

Histone deacetylase HDAC1 expression correlates with the progression and prognosis of lung cancer

A meta-analysis

Lin-Lin Cao, PhD^{a,*}, Xiaoxu Song, BS^b, Lin Pei, MS^a, Lianhua Liu, BS^a, Hui Wang, PhD^a, Mei Jia, MS^{a,*}

Abstract

Background: Histone deacetylase 1 (HDAC1) is an important epigenetic factor, and is thought to be associated with the progression and prognosis of some types of cancer. HDAC1 has been reported to be overexpressed in lung cancer, but the correlation between HDAC1 overexpression and the clinical features or prognosis of lung cancer is controversial. In this study, we investigated the potential association between HDAC1 and lung cancer.

Materials and Methods: Embase, Web of Science, PubMed, and other sources were searched for relevant studies. Pooled odds ratios (ORs) or hazard ratios (HRs) with 95% confidence interval (CI) were calculated to evaluate the association of HDAC1 with lung cancer risk.

Results: Eight eligible studies were included in the final meta-analysis. We found that HDAC1 mRNA or protein expression was closely associated with the differentiation grade of lung cancer (OR=2.36, 95% CI=1.14–4.87, $P=.02$). In addition, the protein expression level of HDAC1 in squamous cell carcinoma was higher than that in adenocarcinoma (OR=1.81, 95% CI=1.13–2.90, $P=.01$). Finally, HDAC1 mRNA or protein expression was negatively correlated with the overall survival rate of patients with lung cancer (HR=2.40, 95% CI=1.48–3.88, $P=.0004$).

Conclusion: In this meta-analysis, our results suggest that HDAC1 may serve as a good diagnostic and prognostic marker for lung cancer.

Abbreviations: CI = confidence interval, HDAC1 = histone deacetylase 1, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OR = odds ratio, OS = overall survival, RT-PCR = real-time polymerase chain reaction.

Keywords: HDAC1, lung cancer, meta-analysis, survival

1. Introduction

Lung cancer presents an ever-increasing global public health threat, including several different subtypes, such as adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, and small-cell lung carcinoma. It was one of the most frequently diagnosed cancer and the leading cause of cancer death.^[1] The overall survival (OS) rate for lung cancer remains low despite the

advances in early diagnosis and clinical treatment over the last several decades.^[2] Therefore, it is urgent to identify new biomarkers to screen out high-risk patients and predict lung cancer prognosis.

Histone deacetylase 1 (HDAC1) is an important epigenetic factor, which antagonizes the acetylation status of histone and nonhistone proteins. It has been well known that HDAC1 is tightly correlated with cancer development and progression. For example, HDAC1 silencing by siRNA resulted in cell cycle arrest, cell growth inhibition, and induction of apoptosis in breast and colon cancer cells,^[3,4] whereas HDAC1 overexpression led to an increase in cell proliferation in prostate cancer cells,^[5] indicating that HDAC1 stimulates cancer cell growth. In addition, HDAC1 was found to be recruited to the promoter of *CDH1* to downregulate the expression of the cell adhesion molecule E-cadherin, thereby inhibiting cancer cell migration in pancreatic cancer.^[6]

HDAC1 has been demonstrated to be overexpressed in many cancers, such as in breast, renal cell cancer, and classical Hodgkin's lymphoma, and HDAC1 expression is often associated with the clinical features and prognosis of cancer patients.^[7–9] Therefore, HDAC1 may be a good diagnostic and prognostic marker for some types of cancer. HDAC1 is also overexpressed in lung cancer,^[10,11] but the correlations between HDAC1 and clinical features and prognosis of patients with lung cancer are controversial.

In this study, we performed a systematic review and a meta-analysis to evaluate the correlation of HDAC1 expression with lung cancer. We found that HDAC1 expression was associated with the differentiation grade of lung cancer. In addition, the

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expression level of HDAC1 in squamous cell carcinoma was higher than that in adenocarcinoma. Finally, HDAC1 expression was negatively correlated with the OS rate of patients with lung cancer. Overall, this study is the first to systematically review the clinical value of HDAC1 in lung cancer.

