

Prognostic significance of *CDH13* hypermethylation and mRNA in NSCLC

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Abstract: Aberrant methylation of CpG dinucleotides is a commonly observed epigenetic modification in human cancer. Thus, detection of aberrant gene promoter methylation as a tool for diagnosis of tumors or as a prognostic marker has been widely described for many types of cancers, including nonsmall cell lung cancer (NSCLC). Emerging evidence indicates that *CDH13* is a candidate tumor suppressor in several types of human tumors, including NSCLC. However, the correlation between *CDH13* hypermethylation and clinicopathological characteristics of NSCLC remains unclear. In the current study, we conducted a systematic review and meta-analysis to quantitatively evaluate the effects of *CDH13* hypermethylation on the incidence of NSCLC and clinicopathological characteristics. Final analysis of 803 NSCLC patients from eleven eligible studies was performed. *CDH13* hypermethylation was observed to be significantly higher in NSCLC than in normal lung tissue, with the pooled odds ratio (OR) from seven studies including 448 NSCLC and 345 normal lung tissue (OR, 7.85; 95% confidence interval, 5.12–12.03; $P < 0.00001$). *CDH13* hypermethylation was also associated with pathological types. The pooled OR was obtained from four studies, including 111 squamous cell carcinoma and 106 adenocarcinoma (OR, 0.35; 95% confidence interval, 0.19–0.66; $P = 0.001$), which indicated that *CDH13* hypermethylation plays a more important role in the pathogenesis of adenocarcinoma. NSCLC with *CDH13* hypermethylation was found more frequently in poorly differentiated NSCLC patients. NSCLC patients with *CDH13* hypermethylation had a lower survival rate than those without *CDH13* hypermethylation. In addition, *CDH13* mRNA high expression was found to correlate with better overall survival for all NSCLC patients followed for 20 years (hazard ratio, 0.81; $P = 0.0056$). Interestingly, *CDH13* mRNA overexpression was found to correlate with better overall survival only in adenocarcinoma patients (hazard ratio, 0.42; $P = 9.6 \times 10^{-9}$), not in squamous cell carcinoma patients (hazard ratio, 0.93; $P = 0.59$). The results of this meta-analysis suggest that *CDH13* hypermethylation is associated with an increased risk and worse survival in NSCLC. *CDH13* hypermethylation and mRNA expression play an important role in carcinogenesis, progression, and development, as well as clinical outcomes.

Keywords: prognosis, methylation, lung cancer, tumor suppressor gene, meta-analysis, odds ratio, hazard ratio

Introduction

Epigenetic modification of gene expression plays an important role in carcinogenesis. Aberrant methylation of CpG dinucleotides is a commonly observed epigenetic modification in human cancer.^{1–3} Loss of function in cancer suppressor genes may hinder cancer cell growth inhibition, which leads to malignant transcription and translation during replication of DNA. Thus, analysis of specific gene promoter methylation as a

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tool for diagnosis of tumors and its use as a prognostic marker have been widely used for many different cancers, including nonsmall cell lung cancer (NSCLC).⁴ A number of genes including the cyclin-dependent kinase inhibitor (p16), the tumor suppressor gene cystic fibrosis transmembrane conductance regulator, the DNA repair gene *MGMT*, Ras association domain family protein 1A, and Kelch-like ECH-associating protein 1, and so on are demonstratively methylated across NSCLC.^{5–8} Cadherins, which function as membrane receptors mediating outside-in signals, activating small GTPases and the β -catenin/Wnt pathway, and resulting in dynamic cytoskeleton reorganization and changes in the phenotype, are important determinants of tumor progression, serving as suppressors of invasion and metastasis in many contexts.^{9,10} Cadherin 13 (CDH13), also known as T-cadherin or H-cadherin (heart), is a unique member of the cadherin superfamily, as it lacks the transmembrane and cytoplasmic domains and is anchored to the cell membrane through the glycosylphosphatidylinositol (GPI) anchor.^{11–13} Although signaling partners and adapter proteins for CDH13 remain to be elucidated, it is well known that CDH13 is involved in low-density lipoproteins, hormone-like effects on Ca^{2+} -mobilization and increased cell migration, phenotype changes, insulin-dependent signaling, eNOS activation, and angiogenesis.^{14–16} Its precise function has been intensively studied in several tumors, with upregulation of inducing cell cycle arrest, apoptosis, and inhibition of angiogenesis.^{17–22} Lack of protein expression of *CDH13* by promoter methylation (hypermethylation) and/or gene deletion has been found to play an important role in lung alveolar differentiation regulation and epithelial tumorigenesis.^{23–27} However, its roles in NSCLC and clinical significance have not been thoroughly investigated. In this study, we review and update the published clinical investigations regarding the effect of *CDH13* on patients with NSCLC.

