Clinicopathological significance and potential drug targeting of CDH1 in lung cancer: a meta-analysis and literature review

Qiaowen Yu¹
Qisen Guo²
Liangan Chen³
Shuwei Liu¹

¹Shandong Provincial Key Laboratory of Mental Disorders, Research Center for Sectional and Imaging Anatomy, Shandong University School of Medicine, ²Respiratory Medicine, Shandong Cancer Hospital, Jinan, ³Department of Respiratory Diseases, People’s Liberation Army General Hospital, Beijing, People’s Republic of China

Background: CDH1 is a protein encoded by the CDH1 gene in humans. Mutations in this gene are linked with several types of cancer. Loss of CDH1 function contributes to the progression of cancer by increasing proliferation, invasion, and/or metastasis. However, the association between and clinicopathological significance of CDH1 promoter methylation and lung cancer remains unclear. In this study, we systematically reviewed the studies of CDH1 promoter methylation and lung cancer, and evaluated the association between CDH1 promoter methylation and lung cancer using meta-analysis methods.

Methods: A comprehensive search of the PubMed and Embase databases was performed up to July 2014. The methodological quality of the studies was also evaluated. The data were extracted and assessed by two reviewers independently. Analyses of pooled data were performed. Odds ratios (ORs) were calculated and summarized.

Results: Finally, an analysis of 866 patients with non-small cell lung cancer from 13 eligible studies was performed. The CDH1 methylation level in the cancer group was significantly higher than in the controls (OR 3.89, 95% confidence interval [CI] 2.87–5.27, \( P < 0.00001 \)). However, there were no correlations between CDH1 promoter methylation and clinicopathological characteristics (sex status, OR 0.78, 95% CI 0.41–1.50, \( P = 0.46 \); smoking history, OR 0.97, 95% CI 0.53–1.79, \( P = 0.93 \); pathological type, OR 0.97, 95% CI 0.59–1.60, \( P = 0.91 \); clinical staging, OR 1.48, 95% CI 0.81–2.68, \( P = 0.2 \); lymph node metastasis, OR 0.68, 95% CI 0.13–3.63, \( P = 0.65 \); or differentiation degree, OR 1.01, 95% CI 0.34–3.02, \( P = 0.99 \)).

Conclusion: The results of this meta-analysis suggest that CDH1 methylation is associated with an increased risk of lung cancer. CDH1 hypermethylation, which induces inactivation of the CDH1 gene, plays an important role in carcinogenesis and may serve as a potential drug target in lung cancer. However, CDH1 methylation does not correlate with other factors, such as smoking history, clinical stage, pathological type, sex status, lymph node metastasis, or degree of differentiation.

Keywords: CDH1, methylation, lung cancer, meta-analysis, tumor suppressor gene, odds ratio

Introduction
Lung cancer is a leading cause of cancer mortality in the USA and other developed countries.¹ The two major forms of the disease are non-small cell lung cancer and small cell lung cancer, which account for 85% and 15% of all lung cancers, respectively.² Despite advances in preliminary detection and standard treatment with combination chemotherapy and radiotherapy, the prognosis for patients with lung cancer has not improved significantly in the last 20 years,³,⁴ and survival rates have changed little over the past 2 decades. Currently, an enormous amount of research is aimed at understanding the molecular and cellular biology of lung cancer; however, much more
work is needed to better understand the correlation between gene regulation and lung cancer.

