

# Role of *CDH13* promoter methylation in the carcinogenesis, progression, and prognosis of colorectal cancer

## A systematic meta-analysis under PRISMA guidelines

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### Abstract

**Background:** H-cadherin (*CDH13*) is commonly downregulated through promoter methylation in various cancers. However, the role of *CDH13* promoter methylation status in patients with colorectal cancer (CRC) remains to be clarified.

**Methods:** Eligible articles were identified from online electronic database based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement criteria. The pooled odds ratio (OR) and the corresponding 95% confidence interval (95% CI) were calculated and analyzed.

**Results:** Eventually, a total of nine studies were included in this meta-analysis, including 488 CRC, 298 adjacent, 144 normal, 68 premalignant tissues. The results demonstrated that *CDH13* promoter methylation was notably higher in CRC than in normal, adjacent, and premalignant tissues (cancer tissues vs normal tissues: OR=16.94,  $P<0.001$ ; cancer tissues vs adjacent tissues: OR=20.06,  $P<0.001$ ; cancer tissues vs premalignant tissues: OR=2.23,  $P=0.038$ ). *CDH13* promoter methylation had a significantly increased risk for poorly differentiated CRC (OR=4.07,  $P=0.001$ ). *CDH13* promoter methylation was not associated with sex status, tumor stage, and lymph node status (all  $P>0.05$ ). One study with 85 CRC patients reported that *CDH13* promoter methylation was correlated with poor prognosis in overall survival (OS).

**Conclusions:** *CDH13* promoter methylation may play an important role in the initiation and progression of CRC, and may be correlated with OS of patients with CRC. Additional studies with large sample sizes are needed to further confirm our findings in the future.

**Abbreviations:** 95% CI = 95% confidence interval, ACF = adenoma and aberrant crypt foci, *CDH13* = H-cadherin, CRC = colorectal cancer, OR = odds ratio, OS = overall survival, TSGs = tumor suppressor genes.

**Keywords:** *CDH13*, CRC, methylation, premalignant lesions, progression

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## 1. Introduction

Colorectal cancer (CRC) is the most frequently digestive malignancy and the fourth leading cause of death of malignant tumors worldwide.<sup>[1]</sup> According to global cancer statistics, approximately 1,360,600 new cases with CRC were diagnosed, leading to killing an estimated 693,900 people in the world in 2012.<sup>[1]</sup> Despite the recent and main improvements in diagnostic and therapeutic opportunities, more than 50% of the patients with CRC easily metastasize to liver, lung, and lymph nodes, and these cases are called as metastatic CRC.<sup>[2]</sup> Thus, the prognosis and survival rate for advanced CRC is very poor.<sup>[3]</sup>

CRC is a multifactorial disease associated with genetic and epigenetic alterations, and develops from normal colonic epithelial cells into colon adenocarcinoma cells.<sup>[4,5]</sup> The hypermethylation of tumor suppressor genes (TSGs) of the promoter region may be correlated with cell cycle control, DNA repair, metabolism of carcinogens, cell-cell interaction, apoptosis, and angiogenesis, and leads to gene silencing, which may facilitate cancer initiation and progression.<sup>[6,7]</sup> *CDH13* as an atypical member of the cadherin family, a TSG, also named as H-cadherin, T-cadherin, or cadherin-13, is located on 16q24 and plays an important role in cell-cell adhesion.<sup>[8,9]</sup> In most malignant tumor cell lines, *CDH13* expression has been showed to be involved in the inhibition of cell invasion and cell proliferation, and the reduction of tumor cell growth.<sup>[9-11]</sup>

However, the relationship between *CDH13* promoter methylation and CRC remains to be assessed. Therefore, the present meta-analysis was carried out to evaluate whether *CDH13* promoter methylation was significantly associated with an increased risk of CRC in cancer versus precancerous, adjacent, and normal tissue samples. In addition, we also determined whether *CDH13* promoter methylation was correlated with clinicopathological features such as sex status, tumor differentiation, tumor stage, and lymph node status in cancer.