Material and methods

Search strategy and selection criteria

We searched PubMed, Embase and ISI Web of Knowledge to identify studies from May 1, 1998, to March 1, 2014, using the search terms “lung,” “cancer or tumor or neoplasm or carcinoma,” “methylation,” and “CDH13 or H-cadherin or T-cadherin or cadherin 13.” We also manually searched the reference lists of the retrieved articles and reviews for additional articles.

Although our search did not have language limits initially, for the full-text reading and final evaluation, we only performed a review of the studies published in the English language. After exclusion of irrelevant and/or redundant

publications from the different databases, the remaining papers were evaluated in the full-text version for inclusion and exclusion criteria, and for relevant articles in the reference lists. All searched data were retrieved. Authors' bibliographies and references from selected studies were also searched for other relevant studies. The most complete study was chosen to avoid duplication if the same patient populations were reported in several publications.

The criteria that an eligible study had to meet were as follows: *CDH13* hypermethylation evaluated in the primary NSCLC tissues, studies revealed the relationship between *CDH13* hypermethylation and NSCLC clinicopathological parameters and prognosis, *CDH13* hypermethylation examined by polymerase chain reaction, and studies provided sufficient information to estimate hazard ratio (HR) about overall survival (OS) and 95% confidence intervals (CIs). The exclusion criteria included the following: letters, reviews, case reports, conference abstracts, editorials, and expert opinion; all publications regarding in vitro/ex vivo studies, cell lines, and human xenografts were also excluded.

Data extraction and methodological assessment

Two authors (RX, CY) independently reviewed and extracted data from eligible studies. Disagreements were resolved by discussion and consensus. Two authors (FZ, DL) reviewed all of the articles that fit inclusion and exclusion criteria. The following information was recorded for each study: first author name, year of publication, sample source, number of cases, clinicopathological parameters, cancer tumor node metastasis stage, methylation detection method, methylation rate and/or expression, and follow-up. Data for study characteristics and clinical responses were summarized and turned into a table. The heterogeneity of the investigation was evaluated to determine whether the data of the various studies could be analyzed for a meta-analysis.

For the methodological evaluation of the studies, three investigators (DL, CY, and FZ) read through the publications independently and assessed and scored them according to Reporting Recommendations for Tumor Marker Prognostic Studies guidelines and the European Lung Cancer Working Party quality scale.^{28,29} The three readers provided the quality scores, compared them, and then reached a consensus value for each item.

Patient survival analysis

An online database³⁰ was used to assess relevance of *CDH13* mRNA expression to relapse-free survival. The database

was established using gene expression data and survival information from 1,405 NSCLC patients downloaded from Gene Expression Omnibus. Briefly, *CDH13* was entered into the database (<http://kmplot.com/analysis/index.php?p=service&cancer=lung>) to obtain Kaplan-Meier survival plots in which the number at risk is indicated below the main plot. HR and 95% CIs and logrank *P* were calculated and displayed on the Web page.

Statistical analysis

Analysis was conducted using the STATA 12.0 (Stata Corporation) and Review Manager 5.2 (Cochrane Collaboration). The pooled frequency of *CDH13* hypermethylation and 95% CIs were estimated. The frequency of *CDH13* hypermethylation was compared in different tumor characteristics. Heterogeneity among studies was evaluated with Cochran's *Q* test³¹ and the *I*² statistic.^{32,33} When heterogeneity was not an issue (*I*² values <50%), a fixed-effect model was used to calculate parameters. If there was substantial heterogeneity (*I*² values ≥ 50%), a random-effects model was used to pool data and to attempt to identify potential sources of heterogeneity based on subgroup analyses. The pooled OR was estimated for the association between *CDH13* hypermethylation and clinicopathological features. *P*-values two-tailed less than 0.05 were considered statistically significant.

Publication bias was assessed by using a method reported by Egger and colleagues.³⁴ We also explored reasons for statistical heterogeneity using meta-regression, subgroup analysis, and sensitivity analysis. The analysis of meta-regression and publication bias was performed by using STATA version 10.0.

Results

Identification of relevant studies

Forty-five publications were identified by the search method, as described earlier. Thirty-four of those were excluded because they were laboratory studies, nonoriginal articles (reviews), or studies irrelevant to the current analysis. Eventually, there were eleven studies included in final meta-analysis, as shown in Figure 1.