2. Materials and methods

2.1. Search strategy and eligibility criteria

A systematic literature search was conducted for original articles analyzing the correlation between HDAC1 expression and the progression and prognosis of lung cancer in Embase, Web of Science, PubMed, and other sources. Studies were selected using the following keywords: “HDAC1” or “histone deacetylase 1” for HDAC1; “lung cancer”; or “lung neoplasms” for lung cancer. The search ended on December 27, 2016, and no lower date limit was used. No language restriction was applied, and the references of the relevant studies were also screened to check for potentially relevant articles.

The full text of each relevant study was carefully evaluated. The studies collected in this meta-analysis were required to meet the following criteria: HDAC1 expression was measured by real-time polymerase chain reaction (RT-PCR) or immunohistochemistry; the clinical features or prognosis of lung cancer were investigated; and the correlation of HDAC1 expression with clinical features and survival outcomes was analyzed. When several studies collected data from the same patient group, the most recent study was used; if the most recent study did not meet the inclusion criteria, the highest-quality study was included. Articles were excluded if they were case reports, letters, or reviews without original data; they focused on animal models or cancer cells; the expression of HDAC1 was determined by western blot; or the full text was unavailable. All evaluations were independently performed by 2 authors, Xiaoxu Song and Lin Pei, to ensure the accurate inclusion of studies. Disagreement between the 2 authors was adjudicated by Lin-Lin Cao. Eight articles were eligible for inclusion in this meta-analysis. This study is a meta-analysis, which extracted data from other original studies, so ethical approval was not necessary.

2.2. Data extraction

Two authors, Xiaoxu Song and Lin Pei, independently extracted data from the eligible studies. The following information was extracted from each included study: first author’s name, publication year, country, sample size, age, HDAC1 detection method, the cut-off value, histology, stage, follow-up period, and outcome. If there were no original data for HDAC1 expression and only a histogram was provided, we used Engauge Digitizer 4.1 (<http://digitizer.sourceforge.net>) to extract the expression data. If the cut-off value of HDAC1 expression was not provided, the mean value of all samples was considered to be the cut-off value. In addition, if hazard ratios (HRs) for OS rates according to HDAC1 expression were not reported directly, the number of deaths and total samples in each article were extracted for HR calculation. If only the Kaplan–Meier curves were available, the survival data were extracted using Engauge Digitizer 4.1 and analyzed as described previously.^[12]

2.3. Quality score assessment

Two reviewers (Xiaoxu Song and Lin Pei) independently assessed the quality of the included studies according to the

Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The scale consists of 3 components related to sample selection, comparability, and ascertainment of exposure.

2.4. Statistical analysis

Analysis was conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) by Lin-Lin Cao. The odds ratios (ORs) with 95% confidence intervals (CIs) were used to analyze the association between the expression level of HDAC1 and clinical features of lung cancer. HRs with 95% CIs were used to evaluate the correlation of HDAC1 expression with the OS of patients with lung cancer. The random-effect model was applied when $I^2 > 50\%$, and the fixed-effect model was used in the absence of between-study heterogeneity ($I^2 \leq 50\%$). *P* values of $< .05$ were considered to be statistically significant. Publication bias was evaluated using the funnel plot.

3. Results

3.1. Study selection and characteristics of the included studies

A total of 3932 articles were retrieved using the search strategy (Fig. 1). After the article titles and abstracts were checked, 3897 studies were excluded because of their irrelevance and duplication. Then, the remaining 35 articles were viewed in their entirety. Among the 35 articles, 27 were excluded according to the exclusion criteria. Finally, 8 studies^[10,11,13–18] matched the criteria for this analysis. All characteristics of the 8 studies are listed in Table 1. Among the studies, 3 originated from Japan, 4 from China, and 1 from Korea. A total of 710 cases were enrolled. An immunohistochemistry assay was used in 5 studies, whereas an RT-PCR assay was used in 3 studies.