## 2. Materials and methods

### 2.1. Search strategy

The PubMed, Embase, EBSCO, and Wanfang databases were systematically searched to achieve eligible studies without any language restriction before July 18, 2016. We used the following search terms: (CDH13 OR cadherin 13 OR H-cadherin OR T-cadherin) AND (methylation OR epigene\*) AND (colorectal cancer OR colorectal tumor OR colorectal carcinoma OR colorectal neoplasm OR CRC). To get other additional studies, we also scanned reference lists from the initially identified articles.

### 2.2. Inclusion criteria

To identify the eligibility of the included studies, the following inclusion criteria was applied: the patients were limited to primary CRC by histopathological examination; premalignant lesions included adenoma and aberrant crypt foci (ACF); articles were case-control or cohort studies; articles must provide sufficient data with regard to *CDH13* promoter methylation in cancer versus premalignant, adjacent, or normal tissues; cohort studies must have sufficient information to evaluate the association between *CDH13* promoter methylation and sex status, tumor differentiation, tumor stage, and lymph node status in CRC. In addition, if articles using the same data were published more than once, only paper with the most complete or up-to-date information was included in this meta-analysis.

### 2.3. Ethical review from patients

Although the present study was not primary research involving human samples, our study was a secondary analysis regarding human subject data published in the public domain.

### 2.4. Data extraction

The following data were independently extracted by 2 reviewers (JL and PY) from the included studies: the surname of first author, publication year, country, ethnic population, detection method of methylation, frequency of methylation, the number of case and control groups, and clinicopathological features such as sex status, tumor differentiation, tumor stage, and lymph node status. Three reviewers discussed (JL, PY, and CN) the disagreements and received the final consensuses.

### 2.5. Data analysis

This meta-analysis was conducted using the version 12.0 Stata statistical software (Stata Corp, College Station, TX). The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of the correlation between *CDH13* promoter methylation and CRC. Moreover, the pooled ORs with 95% CIs were also calculated to assess the association of *CDH13* promoter methylation with sex status, tumor differentiation, tumor stage, and lymph node status in CRC. The assessment of statistical heterogeneity was done based on the Chi-square test.<sup>[12]</sup> Substantial heterogeneity among studies was detected using the random-effects model ( $I^2 \geq 50\%$ ), a fixed-effects model was used without significant heterogeneity ( $I^2 < 50\%$ ).<sup>[13,14]</sup> We also performed a sensitivity analysis to determine the influence and stability of single study on the results by omitting 1 study.<sup>[15]</sup> A *P*-value of less than 0.05 was considered to be statistically significant for the pooled OR.

## 3. Results

### 3.1. Characteristics of eligible studies

The detailed steps of the systematic search and selection procedures of literature are shown in Fig. 1. According to the above inclusion criteria, finally, 9 case-control studies with 998 tissue samples were included in this study.<sup>[16–24]</sup> Of these eligible studies, 6 studies with 258 CRC and 144 normal tissue samples assessed the correlation between *CDH13* promoter methylation and CRC in CRC versus normal tissues,<sup>[16,17,19,21–23]</sup> 5 studies with 316 CRC and 298 adjacent tissue samples assessed the correlation between *CDH13* promoter methylation and CRC in CRC versus adjacent tissues,<sup>[16,18,20,21,24]</sup> 3 studies with 67 CRC