Study characteristics

Eleven studies published from 2001 to 2012 were eligible for meta-analysis. A total of 803 NSCLC patients from China, Japan, South Korea, Italy, Serbia, and the United States were enrolled. There were five studies from Western countries, in which *CDH13* hypermethylation rates were from 15.6%–65.6%, with an average of 44.0%. There were six studies from Asian countries, in which *CDH13* hypermethylation rates were from 26.7%–53.6%, with an average of 39.3%. There are no big differences in *CDH13*

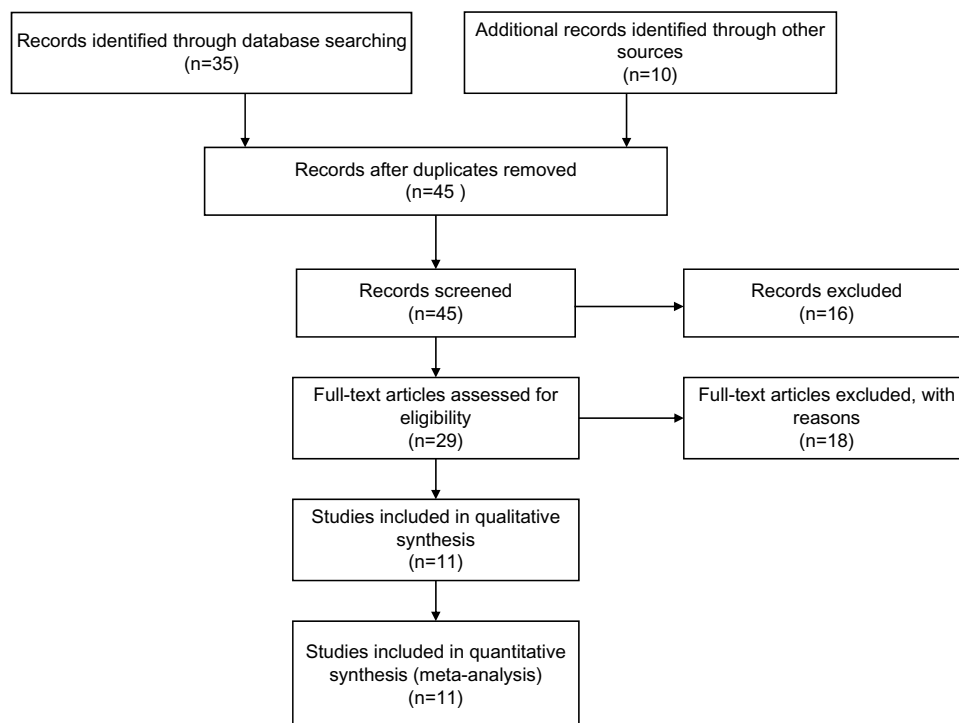


Figure 1 Flow chart of study selection.

hypermethylation rates between Western and Asian patients. Their basic characteristics are summarized in Table 1.

The correlation of *CDH13* hypermethylation with clinicopathological features

The inactivation of *CDH13* through hypermethylation in NSCLC

The loss of *CDH13* mRNA and/or protein expression was strongly correlated with the promoter hypermethylation in several types of cancer including NSCLC.^{25,26,35–43} *CDH13* hypermethylation was significantly higher in NSCLC than normal lung tissue. The pooled OR from seven studies including 448 NSCLCs and 345 normal lung tissues is shown in Figure 2 (OR, 7.85; 95% CI, 5.12–12.03; $P<0.00001$), indicating that *CDH13* inactivation through hyperm-

ethylation plays an important role in the carcinogenesis of NSCLC.

Relationship between the frequency of *CDH13* hypermethylation and pathological types

Histology was associated with *CDH13* hypermethylation, which was observed more frequently in patients with adenocarcinoma.⁴⁴ The pooled OR from 4 studies, including 111 of squamous cell carcinoma and 106 of adenocarcinoma, is shown in Figure 3 (OR, 0.35; 95% CI, 0.19–0.66; $P=0.001$), indicating that *CDH13* hypermethylation plays more important role in the pathogenesis of adenocarcinoma.

The role of *CDH13* hypermethylation in NSCLC progression

We analyzed 363 NSCLC patients pooled from 4 studies to assess whether the aberrant *CDH13* hypermethylation