3.2. Correlation of HDAC1 expression with the clinical features of lung cancer

Next, we analyzed the relationship between HDAC1 expression and the clinical features of lung cancer patients. As shown in Figure 2, there was no significant difference in the expression level

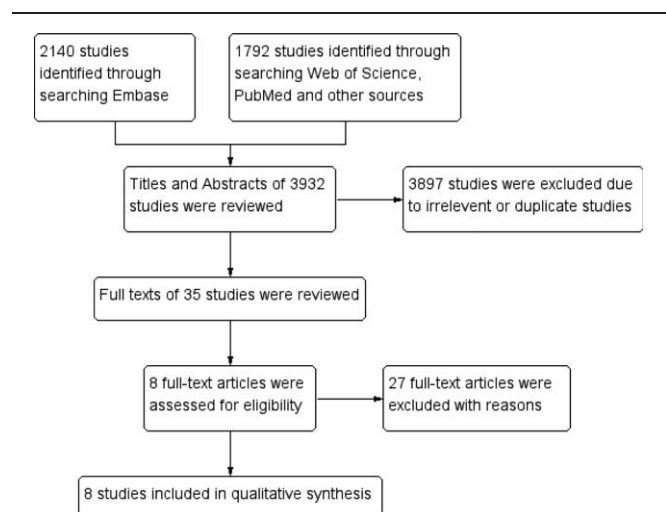


Figure 1. Methodological flow chart of study selection.

Table 1
Main characteristics and results of the included studies.

Study	Year	Country	Sample size	Age	Detection method	Cut-off value	Histology	Stage	Follow-up period, mo	Outcome
Yoshihiro	2011	Japan	94	64.0 (Mean)	RT-PCR	HDAC1/β-actin >2.4	AC	I-III	NR	OS, DFS
Hidefumi	2004	Japan	102	65.4 ± 9.3 (Mean)	RT-PCR	>Mean	AC, SCC, LCC, others	I-IV	NR	NR
Hiroataka	2004	Japan	72	62 (Median)	RT-PCR	T/N ≥ 0.8	AC, SCC, LCC, others	I-IV	63 Months (median)	OS
Jong	2009	Korea	76	63 (Median)	IHC	>50%	AC, SCC	I-IV	NR	NR
Yang	2012	China	95	58 (Median)	IHC	Score ≥ 2	AC, SCC, others	I-IV	NR	OS
Zhu	2010	China	169	59.3 ± 11.1 (Mean)	IHC	IRS ≥ 5	AC, SCC, LCC, others	I-IV	NR	NR
Sun	2010	China	52	NR	IHC	Score ≥ 1	AC, SCC	I-IV	NR	NR
Huang	2013	China	50	62.96 ± 6.5 (Mean)	IHC	IRS ≥ 5	AC	I-IV	NR	NR

AC = adenocarcinoma, DFS = disease-free survival, IHC = immunohistochemistry, IRS = immunoreactivity scoring, LCC = large cell carcinoma, NR = no reported, OS = overall survival, RT-PCR = real-time polymerase chain reaction, SCC = squamous cell carcinoma, T/N = tumor/normal.

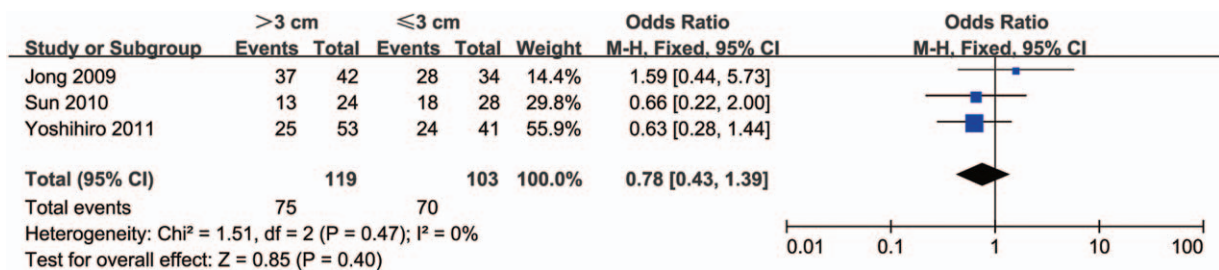


Figure 2. Forest plot of odds ratio (OR). Comparison of the expression level of histone deacetylase 1 (HDAC1) between tumors >3cm and tumors ≤3cm. CI = confidence interval.

of HDAC1 between tumors >3cm and tumors ≤3cm (OR = 0.78, 95% CI=0.43–1.39, P=.40), indicating that HDAC1 expression was not associated with tumor size. In addition, no significant difference in HDAC1 expression was observed between stage III–IV lung cancer and stage I–II lung cancer (OR = 1.29, 95% CI=0.64–2.61, P=.48) (Fig. 3). However, HDAC1 mRNA or protein expression level was higher in patients with low-differentiated lung cancer than that expressed in those with high-differentiated lung cancer (OR = 2.36, 95% CI = 1.14–4.87, P = .02) (Fig. 4). Finally, we analyzed the relationship between HDAC1 expression and the lymph node metastasis state of lung cancer. As shown in Figure 5, the groups positive and negative for lymph node metastasis did not show a significant difference in HDAC1 expression in lung cancer (OR = 1.51, 95% CI = 0.78–2.91, P = .22). Taken together, these results suggest that HDAC1 expression was tightly associated with the

differentiation grade, but not with tumor size, tumor stage, and lymph node metastasis state of lung cancer.