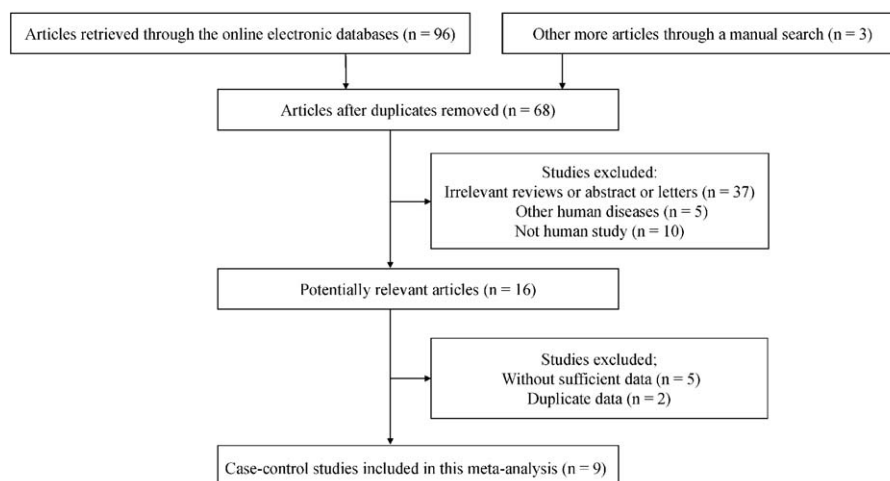


Figure 1. Flow diagram of the literature selection.

**Table 1**  
General characteristics of the included studies in the report.

Refs.	Country	Ethnicity	Method	Sample	CRC tissues	Premalignant tissues	Adjacent tissues	Normal tissues
					N (M %)	N (M %)	N (M %)	N (M %)
Toyooka et al <sup>[21]</sup>	USA	Caucasians	MSP	Tissue	35 (48.6)	19 (42.1)	33 (6.1)	8 (0)
Hibi et al <sup>[20]</sup>	Japan	Asians	MSP	Tissue	84 (32.1)	NA	84 (0)	NA
Luo et al <sup>[19]</sup>	USA	Caucasians	MSP	Tissue	22 (40.9)	35 (14.3)	NA	35 (2.8)
Hibi et al <sup>[18]</sup>	Japan	Asians	MSP	Tissue	61 (37.7)	NA	61 (0)	NA
Joensuu et al <sup>[17]</sup>	Finland	Caucasians	MSP	Tissue	108 (60.2)	NA	NA	40 (2.5)
Leong et al <sup>[16]</sup>	UK	Caucasians	MS-MLPA	Tissue	51 (70.6)	NA	35 (5.7)	19 (5.3)
Zhao and Yu <sup>[22]</sup>	China	Asians	MSP	Tissue	32 (59.4)	NA	NA	12 (8.3)
Wang et al <sup>[24]</sup>	China	Asians	MSP	Tissue	85 (31.8)	NA	85 (9.4)	NA
Scarpa et al <sup>[23]</sup>	Italy	Caucasians	MSP	Tissue	10 (50)	14 (28.6)	NA	30 (23.3)

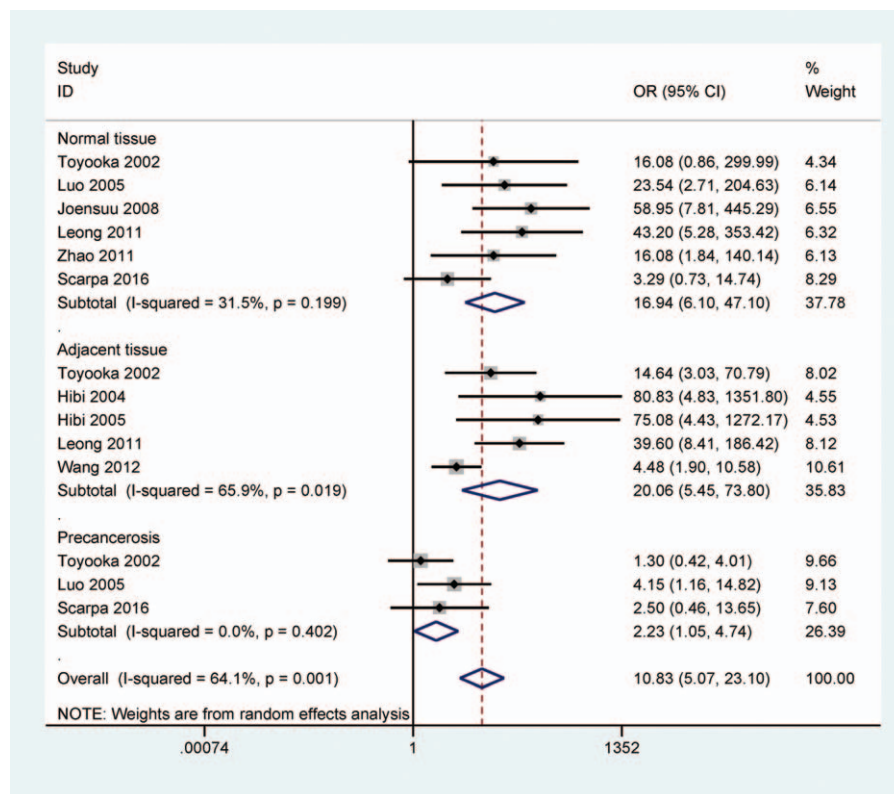
CRC = colorectal cancer, M = methylation, MS-MLPA = methylation-specific multiplex ligation-dependent probe assay, MSP = methylation-specific polymerase chain reaction, N = the number of samples, NA = not applicable.

