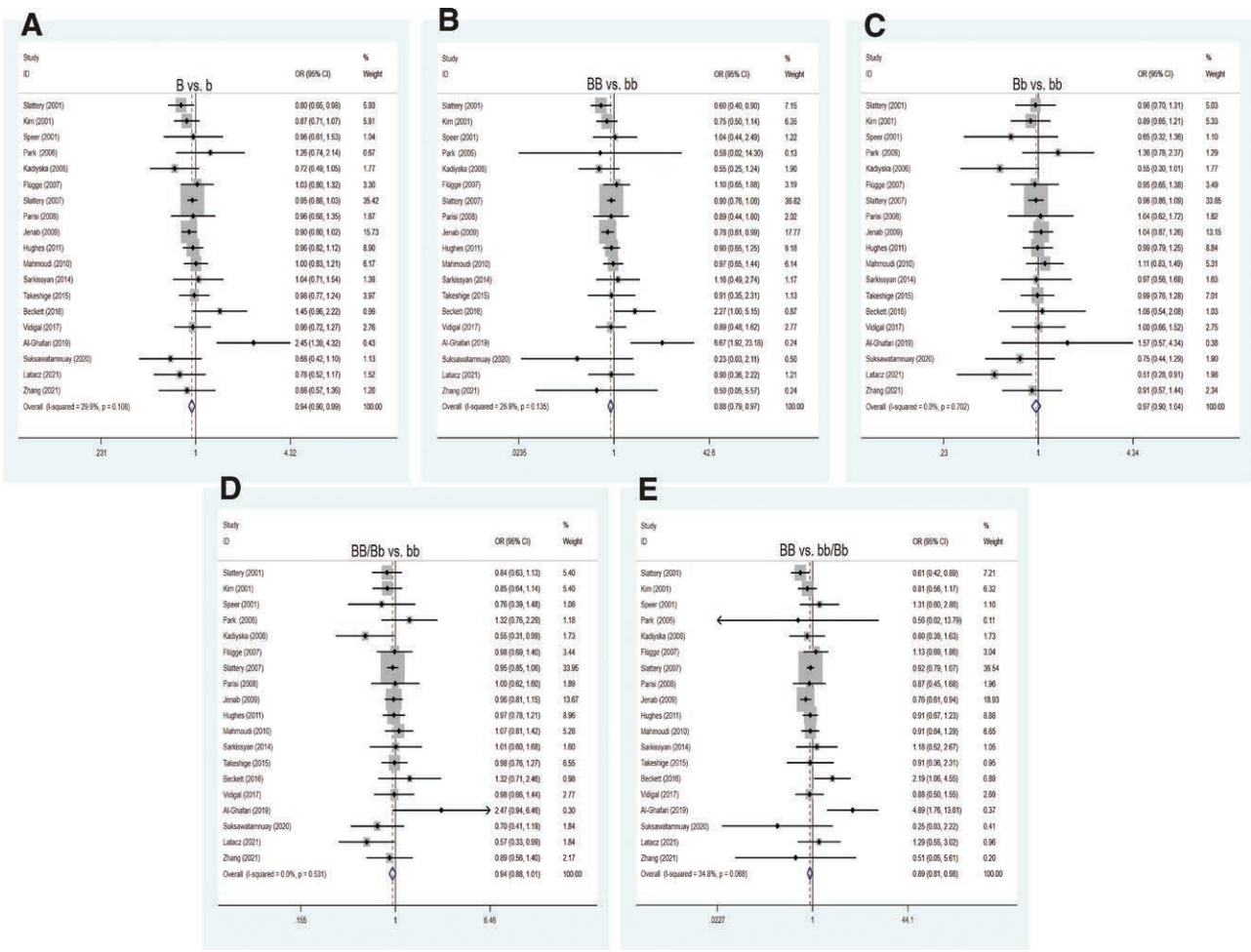


**Figure 3.** Association between VDR BsmI gene polymorphism and CRC susceptibility in 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CRC = colorectal cancer, VDR = vitamin D receptor.