To determine whether there was a difference in HDAC1 expression in different pathological subtypes of lung cancer, we did a meta-analysis to see the difference between squamous cell carcinoma and adenocarcinoma. As shown in Figure 6, the pooled OR was 1.81 (95% CI = 1.13–2.90, P = .01), indicating that the protein expression level of HDAC1 in squamous cell carcinoma was higher than that in adenocarcinoma.

3.3. Impact of HDAC1 expression on overall survival of lung cancer patients

Subsequently, we investigated the association between HDAC1 expression and the OS of lung cancer patients. The pooled HR

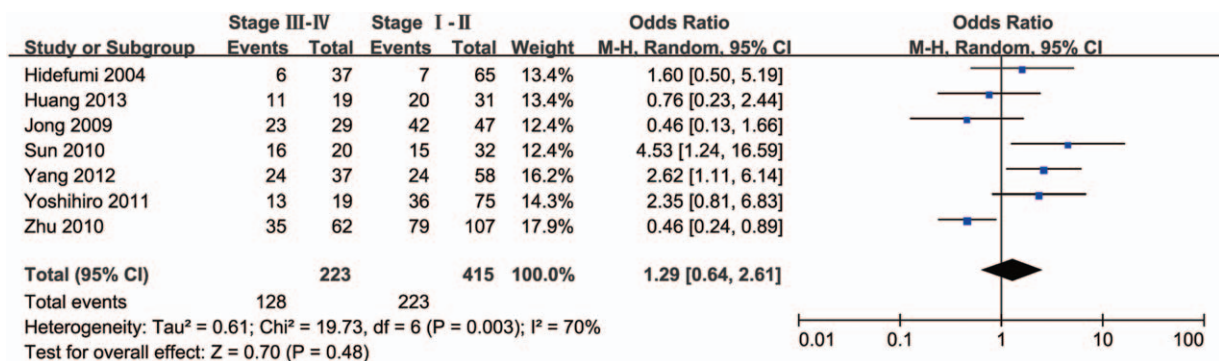


Figure 3. Forest plot of odds ratio (OR). Association between histone deacetylase 1 (HDAC1) expression and tumor stage in lung cancer. CI = confidence interval.

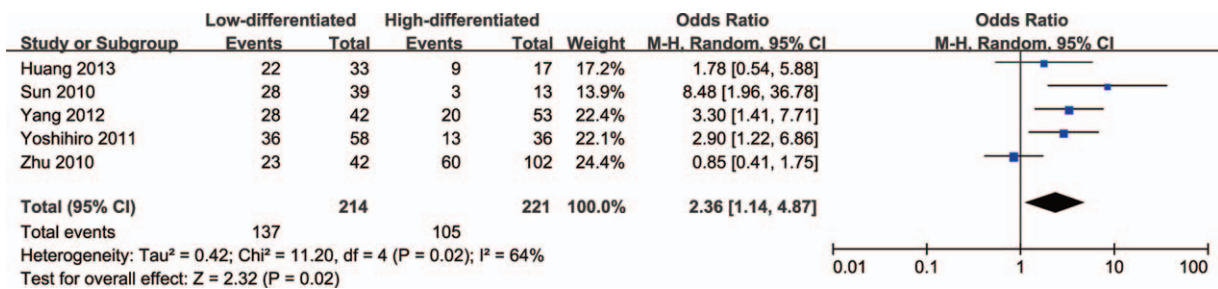


Figure 4. Forest plot of odds ratio (OR). Association between histone deacetylase 1 (HDAC1) expression and tumor differentiation grade in lung cancer. CI = confidence interval.