and 68 premalignant tissue samples assessed the association between *CDH13* promoter methylation and CRC in CRC versus premalignant lesions.<sup>[19,21,23]</sup> Additionally, 3 studies with 191 CRC samples evaluated the association of *CDH13* promoter methylation with clinicopathological features.<sup>[19,20,24]</sup> Table 1 summarizes the main characteristics of the included studies.

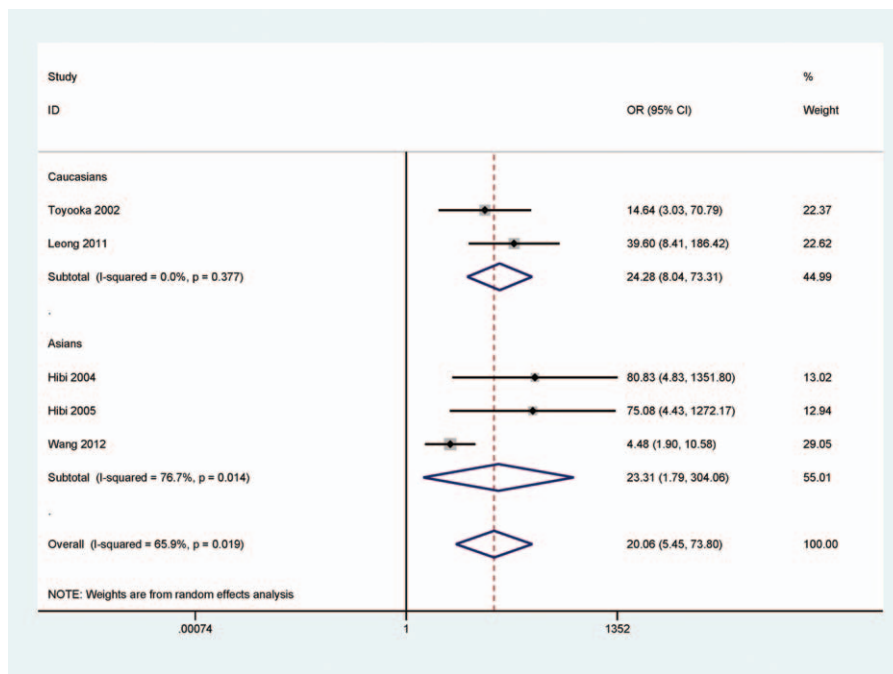
**3.2. Correlation between *CDH13* promoter methylation and CRC in cancer versus controls**

The pooled data from 9 studies including 488 cases with CRC, 48 premalignant tissues, 298 adjacent tissues, and 144 normal

tissues were included in this study. A random-effects model was used in cancer versus control groups. Our findings showed that the rate of *CDH13* promoter methylation was significantly higher in cancer tissues than in normal, adjacent, and premalignant tissues (cancer tissues vs normal tissues: OR = 16.94, 95% CI = 6.10–47.10,  $P < 0.001$ ; cancer tissues vs adjacent tissues: OR = 20.06, 95% CI = 5.45–73.80,  $P < 0.001$ ; cancer tissues vs premalignant tissues: OR = 2.23, 95% CI = 1.05–4.74,  $P = 0.038$ ) (Fig. 2). The above analysis suggested that *CDH13* promoter methylation had a significantly increased risk of CRC. However, more studies comparing CRC and premalignant lesions should be essential to further confirm our results in the future.