Table 1 Basic characteristics of the included studies

Study	Country	Patients	Methods	Primary aim	Methylation site	<i>CDH13</i> expression
Kontic et al ⁴⁴	Serbia	65	MSP	Determine the frequency of <i>CDH13</i> hypermethylation in NSCLC	Promoter, CpG islands	–
Zhang et al ⁵⁵	People's Republic of China	78	MSP	Determine the methylation status of multiple genes in NSCLC	Promoter, CpG islands	–
Kubo et al ⁵⁶	Japan	100	MSP	Determine the methylation status of five tumor suppressor in NSCLC	Promoter, CpG islands	–
Feng et al ⁵⁷	United States	49	DNA methylation (MethyLight) analysis	Determine the clinical significance of seven tumor suppressors in NSCLC	Promoter, CpG islands	–
Brock et al ²³	United States	79	MSP	Determine the association between gene methylation and recurrence in NSCLC	Promoter, CpG islands	–
Wang et al ⁵⁸	People's Republic of China	28	DNA microarray-coupled polymerase chain reaction	Determine 15 genes' methylation status in NSCLC	Promoter, CpG islands	–
Kim et al ⁵⁰	South Korea	88	MSP	Determine the role of <i>CDH13</i> in pathogenesis of NSCLC	Promoter, CpG islands	–
Hsu et al ⁵⁹	People's Republic of China	63	MSP	Determine methylation patterns of six tumor suppressor gene in NSCLC	Promoter, CpG islands	–
Suzuki et al ⁵⁴	Japan	150	MSP	The methylation profile of nine genes for NSCLC were analyzed and correlated with clinical data	Promoter, CpG islands	–
Uliivi et al ⁶⁰	Italy	61	MSP	Detection of promoter methylation of p16 ^{INK4A} and <i>CDH13</i> genes in NSCLC	Promoter, CpG islands	–
Toyooka et al ²⁶	United States	42	MSP	Analyze DNA methylation status of <i>CDH13</i> gene in NSCLC patients	Promoter, CpG islands	+

Abbreviations: NSCLC, nonsmall cell lung cancer; MSP, methylation-specific polymerase chain reaction.

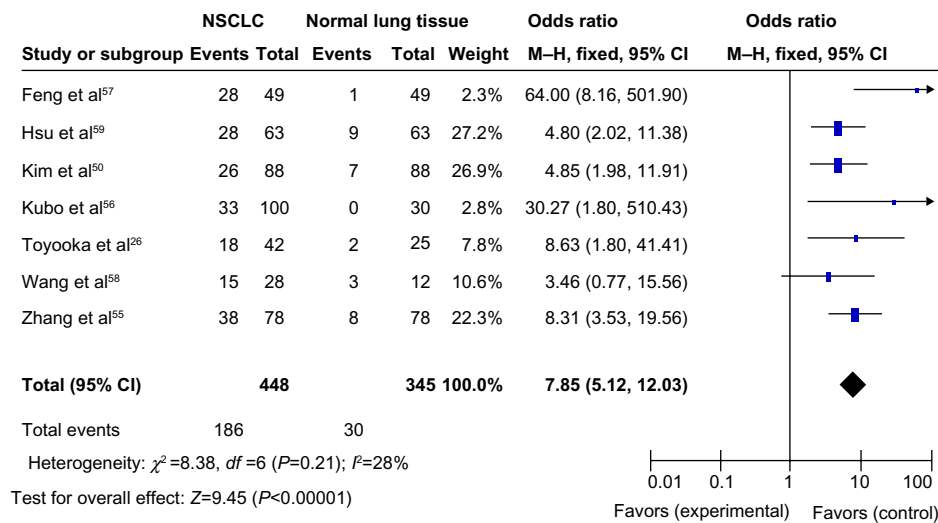


Figure 2 The pooled odds ratio from seven studies including 448 NSCLCs and 345 normal lung tissues.

Notes: Odds ratio, 7.85; 95% CI, 5.12–12.03; $P<0.00001$.

Abbreviations: NSCLC, nonsmall cell lung cancer; CI, confidence interval; M-H, Mantel-Haenszel.

in NSCLC was associated with advanced stage. As shown in Figure 4, aberrant *CDH13* hypermethylation was not significantly higher in advanced NSCLC (stage III and IV) than in early-stage NSCLC (stage I and II; OR, 0.93; 95% CI, 0.57–1.53; $P=0.79$). However, as shown in Figure 5, aberrant *CDH13* hypermethylation was significantly higher in poorly differentiated NSCLC than in moderately and highly differentiated NSCLC (OR, 3.61; 95% CI, 1.76–7.39; $P=0.0004$). These results suggest that *CDH13* hypermethylation may play an important role in NSCLC progression and development.

CDH13 hypermethylation as a prognostic factor for NSCLC

There were four studies that estimated the relationship between *CDH13* hypermethylation and OS in NSCLC. The pooled HR for OS showed that *CDH13* hypermethylation was

associated with worse survival in NSCLC patients, as shown in Figure 6 (HR, 3.21; 95% CI, 1.41–7.31; $P=0.005$).

Sensitivity analyses and publication bias

A sensitivity analysis, in which one study was removed at a time, was conducted to assess the result stability. The pooled ORs and HRs were not significantly changed, indicating the stability of our analyses. The funnel plots were largely symmetric (Figure 7), suggesting there were no publication biases in the meta-analysis of *CDH13* hypermethylation and clinicopathological features.