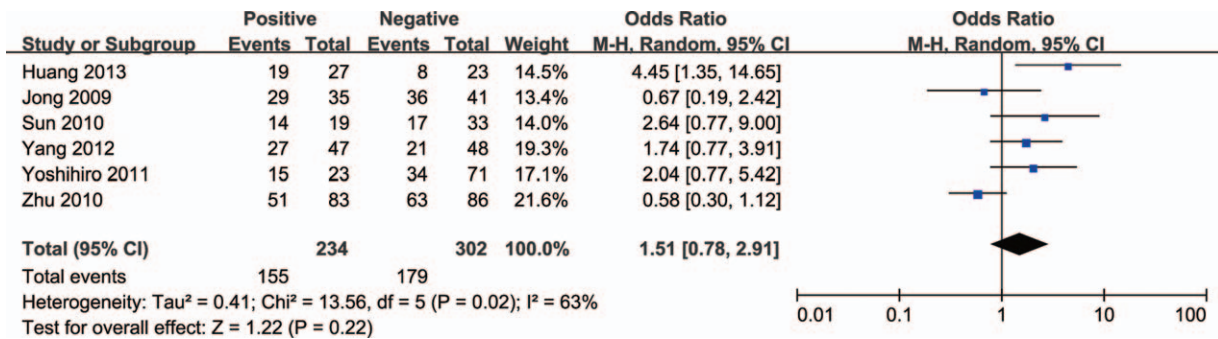


Figure 5. Forest plot of odds ratio (OR). Association between histone deacetylase 1 (HDAC1) expression and lymph node metastasis state in lung cancer. CI = confidence interval.

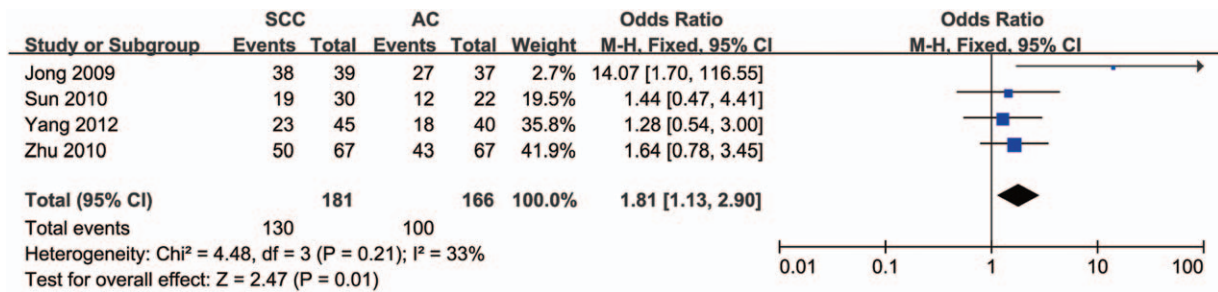


Figure 6. Forest plot of odds ratio (OR). Association between histone deacetylase 1 (HDAC1) expression and pathological subtypes of lung cancer. CI = confidence interval.

with 95% CI is shown in Figure 7 (HR=2.40, 95% CI= 1.48–3.88, P=.0004), indicating that patients with lung cancer with low HDAC1 mRNA or protein expression showed better OS than patients with high HDAC1 expression.

3.4. Publication bias

Most of the funnel plots were almost symmetric, suggesting that there were no significant publication biases in these meta-analyses (Supplemental Figures 1–6, <http://links.lww.com/MD/B818>).

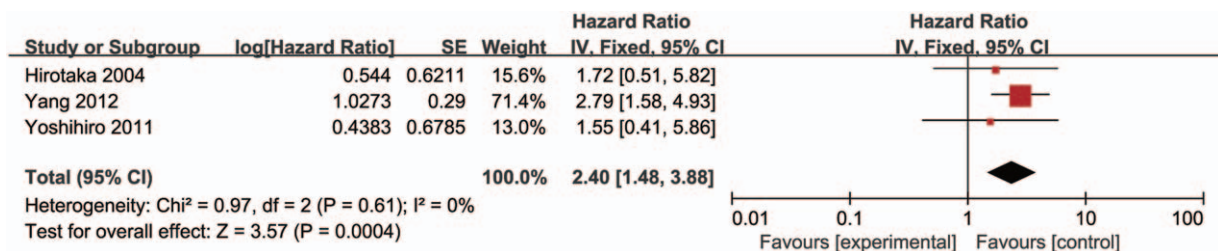


Figure 7. Forest plot of hazard ratio (HR). Association between histone deacetylase 1 (HDAC1) expression and the overall survival of lung cancer patients. CI = confidence interval.