DNA methylation is an important epigenetic mechanism for gene silencing. Growing evidence shows that aberrant hypermethylation in 5′-CpG islands in the promoter regions is a major mechanism for silencing tumor suppressor or other cancer-associated genes in many kinds of human cancer.5–8 Loss of function in cancer suppressor genes may hinder inhibition of growth of cancer cells, which leads to malignant transcription and translation during replication of DNA. A number of genes, including the cyclin-dependent kinase inhibitor (p16), the tumor suppressor gene Ras association domain family protein 1A, Kelch-like ECH-associating protein 1, the DNA repair gene MGMT, and the cystic fibrosis transmembrane conductance regulator are demonstratively methylated in lung cancer.9–12 CDH1, a member of the transmembrane glycoprotein family, also known as cadherin-1, CAM 120/80, epithelial cadherin (E-cadherin), or uvomorulin, is encoded by the CDH1 gene (16q22.1).13 CDH1 is a calcium-dependent cell-cell adhesion glycoprotein containing three domains, ie, five extracellular cadherin repeats, a transmembrane region, and a highly conserved cytoplasmic tail.14 CDH1 as a tumor suppressor gene plays an essential role in maintaining cell adhesion and adherent junctions in normal tissues. CDH1 expression is frequently absent in a variety of epithelial tumors, and loss of normal intercellular junctions results in promotion of cancer invasion and metastasis and is correlated with several types of cancers.15–17 However, the association between and clinicopathological significance of CDH1 promoter hypermethylation and lung cancer remains unclear. In this study, we systematically investigate studies of CDH1 promoter hypermethylation and lung cancer, and validate the association between CDH1 promoter hypermethylation and lung cancer using meta-analysis methods. In addition, we summarize these findings and discuss tumor suppressor function, as well as the clinicopathological significance of CDH1 in lung cancer.

Materials and methods
Publication selection
A systematic literature searching was performed using PubMed, Embase, and the Web of Science up to August 13, 2014 without any language restrictions. The following keywords and terms were used: [methylation or DNA methylation or hypermethylation or de-methylation] and [CDH1 or cadherin-1 or CAM 120/80 or epithelial cadherin (E-cadherin) or uvomorulin] and [lung cancer or lung carcinoma or lung tumor]. References from these publications were manually searched to identify additional studies. The published scientific articles were restricted to English language, and conference abstracts were excluded due to lack of sufficient data. Titles, abstracts, and key words in the articles were initially evaluated for inclusion criteria. Details and additional information were identified and collected from the full text of these articles.

Inclusion and exclusion criteria
A study included for meta-analysis needed to have: evaluated the correlation between CDH1 methylation and lung cancer; included a clinical cohort and controls; included at least three patients and controls; used methylation-specific polymerase chain reaction or quantitative methylation-specific polymerase chain reaction to examine CDH1 methylation and expression; and used tissue data rather than blood data. Studies that did not meet our inclusion criteria were excluded. When the same groups of patients were reported in multiple papers, only the most recent and complete paper was selected to avoid overlap.

Data extraction and quality assessment
Two researchers independently collected the information and extracted the data regarding authorship, year, source of publication, inclusion criteria, CDH1 methylation frequency, sex status, smoking history, pathological type, clinical staging, degree of differentiation, lymph node metastasis, epidermal growth factor receptor status, and prognosis in patients and controls. Any discrepancy was resolved by discussion until agreement was reached. The data are summarized in Table 1 according to the criteria mentioned above. Methodological evaluation was assessed by the researchers according to the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) guidelines and ELCWP (European Lung Cancer Working Party) score.18,19

Data analysis
The meta-analysis was performed using Reviewer Manager 5 (Cochrane Collaboration, Oxford, UK). Pooled odds ratios (ORs) and confidence intervals (CIs) were calculated to assess the correlation between CDH1 methylation and lung cancer. Cochran’s Q test and I² were used to assess heterogeneity among the studies.20 A Q test showing P<0.05 or an F test >50% indicated significant heterogeneity and a fixed-effects model was used to calculate the parameters. Otherwise, a random-effects model was used to pool data and
Clinicopathological significance and drug targeting of CDH1 in lung cancer

The process followed to select the papers used in this report is shown in Figure 1. Ninety papers were identified by electronic database searching and 20 further papers by manual searching. Eighty-five papers were excluded for being duplicate publications, being an irrelevant title or abstract, or being a relevant title and abstract but not published in the English language. After retrieval of the full-text articles, eleven papers were excluded for not having a large enough study population or for being reviews. Thirteen further studies were screened out (involving 866 cases and 757 controls) based on the inclusion and exclusion criteria in the pooled analysis.