## 4. Discussion

It has been reported that vitamin D plays an important role in cancer prevention, and can influence on cellular differentiation proliferation, differentiation, apoptosis, DNA repair mechanisms and immune function.[69] The Vitamin D is a nuclear receptor that modulates gene expression, acting specific biological functions by binding to VDR.[70] Several vitro studies have shown that the VDR ligand ($1,25\ (OH)_2D_3$) inhibits proliferation and maintain the differentiation of colon carcinoma cell.[71] The VDR gene is markedly downregulated in the CRC progression, suggesting that the VDR expression is negatively correlated with the CRC progression. It has been proposed that high VDR expression could be a good prognostic marker for CRC.[72] In our meta-analysis, 9 studies on BsmI polymorphism, 2 studies on FokI polymorphism,[39,41] 5 studies on TaqI polymorphism,[23,29,37,47,64] and 5 studies on ApaI polymorphism[46,47,49,54,55] were deviated from HWE, respectively. A total of 47 reports predicted a possible genetic association, and 45 of which were used to comprehensively estimate the relationship between VDR polymorphisms (FokI, BsmI, TaqI, ApaI, Cdx-2, and Tru9I) and CRC risk.

No association was found between FokI polymorphism and CRC risk in the 5 gene models. As shown in Table 2, BsmI polymorphism was significantly correlated with CRC risk in