Table 2**Newcastle-Ottawa Scale for each included study.**

Study	Selection	Comparability	Exposure	Total quality score
Yoshihiro, 2011	2	2	3	7
Hidefumi, 2004	2	2	2	6
Hirotsuka, 2004	2	1	3	6
Jong, 2009	2	2	3	7
Yang, 2012	3	2	3	8
Zhu, 2010	3	2	3	8
Sun, 2010	2	2	3	7
Huang 2013	3	2	3	8

3.5. Quality assessment

The NOS was used to assess the methodological quality of the included studies. This scale allocated a total of 9 points for the quality of selection (4 points), comparability (2 points), and exposure (3 points). The NOS scores ranged from 0 to 9, and a score of ≥ 6 indicates a good quality. As shown in Table 2, all the studies had high quality.

4. Discussion

In our study, a combined analysis of 8 eligible clinical studies revealed the clinical value of HDAC1 expression in lung cancer. The meta-analysis results suggested that there was a tight correlation between HDAC1 expression and the differentiation grade of lung cancer. In addition, we performed a meta-analysis to determine the difference in HDAC1 expression between squamous cell carcinoma and adenocarcinoma, and found that the expression level of HDAC1 in squamous cell carcinoma was higher than that in adenocarcinoma. Finally, we found that patients with lung cancer with low HDAC1 expression showed better OS than those with high HDAC1 expression.

HDAC1 expression has been reported to be associated with the progression and prognosis of some types of cancer. For example, 2 studies suggested that HDAC1 is overexpressed in gastric cancer, and HDAC1 overexpression is closely correlated with the tumor stage, differentiation grade, or lymph node metastasis state of gastric cancer.^[19,20] In addition, the expression level of HDAC1 in colorectal cancer tissues is also higher than that in noncancerous tissues, and the differences in HDAC1 expression in different tumor stages, differentiation grades, lymph node metastasis states, or distant metastasis states were observed as well.^[4,21–24] These studies indicate that HDAC1 might be useful for clinical cancer diagnosis. However, the correlation between HDAC1 expression and the progression of lung cancer was controversial. In this analysis, the correlation between HDAC1 expression and differentiation grade of lung cancer, and the difference between squamous cell carcinoma and adenocarcinoma were observed, indicating that HDAC1 might be a good biomarker to distinguish different differentiation grades and different pathological subtypes of lung cancer. Therefore, it would be beneficial for the clinical diagnosis of lung cancer. Although there were no correlations between HDAC1 expression and tumor size, tumor stage, or lymph node metastasis, more studies concerning the relationship between HDAC1 and clinical features of lung cancer are needed.

It has been demonstrated that HDAC1 expression was correlated with the OS of some types of cancer. For example, patients with gastric cancer with low HDAC1 expression showed better OS than those with high HDAC1 expression.^[19,25] In addition, there was a tight correlation between HDAC1

expression and OS of patients with pancreatic cancer.^[26] However, the correlation between HDAC1 expression and the prognosis of lung cancer was inconsistent in previous studies. In this analysis, we found that patients with lung cancer with low HDAC1 expression has better OS than those with high HDAC1 expression, indicating that HDAC1 might be a good prognostic marker for patients with lung cancer and could help screen out high-risk patients with lung cancer.

This study has several limitations. At first, the cut-off value to determine positive or negative expression of HDAC1 varied across the included studies. Secondly, the number of studies included for some analyses was insufficient, making the results less convincing. Finally, the cohorts included in this study were all from Asia, and regional bias existed. Therefore, the role of HDAC1 expression in lung cancer progression and prognosis warrants further study.

HDAC1 has been served as a target for cancer therapy, and some small molecule HDAC inhibitors have been used in clinical treatment of patients with several types of cancer, such as T-cell lymphoma and multiple myeloma.^[27] Consistent with this, the present analysis revealed the important clinical value of HDAC1 expression in lung cancer. In conclusion, HDAC1 expression might be a good biomarker for the diagnosis and prognosis of patients with lung cancer.

5. Conclusions

This meta-analysis suggests that the expression level of HDAC1 might be a high risk factor for lung cancer, especially in Asian populations. Further research needs to be conducted in the population of other regions.

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