Effect of *CDH13* mRNA expression on prognosis of NSCLC

The clinical relevance of *CDH13* was further corroborated in a patient survival analysis, using an online database containing

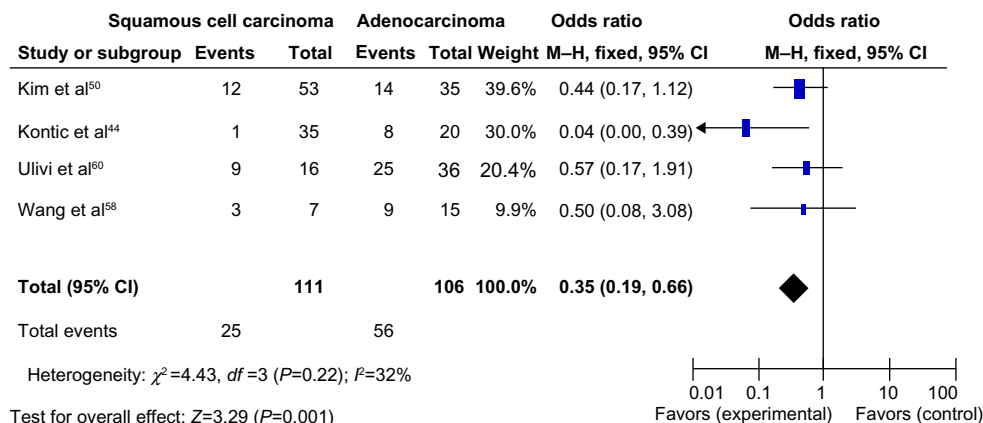


Figure 3 Pooled odds ratio from four studies, including 111 squamous cell carcinomas and 106 adenocarcinomas.

Notes: Odds ratio, 0.35; 95% CI, 0.19–0.66; $P=0.001$, which indicated that *CDH13* hypermethylation plays a more important role in the pathogenesis of adenocarcinoma.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

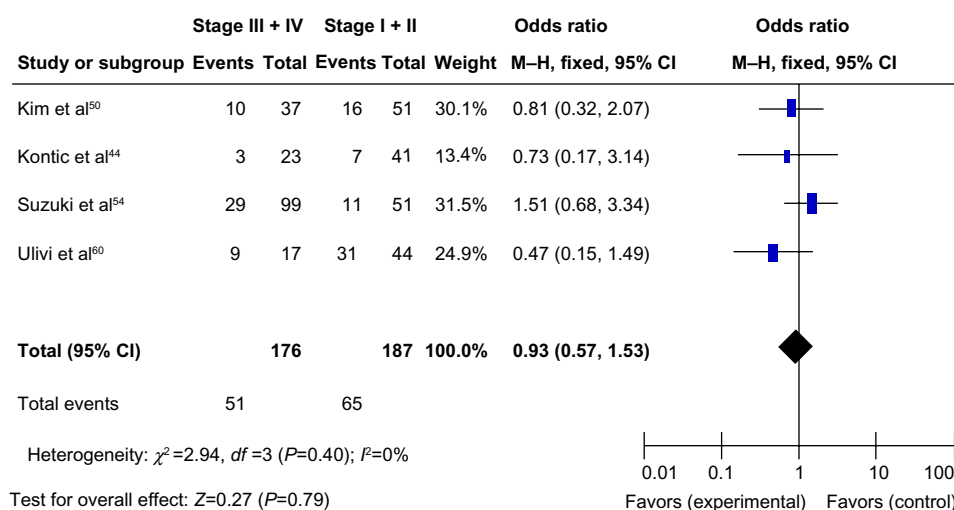


Figure 4 Three hundred and sixty-three nonsmall cell lung cancer patients were pooled from four studies to assess whether the aberrant *CDH13* hypermethylation in nonsmall cell lung cancer was associated with advanced stage.

Notes: Aberrant *CDH13* hypermethylation was not significantly higher in advanced nonsmall cell lung cancer (III and IV) than that in early-staged nonsmall cell lung cancer (I and II). Odds ratio, 0.93; 95% CI, 0.57–1.53; $P=0.79$.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

the expression of 22,277 genes and 20-year survival information of 1,809 patients.³⁰ The database has recently been updated to include survival information of 1,405 NSCLC patients (<http://www.kmplot.com/analysis/>). *CDH13* mRNA high expression was found to correlate with better OS for all NSCLC patients followed for 20 years (Figure 8A; HR, 0.81; $P=0.0056$). In addition, *CDH13* mRNA high expression was found to correlate with better relapse OS only in adenocarcinoma patients (Figure 8B; HR, 0.42; $P=9.6e-09$), but not squamous cell carcinoma patients (Figure 8C; HR, 0.93; $P=0.59$).