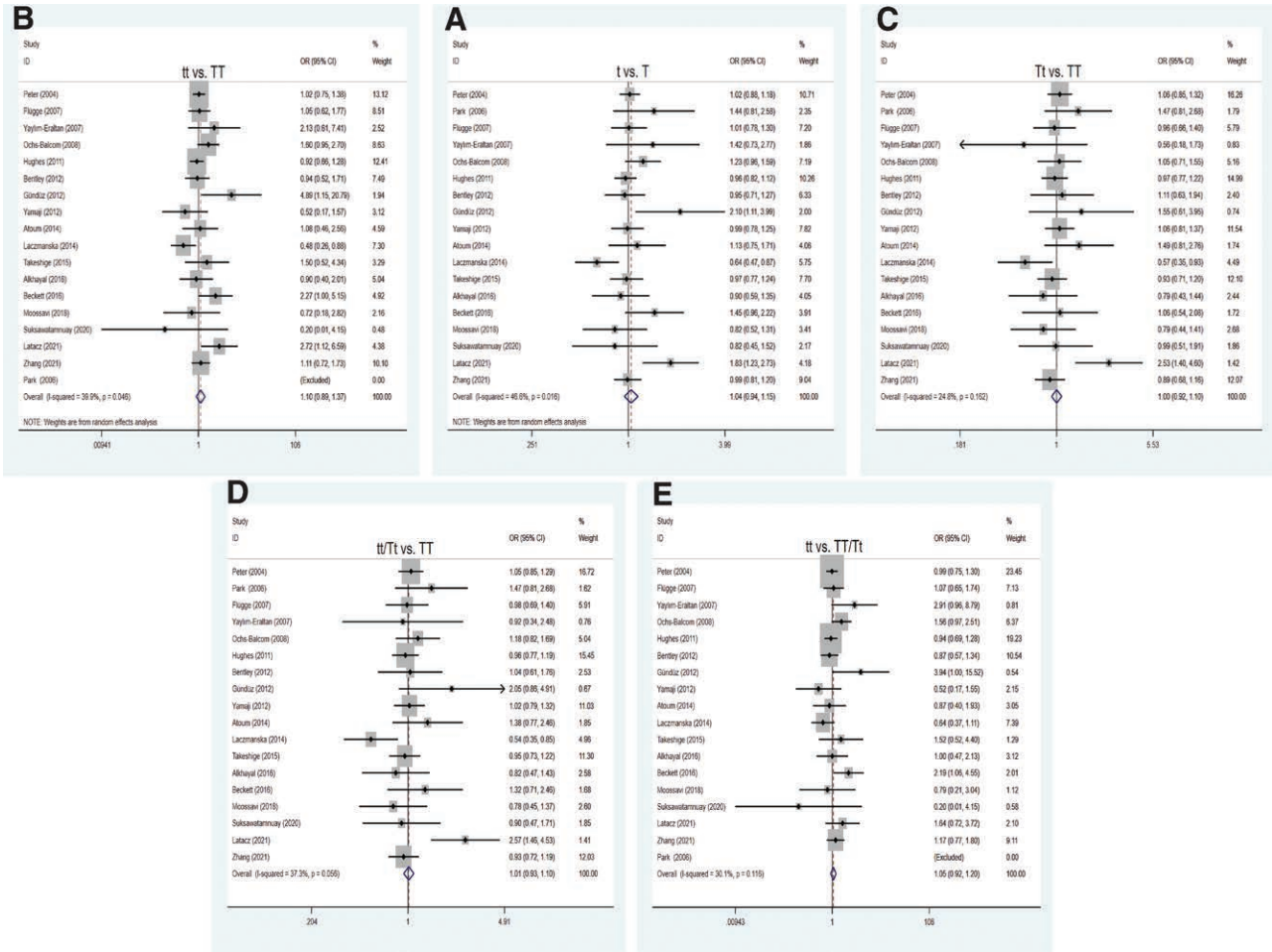


**Figure 4.** Sensitivity analysis via deletion of each individual study reflects the relative influence of each individual dataset on the pooled ORs of VDR BsmI polymorphism in recessive model. CRC = colorectal cancer, OR = odds ratio.

the allelic, homozygous, and recessive models. There were differences between the results of our meta-analysis and those of previous meta-analyses.[73] On the other hand, the VDR BsmI allele and genotype were associated with a lower risk of CRC among Caucasians, but no statistically significant correlation was observed among Asians, suggesting that the BsmI B-allele carriers conferred a protective factor in the Caucasian population.[46] When stratified by anatomic location, slightly inverse associations were found with colon cancer, but not rectal cancer. Accumulating evidence has demonstrated that the protective effect against colon cancer may be primarily mediated by the BsmI B allele.[50] We failed to discover any significant correlations between the TaqI polymorphism and CRC risk in the overall analysis and ethnicity subgroup analyses. Interestingly, the analysis revealed that the allelic model of the ApaI polymorphism was associated with a decreased risk of CRC. Tru9I polymorphism in the heterozygous model was significantly correlated with a lower risk of CRC. Simultaneously, we found a significant association between the Cdx-2 polymorphism and decreased CRC risk among Africans, indicating that Cdx-2 carriers might have a protective effect.

The BsmI site is located on the 3′-UTR of VDR gene, and this region participated in the regulation of gene expression and mRNA stability.[74] It has been reported that VDR BsmI polymorphism had no impact on intestinal VDR protein abundance and mRNA levels, and ligand binding affinity in intronic sequences.[75] It is possible that the BsmI polymorphism influences VDR function via different mechanisms. For example, mutations in other undetected VDR genes, such as CYP24A1 and CYP27B1, could affect VDR BsmI function.[61] In fact, the BsmI site exhibited strong linkage disequilibrium with other VDR polymorphisms, and a combination of more than 2 sites further promoted the transcription activities of VDR proteins.[65] The BsmI variant was observed to be significantly correlated with high expression of erbB-2, showing that expression of other oncogenes may have superimposed effects with BsmI polymorphism in the development and progression of CRC.[76]

The results of the present meta-analysis should be considered with caution owing to some inherent limitations. First, the sample sizes of the TaqI, ApaI, Cdx-2, and Tru9I studies were relatively small, resulting in sufficient statistics for the meta-analysis. Second, there were 32 studies on Caucasians, 10 studies on Asians, and only 1 study on Africans were included in our meta-analysis; thus, the conclusion can be promoted and suitable for other ethnicities. Finally, some gene-environment interactions, such as sun exposure, food consumption, vitamin D supplement intake, and VDR level, were not considered.

