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

A meta-analysis

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Abstract

The meta-analysis aimed to investigate the correlation between the polymorphism of the vitamin D receptor (VDR) TaqI 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 I^2 test. Four assessed 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 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), *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.

No evidence showed that *TaqI* 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, *TaqI*, 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 owing to CRC decreased by 3% from 2003 to 2012 because of the popularization of a westernized lifestyle, CRC prevalence continues to increase in China.[4] Family-based researches have identified multiple delirious germline mutations, such as *MLH1*, *PMS2*, *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$(OH)_2$D], 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$(OH)_2$D signal transduction.[11] Several studies have reported that *VDR* polymorphisms, including *TaqI*, *BsmI*, and *Tru91*, are associated with the susceptibility of CRC.[13] Many studies have focused on the association between *TaqI* 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 *BsmI* polymorphism has been clearly confirmed as a risk factor for CRC; the role of *TaqI* remains unclear.[17] Although Serrano et al[18] have reported that *TaqI* is associated with a significantly increased risk for CRC. Touvier et al[19] demonstrated no significant associations between *TaqI* and CRC, consistent with the findings of Xu et al.[17] Therefore, to further investigate the correlation, in this meta-analysis, the associations between *TaqI* polymorphisms and CRC were assessed with updated publications to provide new insights regarding the CRC mechanism.

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SS and YC equally contributed to this study.

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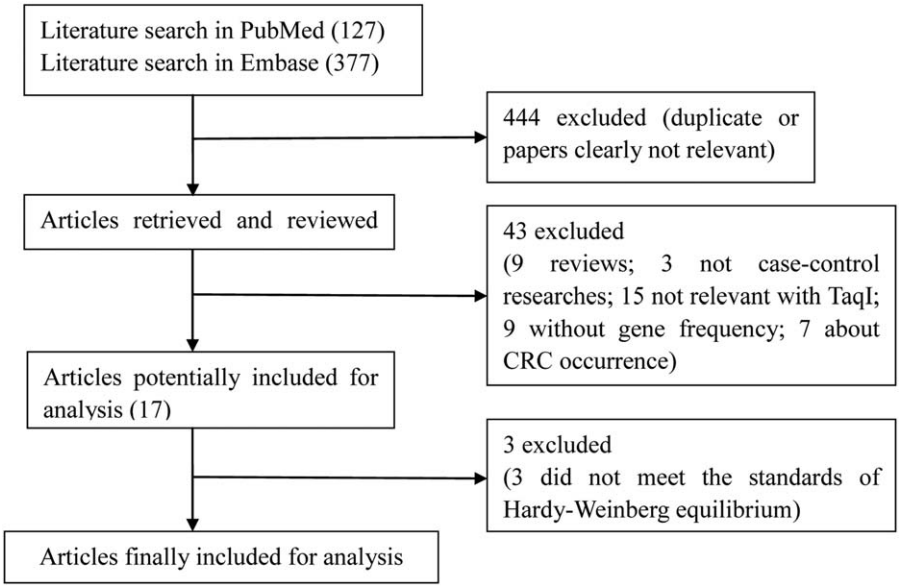

Figure 1. Flow chart of the selection of published articles included in the meta-analysis.

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* vs *Tt*+*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

Table 1

Characteristics of the included studies.

