Correlation between polymorphism of vitamin D receptor Taq1 and susceptibility to colorectal cancer

A meta-analysis

Shihou Sheng, MD, Yahong Chen, MM, Zhen Shen, MD∗

Abstract

The meta-analysis aimed to investigate the correlation between the polymorphism of the vitamin D receptor (VDR) Taq1 and susceptibility of colorectal cancer.

Studies were extracted from the electronic databases of PubMed and Embase. The balance of heredity was estimated by the Hardy–Weinberg equilibrium test, and heterogeneity was assessed by Cochran Q statistics and 2 test. Four assessed models, namely additive (T vs T), dominant (TT + T vs TT), recessive (TT vs T + TT), and codominant (TT vs TT and T vs TT), were used to evaluate the correlations and the effective results were measured as odds ratio (OR) with 95% confidence interval (CI).

A total of 14 studies, including 4632 patients and 5086 controls, were enrolled in this meta-analysis. With no significant heterogeneities observed among the 4 models, the fixed-effect model was used to examine the pooled effect value. There were no significant differences among T vs T (OR = 1.01; 95% CI, 0.94–1.09; P = .70), T + T vs TT (OR = 1.05; 95% CI, 0.98–1.16; P = .32), TT vs T + TT (OR = 1.01; 95% CI, 0.87–1.17; P = .92), T vs TT (OR = 1.03; 95% CI, 0.93–1.13; P = .82), and TT vs TT (OR = 1.00; 95% CI, 0.85–1.17; P = .98) with respect to increasing CRC frequency.

No evidence showed that Taq1 polymorphisms were significantly associated with susceptibility to CRC.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, OR = odds ratio, VDR = vitamin D receptor.

Keywords: colorectal cancer, meta-analysis, Taq1, vitamin D receptor

1. Introduction

Colorectal cancer (CRC) is the third most common cause of cancer-related mortality worldwide in both men and women.[1,2] It was estimated that there would be 95,270 new cases and 49,190 deaths in 2016.[3] Although the incidence of and death rate from CRC increased in China.[4] Family-based researches have the popularization of a westernized lifestyle, CRC prevalence owing to CRC decreased by 3% from 2003 to 2012 because of 19 May 2017 Received: 20 January 2017 / Received in final form: 18 May 2017 / Accepted: 19 May 2017

Meta-Analysis of Observational Studies in Epidemiology

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1. Introduction

Colorectal cancer (CRC) is the third most common cause of cancer-related mortality worldwide in both men and women.[1,2] It was estimated that there would be 95,270 new cases and 49,190 deaths in 2016.[3] Although the incidence of and death rate from CRC increased in China,[4] the popularization of a westernized lifestyle, CRC prevalence continues to increase in China.[4] Family-based researches have identified multiple deleterious germline mutations, such as MLH1, MSH2, MSH6, BMPR1A, SMAD4, POLE, NTHL1, MUTYH, POLD1, and adenomatous polyposis coil (APC), that increase susceptibility to CRC.[5–8] Although gene mutations account for <5% of all CRCs, it is accepted that combinations of these low-risk genes contribute to an increased risk for CRC.[9] Vitamin D is a fat-soluble steroid hormone, which is obtained from the diet and is synthesized in the skin after exposure to ultraviolet light.[10] During the synthesis process, vitamin D is converted to active 1,25 dihydroxyvitamin D [1,25(OH)2D], which is involved in the administration of cell cycle and has been implicated in CRC development.[11,12] The vitamin D receptor, encoded by VDR, is involved in the first step of 1,25(OH)2D signal transduction.[11] Several studies have reported that VDR polymorphisms, including Taq1, Bsm1, and Tru91, are associated with the susceptibility of CRC.[13] Many studies have focused on the association between Taq1 polymorphisms and CRC with conflicting results.[14,15]; thus, the involvement of vitamin D in CRC pathogenesis remains unclear.[12,16]

To our knowledge, although several meta-analyses have been performed to clarify the association between VDR polymorphisms and CRC, only the Bsm1 polymorphism has been clearly confirmed as a risk factor for CRC; the role of Taq1 remains unclear.[17] Although Serrano et al[18] have reported that Taq1 is associated with a significantly increased risk for CRC, Touvier et al[19] demonstrated no significant associations between Taq1 and CRC, consistent with the findings of Xu et al.[17] Therefore, to further investigate the correlation, in this meta-analysis, the associations between Taq1 polymorphisms and CRC were assessed with updated publications to provide new insights regarding the CRC mechanism.
2. Materials and methods

2.1. Search strategy

The electronic databases of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (http://www.embase.com) were searched for English-language publications about the vitamin D receptor TaqI and CRC for all records listed up to December 18, 2016. Key search terms used were as follows: "genetic" (OR "polymorphism" OR "variant") AND "colorectal cancer" (OR "colorectal neoplasm") AND "vitamin D receptor" (OR "VDR"). The references of retrieved articles were also manually searched for further references.