In conclusion, this meta-analysis revealed a significant correlation between the VDR BsmI polymorphism and CRC risk, which may be useful for the prognostic assessment of CRC. Additionally, the Cdx-2 polymorphism is significantly associated with the risk of CRC in Africans. Of the included studies, only 1 focused on an African population. Therefore, large-scale studies in different ethnic groups are needed to clarify the exact role of VDR mutations in CRC susceptibility.

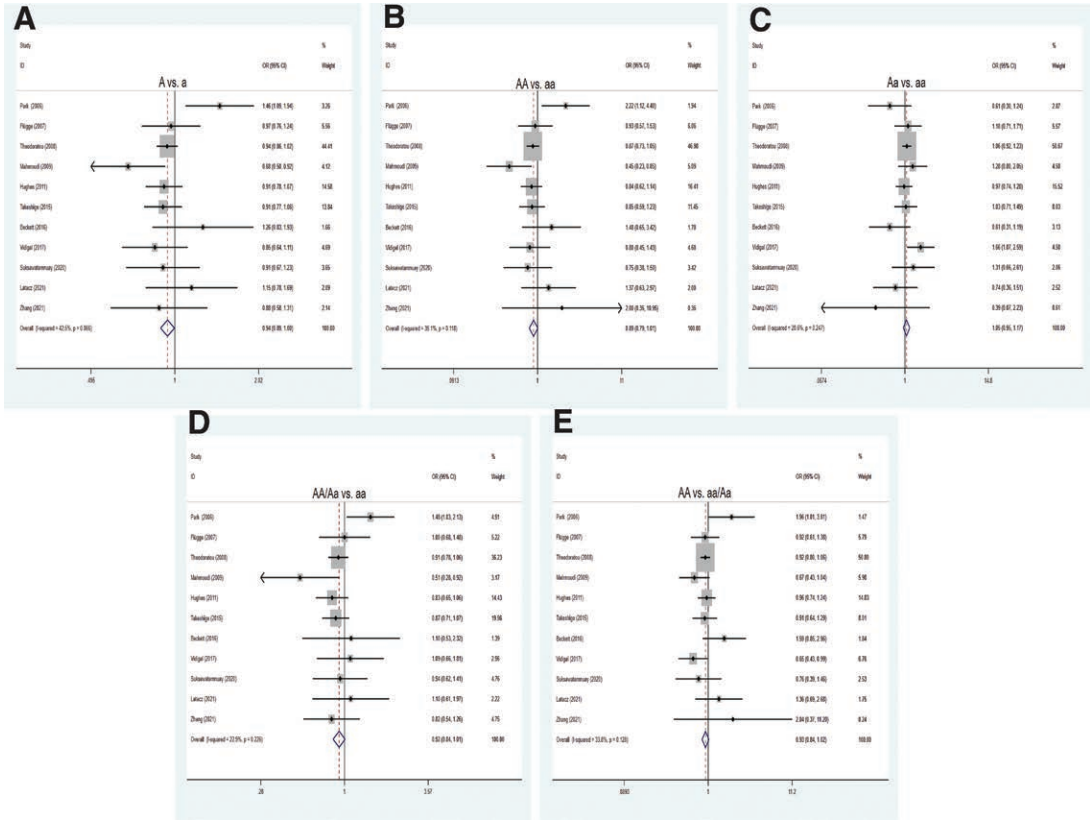


**Figure 5.** Begg funnel plot and Egger linear regression plot for detecting the publication bias through the recessive model. (a) Begg funnel plot for VDR BsmI polymorphism; (b) Egger linear regression plot for VDR BsmI polymorphism. , VDR = vitamin D receptor.