**Figure 2.** Forest plot of the correlation between *CDH13* methylation and CRC, including 9 studies with 488 CRC, 298 adjacent, 144 normal, 68 premalignant tissues (cancer tissues vs normal tissues: OR = 16.94, 95% CI = 6.10–47.10,  $P < 0.001$ ; cancer tissues vs adjacent tissues: OR = 20.06, 95% CI = 5.45–73.80,  $P < 0.001$ ; cancer tissues vs premalignant tissues: OR = 2.23, 95% CI = 1.05–4.74,  $P = 0.038$ ).



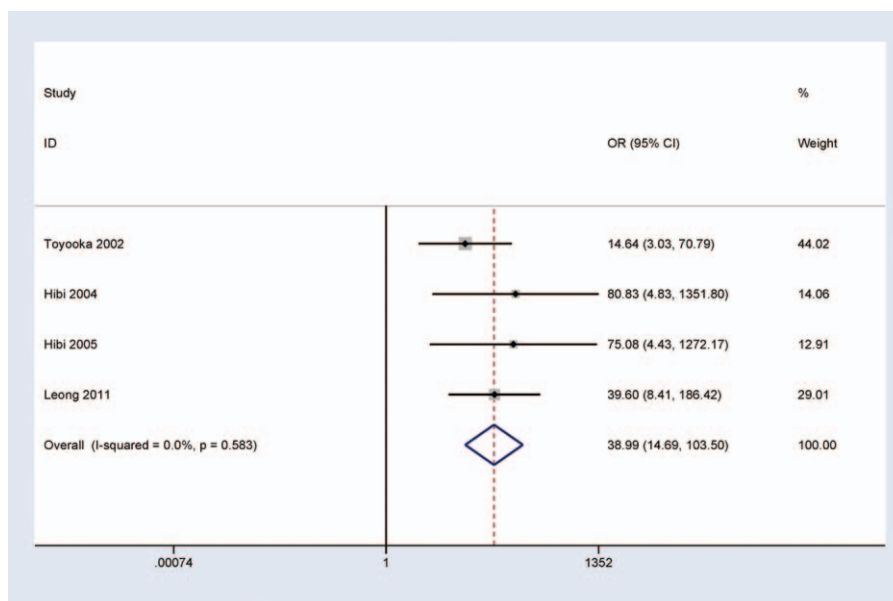
**Figure 3.** Forest plot of subgroup analysis based on ethnicity for *CDH13* promoter methylation in CRC versus adjacent tissues. Asian population: OR=23.31, 95% CI= 1.79–304.06,  $P=0.016$ ; Caucasian population: OR=24.28, 95% CI=8.04–73.31,  $P<0.001$ .

**3.3. Subgroup and sensitivity analyses in CRC versus adjacent tissues**

When cancer tissues were compared to adjacent tissues, significant heterogeneity existed ( $I^2=65.9%$ ). Subgroup analysis based on ethnic population was carried out to find the difference. The result demonstrated that *CDH13* promoter methylation had significantly increased risk of CRC in Asians and Caucasians (OR=23.31, 95% CI=1.79–304.06,

$P=0.016$ ; OR=24.28, 95% CI=8.04–73.31,  $P<0.001$ , respectively) (Fig. 3).

Next, a sensitivity analysis was determined to assess the influence and stability by deleting one study. When we removed this study by Wang et al.<sup>[24]</sup> (Fig. 4),  $I^2$  dramatically reduced to 0.0%, indicating no obvious evidence of heterogeneity. A fixed-effects model was used. The pooled OR was not significantly changed (OR=38.99, 95% CI=14.69–103.50,  $P<0.001$ ), suggesting the stability of our results.



**Figure 4.** Forest plot of a sensitivity analysis by deleting one study for *CDH13* promoter methylation in CRC versus adjacent tissues.  $I^2=0.0%$ , OR=31.92, 95% CI= 12.14–83.92,  $P<0.001$ .