Study	Study design	Geographic area	Ethnicity	Disease	Subjects, n	Control type	Mean age, y	Genotyping method	M/F		Test for HWE	
					Cases/controls		Cases/controls		Cases	Controls	X^2	*P*
Alkhayal (2016)	CCS	Saudi	Caucasians	CRC	100/100	Healthy	57.5 (20–80)/57.5 (21–81)*	PCR-Sanger	64/36	64/36	1.335	.248
Atoum (2014)	CCS	Jordan	Caucasians	CRC	93/102	Healthy		PCR-RFLP	47/46	52/50	1.22	.2694
Bentley (2012)	CCS	New Zealand	Caucasians	CRC	200/200	Healthy	69.5±0.4	TaqMan	106/94	106/94	0.112	.738
Budhathoki (2016)	Nested-CCS	Japan	Asia	CRC	356/709	Subjects with no CRC history	56.7±7.3/56.6±7.2	TaqMan	183/173	366/343	NA	.56
Flugge (2007)	CCS	Russia	Caucasian	CRC	256/256	Patients without malignant disease	61.9±10.0/62.3±11.2	PCR-RFLP	124/132	125/131	0.358	.5495
Gunduz (2012)	CCS	Turkey	Caucasian	CC	43/42	Healthy	54.8/48.8	PCR-RFLP	27/16	26/16	0.013	.9081
Hughes (2011)	CCS	Czech	Caucasian	CRC	754/627	Patients without malignant disease	61 (27–85)/53 (29–91)*	Allele-specific PCR		0.702	0.4021	
Laczmanska 2014	CCS	Poland	Caucasians	CRC	179/180	Healthy	65.7±11.2	PCR-SNaPshot	106/73		1.753	.1855
Ochs-Balcom (2008)	CCS	United States	Caucasian	CRC	250/246	Cancer-free controls	62.76±10.21/58.47±12.11	PCR-TitaniumTM Taq polymerase	120/130	81/165	0	.9927
Park (2006)	CCS	South Korea	Asia	CRC	190/318	Healthy	55 (23–81)†	PCR-RFLP	99/91	NA	0.578	.4472
Peters (2004)	Nested-CCS	United States	Caucasians	CRC	763/774	Patients with negative screening sigmoidoscopy		PCR-RFLP	531/232	535/239	0.953	.329
Takeshige (2015)	CCS	Japan	Asia	CRC	685/778	People without CRC before	Range: 20–74	PCR-RFLP	NA	NA	0.069	.7921
Yamaji (2012)	CCS	Japan	Asia	CRC	737/703	Healthy	NA	TaqMan	526/256	482/256	0.053	.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			0.259	.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).

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	1	0	0	1	1	1	7
Budhathoki (2016)	1	1	1	1	1	1	1	1	1	0	9
Flugge (2007)	1	1	1	1	1	0	0	1	1	0	7
Gunduz (2012)	1	1	1	1	1	0	0	1	1	0	7
Hughes (2011)	1	1	1	1	1	0	1	1	1	1	9
Laczmanska 2014	1	1	1	0	1	0	0	1	1	0	6
Ochs-Balcom (2008)	1	1	1	1	1	1	1	1	1	1	10
Park (2006)	1	1	1	1	1	0	0	1	1	0	7
Peters (2004)	1	1	1	1	1	1	1	1	1	0	9
Takeshige (2015)	1	1	1	1	1	0	0	1	1	0	7
Yamaji (2012)	1	1	1	1	1	1	1	1	0	0	8
Yaylim-Eraltan (2007)	1	1	1	1	1	0	0	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.