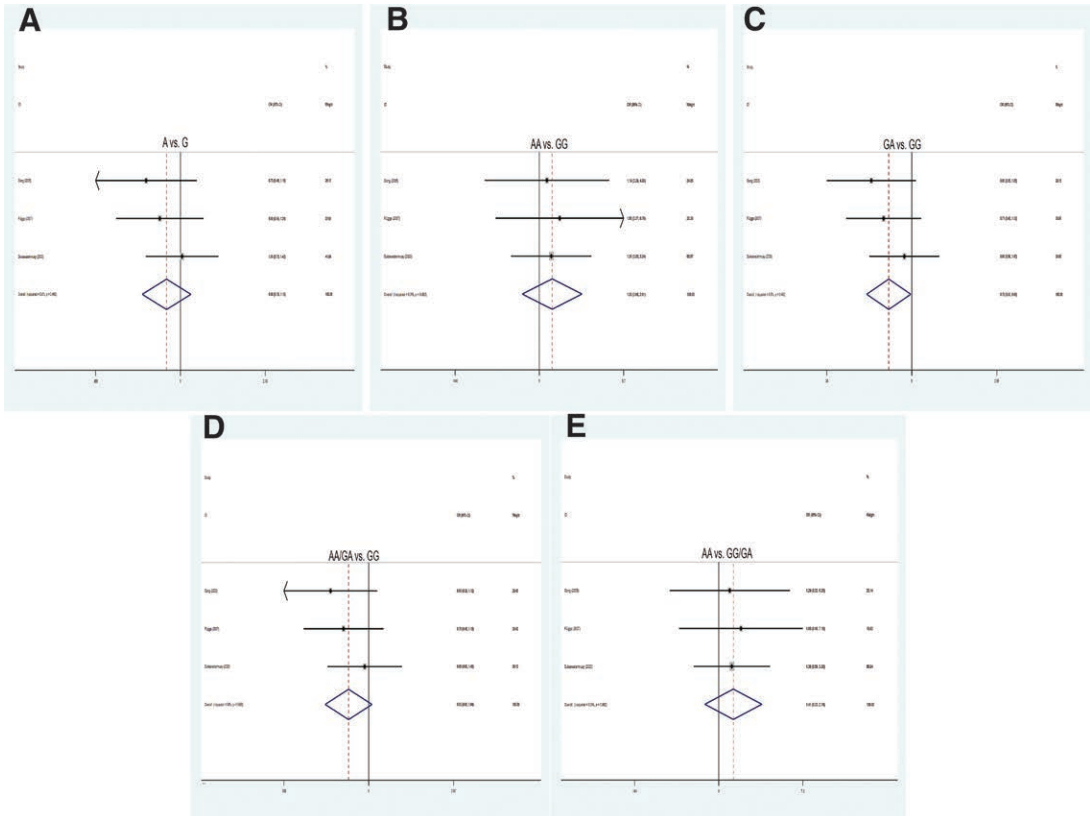


**Figure 6.** Association between VDR TaqI gene polymorphism and CRC susceptibility in 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CRC = colorectal cancer, VDR = vitamin D receptor.