Discussion

CDH13 has been reported to encode T-cadherin, an adiponectin receptor discovered after adipoR1 and adipoR2.⁴⁵ Inactivation

of *CDH13* by promoter hypermethylation plays an important role during normal development and in tumorigenesis in several types of tumors, including NSCLC.^{37,44,46–51} To date, there have been some studies describing the precise expression, prognostic effect, and methylation status of *CDH13* in NSCLC; however, the roles of inactivation of *CDH13* in NSCLC and clinical significance have not been thoroughly investigated. We conducted the meta-analysis to determine the correlation between *CDH13* hypermethylation and clinicopathological characteristics in NSCLC. Analysis of the pooled data showed that NSCLC had a higher hypermethylation than normal lung tissue, *CDH13* hypermethylation plays a more important role in the pathogenesis of adenocarcinoma, and aberrant *CDH13* hypermethylation was not

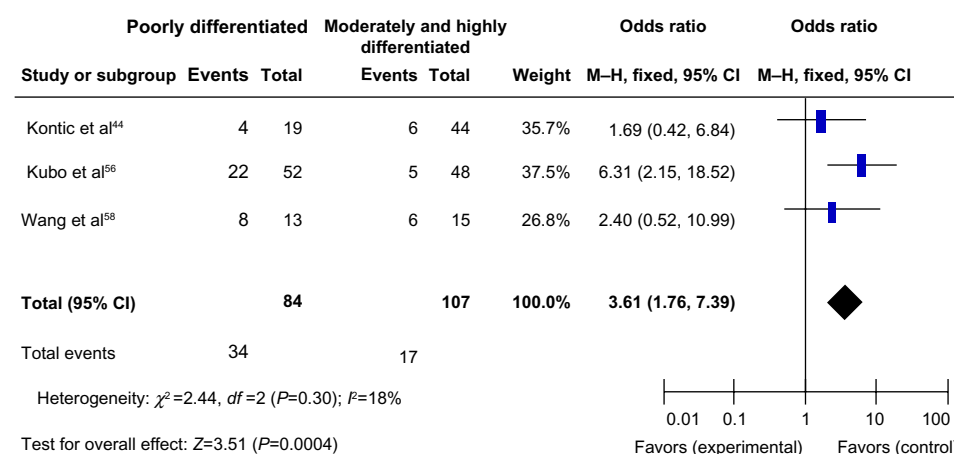


Figure 5 Aberrant *CDH13* hypermethylation was significantly higher in poorly differentiated nonsmall cell lung cancer than that in moderately and highly differentiated nonsmall cell lung cancer.

Notes: Odds ratio, 3.61; 95% CI, 1.76–7.39; $P=0.0004$.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

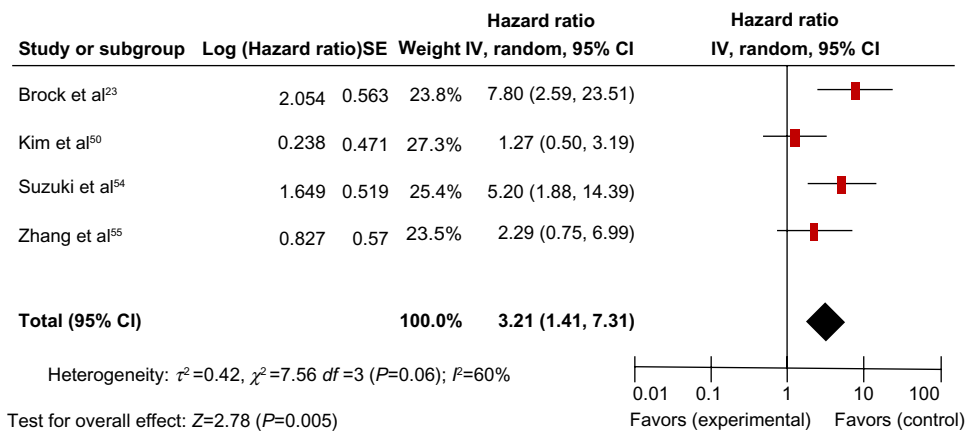


Figure 6 The four studies included investigated the relationship between overall survival and *CDH13* hypermethylation.

Notes: The pooled hazard ratio for overall survival showed that *CDH13* hypermethylation was associated with worse survival in nonsmall cell lung cancer. Hazard ratio, 3.21; 95% CI, 1.41–7.31; $P=0.005$.