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

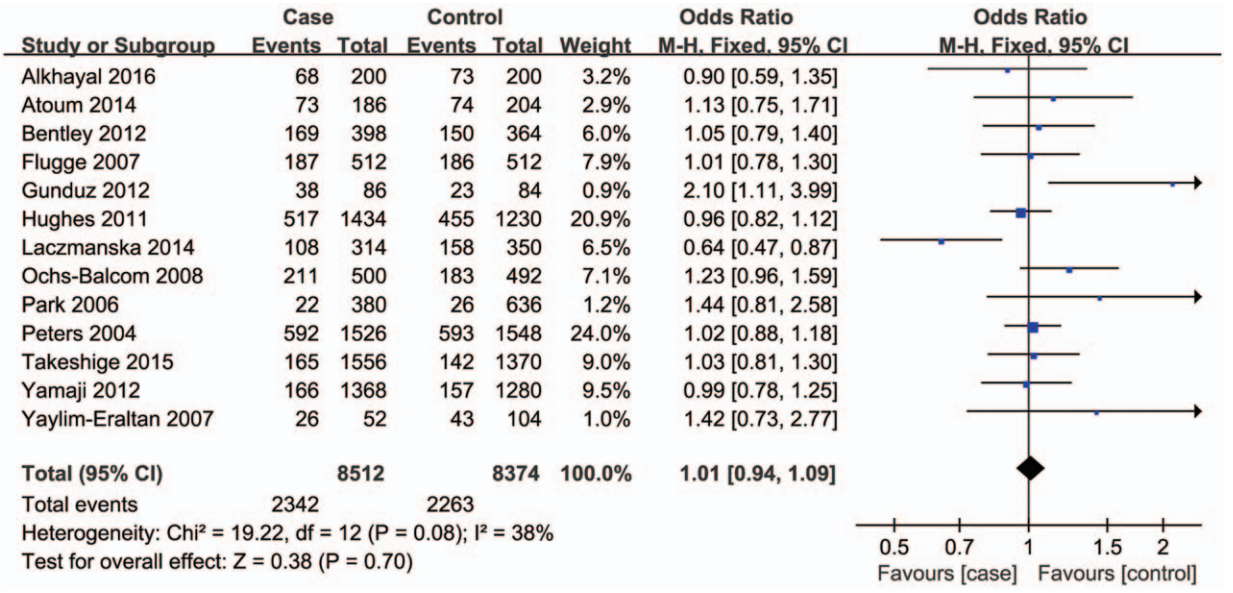

Figure 2. Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in the additive model (*t* vs *T*).

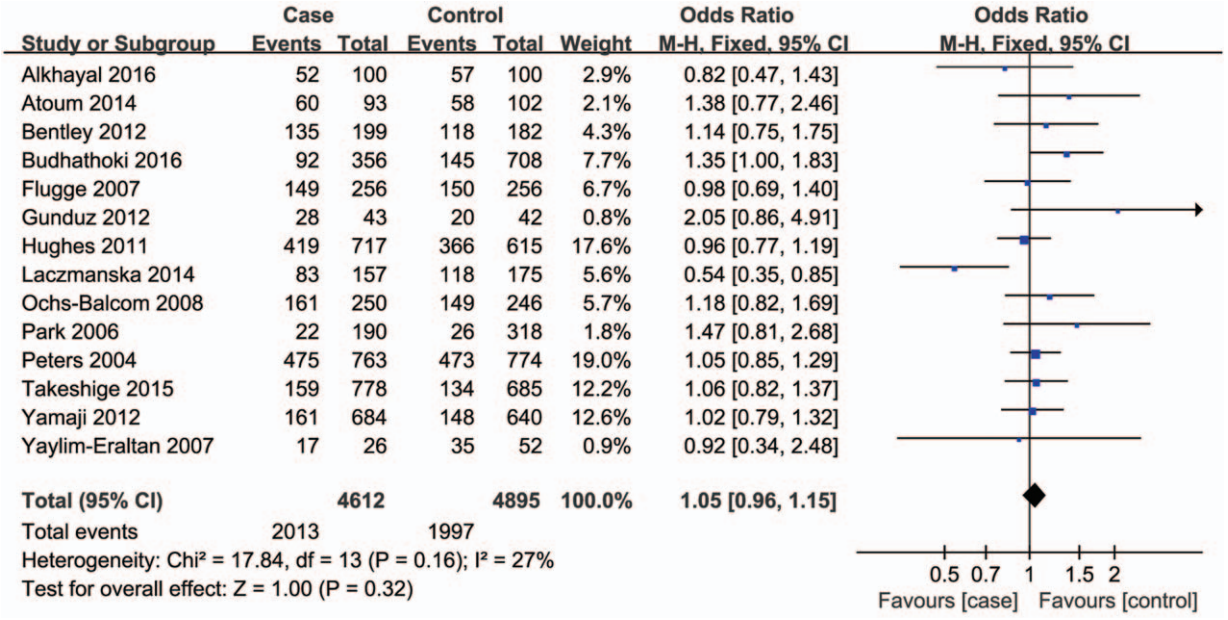

Figure 3. Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in the dominant model (*Tt*+*tt* vs *TT*).

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.[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.[33] Atoum and Tchoporyan[13] have reported that Jordanians with *TaqI TT* and *Tt* genotypes had an increased CRC risk, and Yaylim-Elaltan et al[15] indicate that a VDR gene with *TTFf* or *TtFf* genotypes appears to be protective against CRC. However, studies in New Zealand[38] and Saudi Arabian[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.[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