2.2. Inclusion and exclusion criteria

Articles included in this meta-analysis had to meet the following criteria: research designed as a case-control study, the research subjects were humans, patients in case group had CRC, research focused on the correlation between TaqI and susceptibility to CRC, and gene numbers were provided or could be computed. Articles were excluded if they met any of the following criteria: publications were reviews, comments, or letters; studies included only were family members or relatives; allele frequencies were not according to Hardy-Weinberg equilibrium (HWE); and studies focused on the correlation between TaqI polymorphism and CRC occurrence.

2.3. Data extracted and quality evaluation

Two authors independently screened the literatures based on the inclusion and exclusion criteria. When the selected studies were confirmed, the data were extracted and summarized in tables, including data regarding the first author, publication year, geographical region where the study was conducted, age and sex of subjects, sample size of both case and control groups, source of control groups, and data of gene types. After extraction, the authors exchanged the tables, and disagreements were resolved by discussion. The quality of the included papers was estimated by the standard provided by Clark and Baudouin.[20] For this measurement, 10 terms were included, and each with a score of 1. A final score of ≥6 was considered to indicate high quality, with lower scores indicating low quality.[21]

2.4. Statistical analysis

The HWE test for each study was performed using Stata version 11.0 software (Stata Corporation, College Station, TX), and \( P < .05 \) was considered to indicate significant disequilibrium. The codominant (\( TT \) vs \( TT, \) \( TT \) vs \( TT \)), dominant (\( TT + TT \) vs \( TT \)), recessive (\( TT + TT \) vs \( TT \)), and additive (\( T \) vs \( T \)) were compared. Odds ratio (OR) and 95% confidence interval (CI) calculated. A heterogeneity test of the studies was conducted using Cochran Q statistics and \( I^2 \) tests.[22] When the \( Q \) statistic indicated a \( P < .05 \) and/or \( I^2 > 50\% \), significant heterogeneity was considered to be presented, and the statistics were merged with a random-effect model; otherwise, the fixed-effect model was utilized. Sensitivity was assessed by the leave one-out method. OR with 95% CI and \( P \) values were used to report the effect size. OR values were calculated using RevMan 5.3 software.

3. Results

3.1. Literature retrieval

Using the search items, we identified 127 articles in PubMed and 377 papers in Embase. Of the 504 articles, 444 were excluded as duplicates or not relevant. Of the remaining 60 articles, 43 studies were rejected, including 9 reviews, 3 not case-control studies, 15 not relevant to TaqI, 9 without gene frequency, and 7 on CRC incidence. The complete text of the remaining 17 articles was reviewed, and 3 articles were ruled out because of significant disequilibrium identified by the HWE test. Therefore, 14 articles were enrolled in this meta-analysis (Fig. 1).[23–36]