![Flow Diagram](image)

**Figure 1** Flow diagram of the literature search strategy and assessment of studies identified for meta-analysis.

**Table 1** Characteristics of the included studies

| Authors                  | Years | Samples | Sex status | Smoking history | Pathological types | Clinical staging |
|--------------------------|-------|---------|------------|-----------------|-------------------|------------------|
|                          |       |         | Cases      | Controls        | Squamous cell carcinomas | Adenocarcinomas |
|                          |       | Male    | Female     | Yes | No | I | II | III and IV |
| Zochbauer-Muller et al   | 2001  | 107     | 104        | 76 | 31 |   |    | 43 | 45 | 61 | 21 | 25 |
| Yanagawa et al           | 2003  | 75      | 75         | 54 | 21 |   |    | 20 | 55 | 29 |   | 43 |
| Russo et al              | 2005  | 49      | 49         |   |    |   |    | 22 | 5  |   |   | 24 |
| Tsou et al               | 2005  | 7       | 11         |   |    |   |    |    |    |   |   | 21 |
| Kim et al                | 2007  | 88      | 88         | 70 | 18 |   |    | 72 | 16 | 53 | 35 |   |
| Tan et al                | 2007  | 20      | 10         |   |    |   |    |    |    |   |   | 31 |
| Feng et al               | 2007  | 49      | 49         | 26 | 23 |   |    |    |    | 14 | 20 |   |
| Wang et al               | 2007  | 28      | 12         | 17 | 11 |   |    |    |    | 7  | 15 |   |
| Wang et al               | 2008  | 95      | 95         | 19 | 76 |   |    |    |    | 35 | 45 |   |
| Vaissiere et al          | 2009  | 209     | 164        | 171| 38 |   |    | 173| 36 | 121| 58 |   |
| Begum et al              | 2011  | 76      | 30         | 40 | 36 |   |    |    |    | 26 | 36 |   |
| Guzman et al             | 2012  | 26      | 33         | 26 | 33 |   |    |    |    | 25 | 7  |   |
| Zheng et al              | 2012  | 37      | 37         | 26 | 11 |   |    |    |    | 15 | 17 |   |

**Note:** “–” means data not available.
The characteristics of the studies are shown in Table 1.

Six papers were used to study the correlation between CDH1 methylation and sex status. Five papers provided smoking history data, allowing an investigation of the influence of smoking on CDH1 methylation. Six studies included pathological typing (squamous small carcinoma or adenocarcinoma). Three studies investigated the effect of clinical stage, ie, stage I, II, III, or IV. One paper discussed lymph node metastasis and another discussed degree of differentiation.

Analyzing tissue samples from 657 patients and 593 controls, the mean frequency of CDH1 methylation was 32% (range 8.33% to 66.32%) in tumor tissue and 9% (range 0.00%–27.78%) in tissue from controls. This result indicates that the occurrence of CDH1 methylation is higher in tumor tissue than in normal tissue. Using the fixed model, meta-analysis showed that 657 cases and 593 controls from 12 studies were pooled OR as shown in Figure 2 (OR 3.89, 95% CI 2.87–5.27, \( P < 0.00001 \)). These findings indicate that CDH1 methylation is a key molecular event in tumor tissue but not in normal tissue.

The results also show heterogeneity across the included studies (\( I^2 \) is 61%, ie, more than 50%). Given this significant heterogeneity, a subgroup analysis was performed to investigate sex status, smoking history, pathological type, clinical stage, differentiation degree, and lymph node metastasis to observe the relationship between CDH1 methylation and clinical characteristics (see Figure 3). However, there was no correlation between CDH1 promoter methylation and any of these factors (sex status, OR 0.78, 95% CI 0.41–1.50, \( P = 0.46 \); smoking history, OR 0.97, 95% CI 0.53–1.79, \( P = 0.93 \); pathological type, OR 0.97, 95% CI 0.59–1.60, \( P = 0.91 \); clinical stage, OR 1.48, 95% CI 0.81–2.68, \( P = 0.2 \); lymph node metastasis, OR 0.68, 95% CI 0.13–3.63, \( P = 0.65 \); and differentiation degree, OR 1.01, 95% CI 0.34–3.02, \( P = 0.99 \)).

The stability of the results was tested by sensitivity analysis. The OR ranged from 0.78 to 3.89, which was not a significant change, suggesting that the results of our meta-analysis were not significantly unstable. The funnel plot shown in Figure 4 is partially symmetric, indicating low publication bias regarding CDH1 methylation in lung cancer.