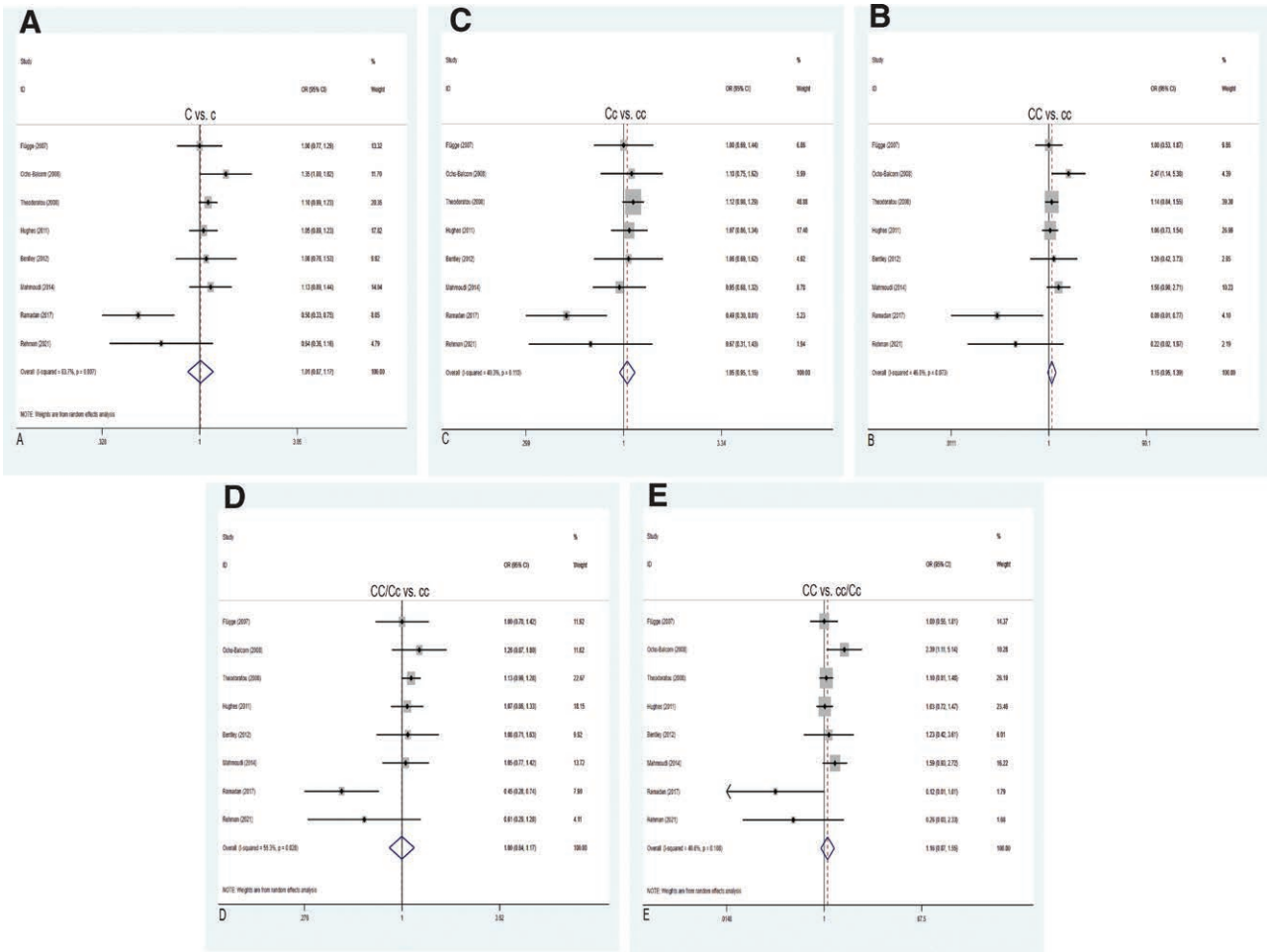


**Figure 7.** Association between VDR ApaI gene polymorphism and CRC susceptibility in 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CRC = colorectal cancer, VDR = vitamin D receptor.