**Table 2**  
**Association of CDH13 promoter methylation with clinicopathological features.**

Refs.	Ethnicity	Method	M+	Cases	M+		M+	
					Male	Female	Male	Female
Hibi et al <sup>[20]</sup>	Asians	MSP	27	84 (32.1)	18	45 (40)	9	39 (23.1)
Wang et al <sup>[24]</sup>	Asians	MSP	27	85 (31.8)	18	52 (34.6)	9	33 (27.3)
The pooled OR (95% CI): 1.77 (0.90–3.48), $I^2=0.0\%$ , $P=0.096$								
					Poorly differentiated		Moderately or highly	
Hibi et al <sup>[20]</sup>	Asians	MSP	27	84 (32.1)	5	6 (83.3)	22	78 (28.2)
Wang et al <sup>[24]</sup>	Asians	MSP	27	85 (31.8)	14	29 (48.3)	13	56 (23.2)
The pooled OR (95% CI): 4.07 (1.73–9.57), $I^2=25.9\%$ , $P=0.001$								
					Node+		Node–	
Hibi et al <sup>[20]</sup>	Asians	MSP	27	84 (32.1)	6	31 (19.4)	21	53 (39.6)
Wang et al <sup>[24]</sup>	Asians	MSP	27	85 (31.8)	17	44 (38.6)	10	41 (24.4)
The pooled OR (95% CI): 0.86 (0.17–4.44), $I^2=81.7\%$ , $P=0.857$								
					Stage 1–2		Stage 3–4	
Hibi et al <sup>[20]</sup>	Asians	MSP	27	84 (32.1)	19	54 (35.2)	8	30 (26.7)
Luo 2005 <sup>[19]</sup>	Caucasians	MSP	9	22 (40.9)	5	11 (45.5)	4	11 (36.4)
Wang et al <sup>[24]</sup>	Asians	MSP	27	85 (31.8)	9	40 (22.5)	18	45 (40)
The pooled OR (95% CI): 1.17 (0.63–2.15), $I^2=43.5\%$ , $P=0.624$								

95% CI = 95% confidence interval, M = methylation, MSP = methylation-specific polymerase chain reaction, OR = odds ratio, total = the number of samples.

### 3.4. Correlation of CDH13 promoter methylation with clinicopathological features

Table 2 shows that the association between *CDH13* promoter methylation and clinicopathological characteristics in cancer, including 3 studies with 191 CRC patients. The results of *CDH13* promoter methylation demonstrated that no significant association was observed in relation to sex status, tumor stage, and lymph node status in CRC (OR = 1.77, 95% CI = 0.90–3.48,  $P=0.096$ ; OR = 1.17, 95% CI = 0.63–2.15,  $P=0.624$ ; OR = 0.86, 95% CI = 0.17–4.44,  $P=0.857$ , respectively). The result from 2 studies demonstrated that *CDH13* promoter methylation was significantly higher in poorly differentiated CRC than in moderately or highly differentiated CRC (OR = 4.07, 95% CI = 1.73–9.57,  $P=0.001$ ). However, the relationships between *CDH13* promoter methylation and clinicopathological characteristics should be cautious as only smaller cases were analyzed in this study.

### 3.5. Prognosis of CDH13 promoter methylation

Only Wang et al<sup>[24]</sup> reported that *CDH13* promoter methylation was associated with poor prognosis in 5-year overall survival (OS), including 85 patients with CRC. More studies with larger sample sizes are necessary to future validate the prognostic value of *CDH13* promoter methylation in the future.