Abbreviations: SE, standard error; CI, confidence interval.

significantly higher in advanced NSCLC (stage III and IV) than in early-staged NSCLC (stage I and II). However, aberrant *CDH13* hypermethylation was significantly higher in poorly differentiated NSCLC than in moderately and highly differentiated NSCLC. In addition, NSCLC patients with *CDH13* hypermethylation had a lower survival rate than those without *CDH13* hypermethylation. The results from the

current study demonstrated that the hypermethylation rate of the *CDH13* gene promoter in NSCLC was significantly higher than that in the normal lung tissues, indicating that *CDH13* promoter hypermethylation was common in NSCLC. Because changes in *CDH13* promoter hypermethylation are reversible, drug treatment through demethylation may be useful to delay carcinogenesis and progression and improve prognosis.

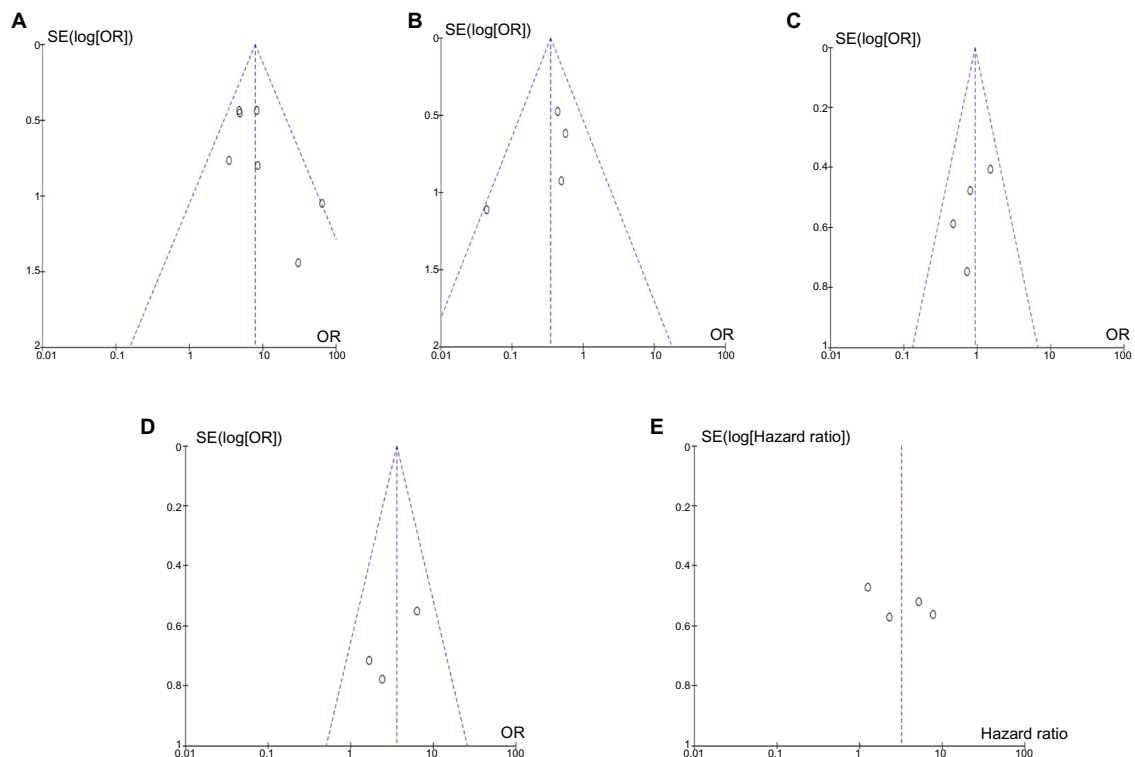


Figure 7 The funnel plots were largely symmetric, suggesting there were no publication biases in the meta-analysis of *CDH13* hypermethylation and clinicopathological features.

Notes: (A) The funnel plot from seven studies comparing nonsmall cell lung cancer and normal lung tissue. (B) The funnel plot from four studies comparing *CDH13* hypermethylation between squamous cell carcinoma and adenocarcinoma. (C) The funnel plot from four studies in determining *CDH13* hypermethylation in differently staged nonsmall cell lung cancer. (D) The funnel plot from three studies determining *CDH13* hypermethylation in different differentiated nonsmall cell lung cancer. (E) The funnel plot from four studies determining the relationship between *CDH13* hypermethylation and overall survival in nonsmall cell lung cancer.

Abbreviations: OR, odds ratio; SE, standard error.