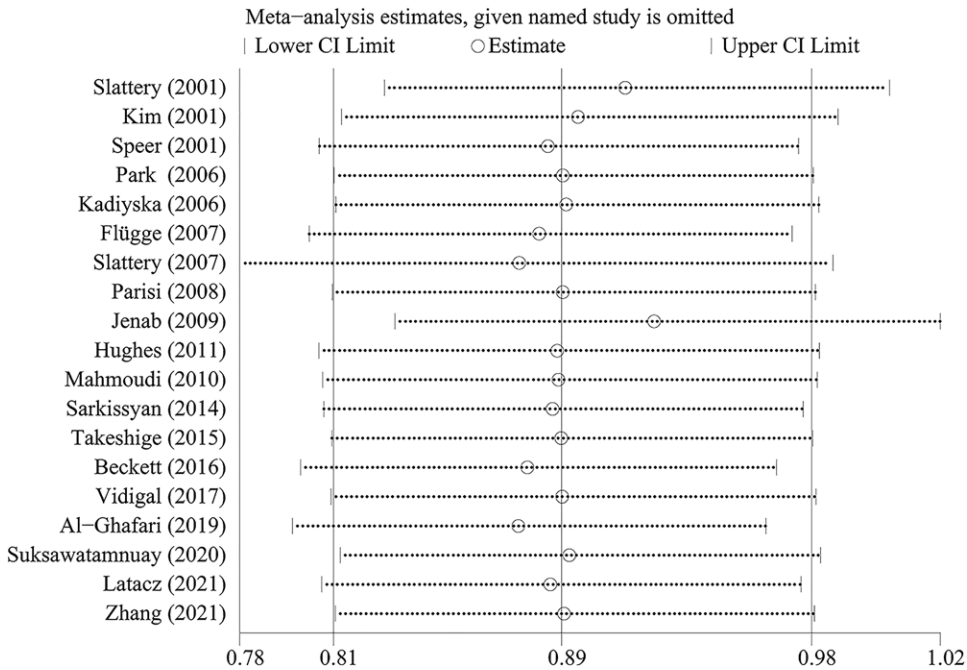


**Figure 8.** Forest plots for the association between VDR Cdx-2 gene polymorphism and CRC susceptibility in 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CRC = colorectal cancer, VDR = vitamin D receptor.

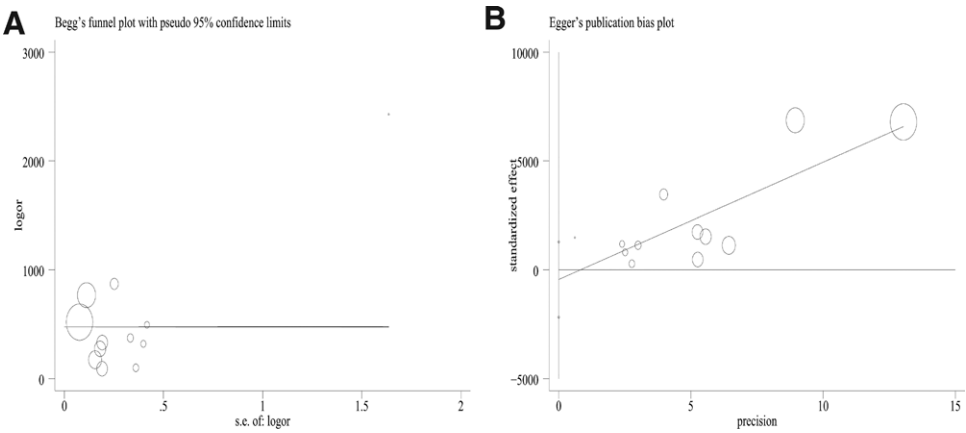


**Figure 9.** Forest plots for the association between VDR Tru9I gene polymorphism and CRC susceptibility in 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CRC = colorectal cancer, VDR = vitamin D receptor.

## Authors contributions

Maoquan Yang made substantial contributions to the conception and design of the work; Maoquan Yang, Li Zhang, and Wansheng Ji searched, selected materials, and extracted data; Maoquan Yang wrote this manuscript; Ning Xu, Chuanju Zong, Jinhua Gu, and Xiaojing Guo revised the paper carefully and contributed to the statistical analyses. All authors have read and approved the final manuscript.

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