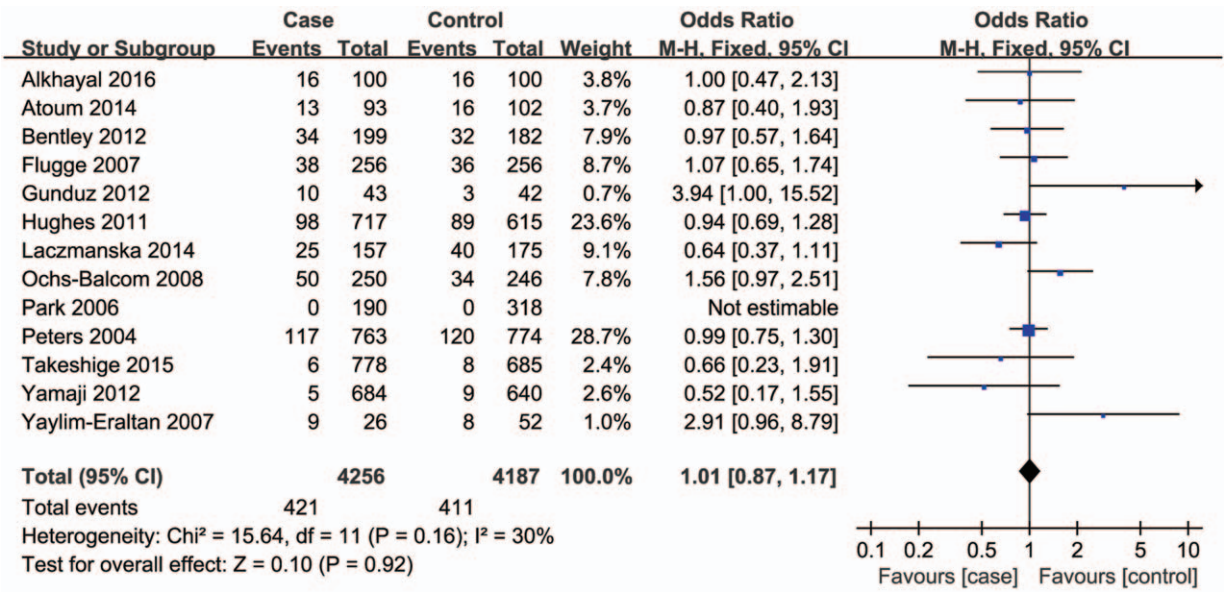

Figure 4. Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in the recessive model (*tt* vs *Tt*+*TT*).

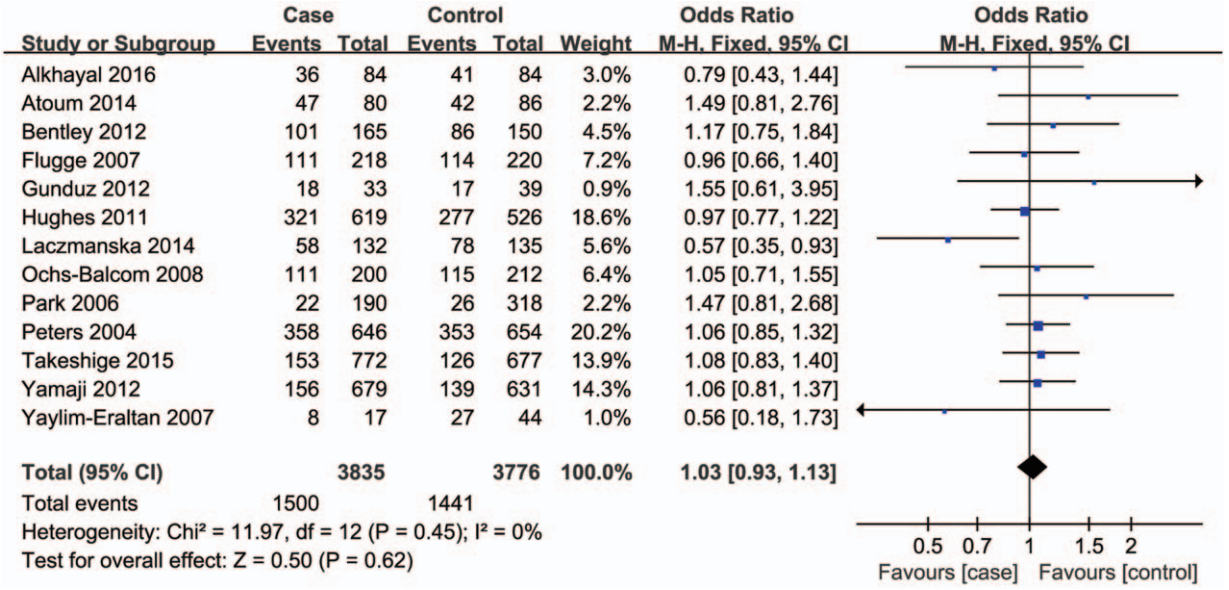

Figure 5. Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in the codominant model (*Tt* vs *TT*).