3.2. Characteristics of included studies

In this meta-analysis, 9718 subjects from 14 studies were reviewed, including 4632 subjects in case groups and 5086 in control groups (Table 1). Among the included studies, 4 were
| Study | Study design | Geographic area | Ethnicity | Disease | Subjects, n | Control type | Subjects, n | Genotyping method | M/F | Test for HWE |
|-------|--------------|-----------------|-----------|---------|-------------|--------------|-------------|------------------|-----|--------------|
| Alkhayal (2016) | CCS | Saudi | Caucasians | CRC | 100/100 | Healthy | 57.5 (20–80)/57.5 (21–81) | PCR-Sanger | 64/46 | 64/36 | 1.335 | .248 |
| Atoum (2014) | CCS | Jordan | Caucasians | CRC | 93/102 | Healthy | 69.5±0.4 | PCR-RFLP | 47/46 | 52/50 | 0.112 | .738 |
| Bentley (2012) | CCS | New Zealand | Caucasians | CRC | 200/200 | Healthy | 56.7±7.3/61.6±7.2 | TagMan | 106/94 | 106/94 | 0.96 | 0.56 |
| Budhathoki (2016) | Nested-CCS | Japan | Asia | CRC | 396/709 | Subjects with no CRC history | 61.9±10.6/63.2±11.2 | PCR-RFLP | 124/130 | 125/131 | 0.358 | .549 |
| Rogge (2007) | CCS | Russia | Caucasians | CRC | 250/256 | Patients without malignant disease | 54.8±48.8 | PCR-RFLP | 27/16 | 26/16 | 0.013 | .908 |
| Gunduz (2012) | CCS | Turkey | Caucasian | CC | 43/42 | Healthy | 61 (27–85)/53 (29–91) | Allele-specific PCR | 0.702 | 0.0421 |
| Hughes (2011) | CCS | Czech | Caucasian | CRC | 754/627 | Patients without malignant disease | 54.8±0.8 | PCR-SNAPshot | 106/73 | 106/73 | 1.733 | .1855 |
| Laczmanska 2014 | CCS | Poland | Caucasians | CRC | 179/180 | Healthy | 65.7±11.2 | PCR-SNAPshot | 120/130 | 81/165 | 0 | 0.9927 |
| Ochs-Balcom (2008) | CCS | United States | Caucasians | CRC | 250/246 | Cancer-free controls | 62.76±21.68/62.47±12.11 | PCR-Titanium Taq polymerase | 99/99 | 10/10 | 0.578 | .442 |
| Park (2006) | CCS | South Korea | Asia | CRC | 179/180 | Healthy | 55 (23–81) | PCR-RFLP | 531/232 | 535/239 | 0.935 | .329 |
| Peters (2004) | CCS | United States | Caucasians | CRC | 763/774 | Patients with negative screening sigmoidoscopy | Range: 20–74 | PCR-RFLP | 526/256 | 482/256 | 0.069 | .791 |
| Takeshige (2015) | CCS | Japan | Asia | CRC | 685/788 | People without CRC before | Range: 20–74 | PCR-RFLP | NA | NA | 0.069 | .7921 |
| Yamaji (2012) | CCS | Japan | Asia | CRC | 737/703 | Healthy | NA | TagMan | 526/256 | 482/256 | 0.069 | .8174 |
| Yaylim-Eraltan (2007) | CCS | Turkey | Caucasians | CRC | 26/52 | Patients attending the general surgery and orthopedic clinics of the same hospital | 59.07±4.01/52.0±0.77 | PCR-RFLP | 259 | 259 | 0.299 | .611 |

CCS = case-control study; CRC = colorectal cancer; F = female; HWE = Hardy-Weinberg equilibrium; M = male; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphisms.

* Median (range).

† Mean (range).
preformed among the Asians and 10 among the Caucasians. Among the control groups, half comprised healthy individuals and the other half included subjects without CRCs. No significant deviations of HWE were identified for allele frequencies in both the case and control groups. All included studies were published between 2004 and 2016 and were of high quality (Table 2).

3.3. Correlation between TaqI polymorphisms and CRC

To investigate the correlation between TaqI polymorphisms and CRC, 4 models, namely additive (t vs T), dominant (Tt + tt vs TT), recessive (tt vs Tt + TT), and codominant (Tt vs TT and tt vs TT), were brought out (Figs. 2–6). Because there were no significant heterogeneities among the 4 models ($I^2 = 38\%, P = .08; I^2 = 27\%, P = .16; I^2 = 30\%, P = .16; I^2 = 0\%, P = .45$; and $I^2 = 35\%, P = .11$, respectively), the fixed-effect model was used to estimate the pooled effects. After evaluation, there were no significant differences among t vs T ($OR = 1.01; 95\% CI, 0.94–1.09; P = .70$), Tt + tt vs TT ($OR = 1.05; 95\% CI, 0.96–1.15; P = .32$), tt vs Tt + TT ($OR = 1.01; 95\% CI, 0.87–1.17; P = .92$), Tt vs TT ($OR = 1.03; 95\% CI, 0.93–1.13; P = .62$), and tt vs TT ($OR = 1.00; 95\% CI, 0.85–1.17; P = .98$) with respect to increasing CRC frequency of CRC. Sensitivity testing showed that the pooled result could not be reversed by leave-one-out method (Table 3).

Subgroup analyses based on ethnicity and control group composition were also performed. However, no statistically significant relevance was identified between TaqI polymorphisms and CRC (Table 4). Finally, publication bias was also examined, and no obvious bias was identified in the funnel plot (Fig. 7).