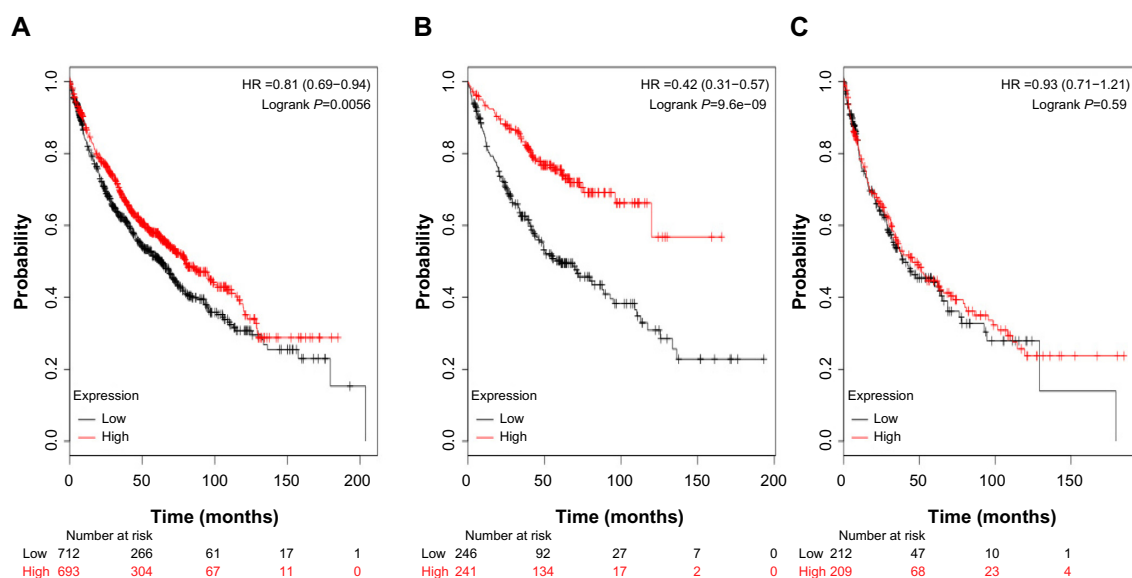


Figure 8 The clinical relevance of *CDH13* was corroborated in a patient survival analysis using an online database containing the expression of 22,277 genes and 20-year survival information of 1,405 patients.

Notes: *CDH13* mRNA high expression was found to correlate with better overall survival for all nonsmall cell lung cancer patients followed for 20 years. (A) HR, 0.81; $P=0.0056$. In addition, *CDH13* mRNA high expression was found to correlate with better overall survival only in adenocarcinoma patients. (B) HR, 0.42; $P=9.6e-09$, but not patients with squamous cell carcinoma. (C) HR, 0.93; $P=0.59$.

Abbreviation: HR, hazard ratio.

This approach may bring new direction and hope for cancer treatment through gene-targeted therapy.

Epigenetic alterations, particularly aberrant DNA methylation, one of the best-characterized epigenetic modifications, contribute to tumor initiation and progression.^{2,3} *CDH13* is thought to affect cellular function and behavior largely through its signaling properties.²² *CDH13* reexpression in most cancer cell lines inhibits cell proliferation and invasiveness, increases susceptibility to apoptosis, and reduces tumor growth in vivo models.^{36,52,53} Therefore, *CDH13* can be considered a tumor suppressor, and its inactivation could contribute to tumor progression and poor prognosis. Although only four studies evaluated the relationship between overall survival and *CDH13* hypermethylation in NSCLC, they showed very similar results.^{23,50,54,55} According to this meta-analysis, we may consider that *CDH13* hypermethylation in NSCLC tends to indicate a poor prognosis. We further determined the clinical relevance of *CDH13* mRNA expression in a patient survival analysis, using an online database containing the expression of 22,277 genes and 20-year survival information of 1,405 patients.³⁰ As expected, *CDH13* mRNA high expression was found to correlate with OS for all NSCLC patients followed for 20 years. Interestingly, *CDH13* mRNA high expression was found to correlate with better OS only in adenocarcinoma patients, but not squamous cell carcinoma patients.

Consistent results were shown in sensitivity analyses, and no evidence of publication bias was found. This study has several

potential limitations. First, the possibility of information and selection biases and unidentified confounders could not be completely excluded because all of the included studies were observational. Second, the searching strategy was restricted to articles published in English. Articles with potentially high-quality data that were published in other languages were not included because of anticipated difficulties in obtaining accurate medical translation. Hence, caution should be taken when our findings are interpreted among the general population.

In conclusion, our meta-analysis showed *CDH13* may play an important role in NSCLC initiation and progression. In addition, *CDH13* hypermethylation is associated with an increased risk and worse survival in NSCLC. Further large-scale studies, especially multicenter and well-matched cohort research, will provide more insight into the role of *CDH13* in the prognosis and clinical implementation of NSCLC patients.

Disclosure

The authors report no conflicts of interest in this work.

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