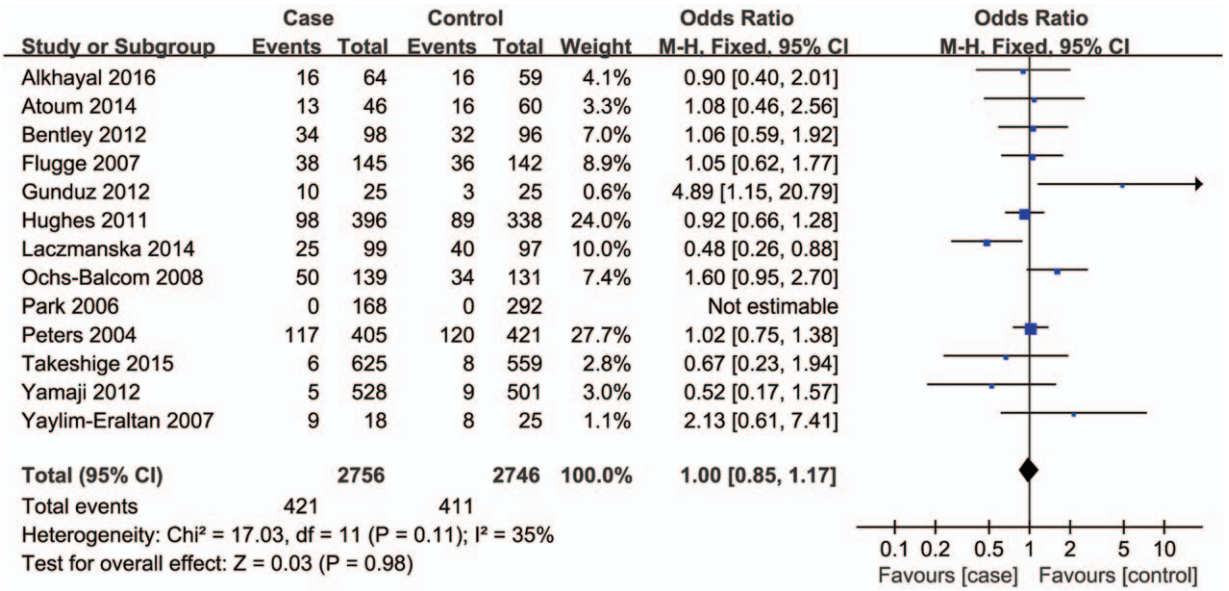

Figure 6. Forest plot to estimate the effect of the TaqI polymorphism on colorectal cancer in codominant model (*tt* vs *TT*).

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

Table 3

Sensitivity assessed by the leave-one-out method.