4. Discussion

In this meta-analysis, 14 investigations involving 9718 subjects were evaluated. With no obvious heterogeneities, the fixed-effect

Table 2

Quality assessment of the included literatures.

| Author          | A | B | C | D | E | F | G | H | I | J | Sum |
|-----------------|---|---|---|---|---|---|---|---|---|---|-----|
| Alkhayal (2016) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 8   |
| Atoum (2014)    | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 6   |
| Bentley (2012)  | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |   |
| Budhathoki (2016)| 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 9   |
| Flugge (2007)   | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 7   |
| Gunduz (2012)   | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 7   |
| Hughes (2011)   | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 6   |
| Laczmanska 2014 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 6   |
| Ochs-Balcom (2008)| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10  |
| Park (2006)     | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 7   |
| Peters (2004)   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 9   |
| Takeshige (2015)| 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 7   |
| Yamaji (2012)   | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 8   |
| Yaylim-Eraltan (2007)| 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 6   |

0 = undone or unclear, 1 = done, A = control group, B = Hardy-Weinberg equilibrium, C = case group, D = primer, E = reproducibility, F = blinding, G = power calculation, H = statistics, I = corrected statistics, J = independent replication, Sum = sum of quality assessment score.

Figure 2. Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in the additive model (t vs T).
model was used to estimate the pooled effects, and no significant differences were among $t$ vs $T$, $Tt+tt$ vs $TT$, $tt$ vs $Tt+TT$, $Tt$ vs $TT$, and $tt$ vs $TT$ with respect to increasing CRC frequency. There were also no remarkable correlations detected between $TaqI$ polymorphisms and CRC in the ethnicity or control subgroup analyses.

VDR, which codes a type II nuclear receptor, is located on the chromosome 12q12-q14, with 6 polymorphic sites described.\cite{27,37}\(TaqI\) is one of these sites located in the 3’UTR of VDR that has been considered to be a risk factor for CRC.\cite{33} Atoum and Tchoporyan\cite{13} have reported that Jordanians with $TaqI TT$ and $Tt$ genotypes had an increased CRC risk, and Yaylim-Elaltan et al\cite{15} indicate that a VDR gene with $TTFf$ or $TtFf$ genotypes appears to be protective against CRC. However, studies in New Zealand\cite{38} and Saudi Arabian\cite{39} found no evidences, suggesting that the $TaqI$ polymorphisms correlated with susceptibility to CRC. Meta-analyses that included studies of $TaqI$ polymorphism have also reached conflicting conclusions.\cite{17,40} Our meta-analysis included 5 new and stricter criteria. Although the population size in our meta-analysis was larger than that in previous meta-analyses and the quality of included studies were good, no significant association was found

### Table 1: Odds Ratio for the Association of $TaqI$ Polymorphism with CRC

| Study or Subgroup | Case Events | Case Total | Control Events | Control Total | Weight | M-H Fixed, 95% CI |
|-------------------|-------------|------------|----------------|---------------|--------|-------------------|
| Akhayal 2016      | 52          | 100        | 57             | 100           | 2.9%   | 0.62 [0.47, 1.43] |
| Atoum 2014        | 60          | 93         | 68             | 102           | 2.1%   | 1.38 [0.77, 2.46] |
| Bentley 2012      | 135         | 199        | 118            | 182           | 4.3%   | 1.14 [0.75, 1.75] |
| Budhatthodi 2016  | 92          | 356        | 145            | 708           | 7.7%   | 1.35 [1.00, 1.83] |
| Fluge 2007        | 149         | 256        | 150            | 256           | 6.7%   | 0.98 [0.69, 1.40] |
| Gunduz 2012       | 28          | 43         | 20             | 42            | 0.8%   | 2.05 [0.86, 4.91] |
| Hughes 2011       | 419         | 717        | 366            | 615           | 17.6%  | 0.96 [0.77, 1.19] |
| Laczmanska 2014   | 83          | 157        | 118            | 175           | 5.6%   | 0.54 [0.35, 0.85] |
| Ochs-Balcum 2008  | 161         | 250        | 149            | 246           | 5.7%   | 1.18 [0.82, 1.69] |
| Park 2006         | 22          | 190        | 26             | 318           | 1.8%   | 1.47 [0.81, 2.68] |
| Peters 2004       | 475         | 763        | 473            | 774           | 19.0%  | 1.05 [0.85, 1.29] |
| Takeshige 2015    | 159         | 778        | 134            | 685           | 12.2%  | 1.06 [0.82, 1.37] |
| Yamaji 2012       | 161         | 884        | 148            | 640           | 12.6%  | 1.02 [0.79, 1.32] |
| Yaylim-Eraltan 2007 | 17       | 26         | 35             | 52            | 0.9%   | 0.92 [0.34, 2.48] |

| Total (95% CI)    | 4612        | 4985       | 100.0%         |               |        |

Heterogeneity: $\chi^2 = 17.84$, df = 13 ($P = 0.16$); $I^2 = 27$

Test for overall effect: $Z = 1.00$ ($P = 0.32$)

**Figure 3.** Forest plot to estimate the effect of the $TaqI$ polymorphism on colorectal cancer in the dominant model ($Tt+tt$ vs $TT$).