## 4. Discussion

The reduction of *CDH13* expression has been reported to be correlated with poor prognosis in several types of human cancers.<sup>[8]</sup> *CDH13* is frequently downregulated by promoter methylation in the CpG islands in various carcinomas, including endometrial carcinoma,<sup>[25]</sup> breast cancer,<sup>[26]</sup> cervical cancer,<sup>[27]</sup> and CRC.<sup>[20]</sup> The site of the *CDH13* methylation was located in the promoter of its 5'-flanking region in this study. However, there were contradictory results regarding the frequency of *CDH13* promoter methylation in CRC, precancerous, adjacent, and normal tissues. The methylation frequency of *CDH13* promoter was inconsistent in CRC, with a range from 31.8%<sup>[24]</sup> to

70.6%.<sup>[16]</sup> In addition, Toyooka et al<sup>[21]</sup> reported that *CDH13* promoter had different methylation rates in CRC, precancerous, adjacent, and normal tissues (CRC: 48.6%; precancerous tissues: 42.1%; adjacent tissues: 6.1%; normal tissues: 0.0%). While Luo et al<sup>[19]</sup> reported that *CDH13* promoter had different methylation frequencies in CRC, precancerous, and normal tissues (CRC: 40.9%; precancerous tissues: 14.3%; normal tissues: 2.8%). Thus, the present study was carried out to assess the correlation between *CDH13* promoter methylation and CRC risk.

Although most patients with CRC develop as a consequence of tumor progression from adenomas into adenocarcinomas, adenomas are not defined as the only type of precancerous lesions. Additionally, some studies have shown that serrated polyps or aberrant crypt foci (ACF) are also premalignant lesions.<sup>[19,28,29]</sup> In the present study, *CDH13* promoter methylation status was shown to be significantly higher in CRC tissues than in premalignant, normal, and adjacent tissues, suggesting that *CDH13* promoter methylation may play an important role in the carcinogenesis of CRC. However, the result comparing CRC and premalignant lesions should be carefully considered as only 67 CRC tissues and 68 precancerous lesions were included in this study.

Significant heterogeneity was detected in the comparison of CRC and adjacent tissues ( $I^2=65.9\%$ ). Subgroup analysis by ethnicity was analyzed to find the different association. The result showed that *CDH13* promoter methylation was significantly correlated with an increased risk of CRC in Asian and Caucasian patients, indicating that Asian and Caucasian populations were susceptible to the promoter methylation of *CDH13*. Next, a sensitivity analysis was conducted by omitting this study (Wang et al.<sup>[24]</sup>), the result showed that the pooled OR of *CDH13* promoter methylation was not significantly changed, with no substantial heterogeneity, which suggested that the stability of our analyses. The result of this study (Wang et al.<sup>[24]</sup>) was different from other studies, the reason was not very clear. The adjacent tissue samples might have been slightly contaminated by CRC cells, which may lead to bias in cancer versus adjacent tissues.

Furthermore, our findings revealed that *CDH13* promoter methylation was not associated with sex status, tumor stage, and

lymph node status in cancer. While *CDH13* promoter methylation had an increased risk for poorly differentiated CRC, suggesting that *CDH13* promoter methylation may play a key role in CRC progression. However, the results of *CDH13* promoter methylation with clinicopathological features should be carefully considered as only 191 CRC patients were analyzed.

This meta-analysis had several limitations. First, the main ethnic population were Asians and Caucasians, such as other ethnicities, Africans, were lack. Second, blood or feces samples were insufficient; the studies with large sample sizes are needed to determine whether *CDH13* promoter methylation could be a specific noninvasive biomarker for CRC diagnosis. Third, the results from less than 4 studies with small sample sizes were analyzed in CRC versus precancerous lesions, and in relation to clinicopathological features in cancer. Fourth, although studies published in English or Chinese language were included in this meta-analysis, articles published in other languages were missed, which may lead to a selection bias. Finally, only Wang et al<sup>[24]</sup> reported that *CDH13* promoter methylation was correlated with 5-year OS of patients with CRC. Additional studies with large sample sizes are needed to validate the prognostic value as a potential drug target in the future.

In conclusion, our findings showed that CRC had a higher *CDH13* promoter methylation than premalignant, normal, and adjacent tissues, and higher in poorly differentiated CRC than in moderately or highly differentiated CRC. Moreover, *CDH13* promoter methylation was not correlated with sex status, tumor stage, and lymph node status in cancer. Further well-designed studies with larger sample sizes are very essential to confirm our results in the future.

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