Omitted	Codominant model (Tt vs TT)		Codominant model (tt vs TT)		Dominant model (Tt + tt vs TT)		Recessive model (tt vs Tt + TT)		Additive model (t vs T)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Alkhayal (2016)	1.03 (0.93–1.14)	.53	1.00 (0.85–1.18)	.98	1.05 (0.96–1.15)	.26	1.01 (0.87–1.17)	.92	1.02 (0.95–1.09)	.63
Atoum (2014)	1.02 (0.92–1.12)	.77	0.99 (0.85–1.17)	.95	1.04 (0.95–1.14)	.40	1.01 (0.87–1.18)	.86	1.01 (0.94–1.09)	.78
Bentley (2012)	1.02 (0.92–1.13)	.73	0.99 (0.84–1.17)	.93	1.04 (0.95–1.14)	.37	1.01 (0.87–1.18)	.88	1.01 (0.94–1.09)	.76
Budhathoki (2016)*	—	—	—	—	1.02 (0.93–1.12)	.66	—	—	—	—
Flugge (2007)	1.03 (0.96–1.14)	.57	0.99 (0.84–1.17)	.94	1.05 (0.96–1.15)	.29	1.00 (0.86–1.17)	.98	1.01 (0.94–1.09)	.71
Gunduz (2012)	1.02 (0.92–1.13)	.69	0.97 (0.83–1.14)	.75	1.04 (0.95–1.14)	.40	0.99 (0.85–1.15)	.88	1.00 (0.93–1.08)	.90
Hughes (2011)	1.04 (0.93–1.16)	.50	1.02 (0.85–1.23)	.81	1.07 (0.97–1.18)	.20	1.03 (0.87–1.22)	.73	1.03 (0.95–1.11)	.50
Laczmanska (2014)	1.05 (0.95–1.16)	.33	1.06 (0.89–1.25)	.52	1.08 (0.98–1.18)	.11	1.04 (0.90–1.22)	.58	1.04 (0.97–1.12)	.29
Ochs-Balcom (2008)	1.02 (0.92–1.13)	.66	0.95 (0.80–1.12)	.54	1.04 (0.95–1.14)	.42	0.96 (0.82–1.12)	.62	1.00 (0.93–1.07)	.94
Park (2006)	1.02 (0.92–1.12)	.77	1.00 (0.85–1.17)	.98	1.04 (0.95–1.14)	.41	1.01 (0.87–1.17)	.92	1.01 (0.94–1.08)	.81
Peters 2004	1.02 (0.91–1.14)	.77	0.99 (0.82–1.19)	.91	1.05 (0.96–1.16)	.38	1.02 (0.86–1.21)	.86	1.01 (0.93–1.10)	.78
Takeshige (2015)	1.02 (0.91–1.13)	.77	1.01 (0.86–1.18)	.93	1.05 (0.95–1.15)	.36	1.02 (0.88–1.18)	.83	1.01 (0.94–1.09)	.74
Yamaji (2012)	1.02 (0.92–1.14)	.71	1.01 (0.86–1.19)	.88	1.05 (0.95–1.16)	.32	1.02 (0.88–1.19)	.78	1.02 (0.94–1.10)	.66
Yaylim-Eraltan (2007)	1.03 (0.93–1.14)	.56	0.99 (0.84–1.16)	.86	1.05 (0.96–1.15)	.31	0.99 (0.85–1.15)	.88	1.01 (0.94–1.09)	.78

* Budhathoki (2016) was only enrolled in the dominant model (Tt + tt vs TT).

Table 4

Outcomes of subgroup analyses.

	Codominant model (Tt vs TT)		Codominant model (tt vs TT)		Dominant model (Tt + tt vs TT)		Recessive model (tt vs Tt + TT)		Additive model (t vs T)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Subgroup: ethnicity (Caucasians vs Asia)										
Caucasians (n = 10)	0.99 (0.88–1.12)	.92	1.05 (0.82–1.33)	.71	1.00 (0.90–1.12)	.98	1.03 (0.89–1.20)	.70	1.02 (0.90–1.16)	.73
Asia (n = 4)	1.10 (0.92–1.31)	.30	0.59 (0.28–1.27)	.18	1.13 (0.98–1.32)	.10	0.58 (0.27–1.25)	.17	1.03 (0.88–1.21)	.68
Subgroup: control (healthy vs patients without CRC)										
Healthy (n = 7)	1.04 (0.87–1.23)	.69	0.91 (0.55–1.48)	.69	1.04 (0.79–1.38)	.76	0.88 (0.66–1.18)	.39	1.03 (0.82–1.29)	.80
Patients without CRC (n = 7)	1.02 (0.90–1.15)	.74	1.05 (0.87–1.27)	.58	1.06 (0.96–1.18)	.26	1.06 (0.89–1.26)	.53	1.03 (0.95–1.12)	.51

CI = confidential interval, CRC = colorectal cancer, OR = odds ratio.

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.

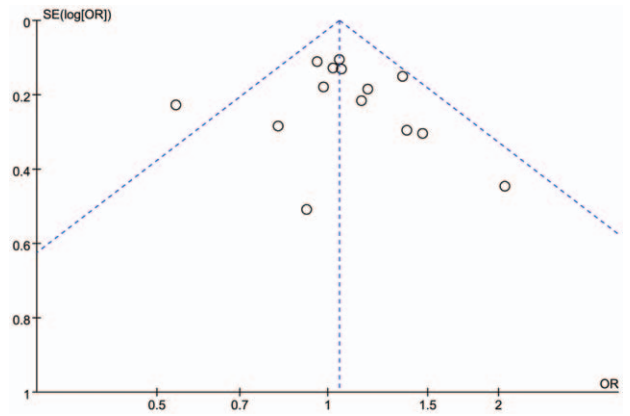

Figure 7. Funnel plot to estimate the publication bias of enrolled studies.

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