### Table 2: Odds Ratio for the Association of $TaqI$ Polymorphism with CRC

| Study or Subgroup | Case Events | Case Total | Control Events | Control Total | Weight | M-H Fixed, 95% CI |
|-------------------|-------------|------------|----------------|---------------|--------|-------------------|
| Akhayal 2016      | 16          | 100        | 16             | 100           | 3.8%   | 1.00 [0.47, 2.13] |
| Atoum 2014        | 13          | 93         | 16             | 102           | 3.7%   | 0.87 [0.40, 1.93] |
| Bentley 2012      | 34          | 199        | 32             | 182           | 7.9%   | 0.97 [0.57, 1.64] |
| Fluge 2007        | 38          | 256        | 36             | 256           | 8.7%   | 1.07 [0.65, 1.74] |
| Gunduz 2012       | 10          | 43         | 3              | 42            | 0.7%   | 3.94 [1.00, 15.52] |
| Hughes 2011       | 98          | 717        | 89             | 615           | 23.6%  | 0.94 [0.69, 1.28] |
| Laczmanska 2014   | 25          | 157        | 40             | 175           | 9.1%   | 0.64 [0.37, 1.11] |
| Ochs-Balcum 2008  | 50          | 250        | 34             | 246           | 7.8%   | 1.56 [0.97, 2.51] |
| Park 2006         | 0           | 190        | 0              | 318           | Not estimable |
| Peters 2004       | 117         | 763        | 120            | 774           | 28.7%  | 0.99 [0.75, 1.30] |
| Takeshige 2015    | 6           | 778        | 8              | 685           | 2.4%   | 0.66 [0.23, 1.91] |
| Yamaji 2012       | 5           | 684        | 9              | 640           | 2.6%   | 0.52 [0.17, 1.55] |
| Yaylim-Eraltan 2007 | 9       | 26         | 8              | 52            | 1.0%   | 2.91 [0.96, 8.79] |

| Total (95% CI)    | 4256        | 4517       | 100.0%         |               |        |

Heterogeneity: $\chi^2 = 15.64$, df = 11 ($P = 0.16$); $I^2 = 30$

Test for overall effect: $Z = 0.10$ ($P = 0.92$)

**Figure 4.** Forest plot to estimate the effect of the $TaqI$ polymorphism on colorectal cancer in the recessive model ($tt$ vs $Tt+TT$).
between TaqI polymorphisms and susceptibility to CRC. This indicated that different TaqI gene types likely have no significant effect on CRC occurrence.

CRC is a result of the interaction of various risk factors such as age, lifestyle, physical activity, and genetic and ethnic backgrounds. Thus, we conducted subgroup analyses based on ethnicity and the types of control groups. However, no significant correlation was identified between the TaqI polymorphisms and susceptibility to CRC. Considering the absence of such subgroup analysis in previous meta-analyses,[17,40,41] whether ethnicity correlates with the CRC incidence still needs to be further investigated. However, it does seem clear that regardless of the comparison with control groups of healthy people or those with diseases other than CRC, the TaqI polymorphisms are not correlated with susceptibility to CRC.

This meta-analysis had some limitations. Despite the large sample size, the percentage of Asians was still limited; therefore, results from the subgroup analysis of ethnicity may not be robust. Further high-quality research among Asians is required to verify our findings. In addition, because of incomplete information regarding sex, age, and other factors, subgroup analyses of these factors are still required. However, despite these limitations, the results of this meta-analysis provide knowledge regarding the

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**Figure 5.** Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in the codominant model (Tt vs TT).

**Figure 6.** Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in codominant model (tt vs TT).
lack of association between TaqI polymorphism and susceptibility to CRC.

In conclusion, this meta-analysis indicates the absence of an obvious correlation between TaqI polymorphisms and susceptibility to CRC. Further high-quality research is required to address questions of factors affecting the results among various subgroups.

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