**Discussion**

DNA methylation is an important epigenetic mechanism for regulation of gene expression. An imbalance of gene methylation can cause a variety of human diseases. Hypermethylation of tumor suppressor genes and hypomethylation of oncogenes are two essential components of the molecular mechanism involved in the epigenomic regulation of initiation and progression of cancer. As a tumor suppressor gene, CDH1 maintains cell-cell adhesion and keeps epithelial cells arranged in normal arrangement and layer. In vitro studies demonstrate that loss of expression or function of CDH1 can activate transcription factors associated with epithelial-mesenchymal transition, leading to metastasis of cancer cells.\(^ {37} \) CDH1 methylation has been detected in several types of carcinoma, including breast cancer, gastric cancer, and lung cancer.\(^ {38}–\text{40} \) A comprehensive evaluation of markers of methylation in lung cancer is needed to better understand the relationship between CDH1 methylation and lung cancer. Although a large number of studies have demonstrated a possible relationship between

| Study or subgroup | Cases events | Total | Control events | Total | Weight | OR M–H, fixed, 95% CI | OR M–H, fixed, 95% CI |
|-------------------|--------------|-------|----------------|-------|--------|-----------------------|-----------------------|
| Begum et al\(^ {34} \) | 47 | 76 | 9 | 30 | 10.8% | 3.78 (1.53, 9.37) | 0.053 (0.15, 1.95) |
| Feng et al\(^ {36} \) | 4 | 49 | 7 | 49 | 14.1% | 1.22 (0.41, 3.65) | 8.59 (3.14, 23.44) |
| Guzman et al\(^ {35} \) | 9 | 26 | 10 | 33 | 12.6% | 2.01 (0.83, 4.87) | 0.1% (0.28, 117.65) |
| Kim et al\(^ {28} \) | 30 | 88 | 5 | 88 | 7.2% | 1.32 (0.12, 14.14) | 0.97 (0.53–1.79, \( P = 0.93 \)) |
| Russo et al\(^ {26} \) | 18 | 49 | 11 | 49 | 15.2% | 0.97 (0.59–1.60, \( P = 0.91 \)) | 48.97 (2.92, 821.28) |
| Tan et al\(^ {25} \) | 4 | 20 | 0 | 10 | 1.1% | 5.73 (0.83, 43.65) | 0.78 (0.41–1.50, \( P = 0.46 \)) |
| Tsou et al\(^ {27} \) | 2 | 7 | 0 | 11 | 0.6% | 10.45 (0.43, 256.96) | 0.97 (0.53–1.79, \( P = 0.93 \)) |
| Wang et al\(^ {21} \) | 3 | 28 | 1 | 12 | 2.7% | 1.32 (0.12, 14.14) | 0.97 (0.59–1.60, \( P = 0.91 \)) |
| Wang et al\(^ {22} \) | 63 | 95 | 23 | 95 | 17.0% | 6.16 (3.27, 11.61) | 0.97 (0.59–1.60, \( P = 0.91 \)) |
| Yangawata et al\(^ {25} \) | 22 | 75 | 11 | 75 | 17.0% | 2.42 (1.07, 5.43) | 0.97 (0.59–1.60, \( P = 0.91 \)) |
| Zheng et al\(^ {16} \) | 12 | 37 | 0 | 37 | 0.7% | 36.76 (2.08, 649.15) | 0.97 (0.59–1.60, \( P = 0.91 \)) |
| Zochbauer-Muller et al\(^ {24} \) | 20 | 107 | 0 | 104 | 0.9% | 48.97 (2.92, 821.28) | 0.97 (0.59–1.60, \( P = 0.91 \)) |

Total (95% CI) 657 593 100.0% 3.89 (2.87, 5.27)
Clinicopathological significance and drug targeting of CDH1 in lung cancer

Figure 3 (Continued)
CDH1 methylation and lung cancer, a meta-analysis can summarize the relevant studies and compare different subgroup characteristics.

In this meta-analysis, we mainly focus on the correlation between CDH1 methylation and lung cancer. We analyzed data from 13 studies that included 657 tumor tissue samples and 593 control samples. The results show that the CDH1 methylation level in the cancer group was significantly higher than in the control group. The pooled OR using the fixed-effect model was 3.89 (95% CI 2.87–5.27 versus the control group). CDH1 methylation plays a key role in the induction of lung cancer due to silencing of the tumor suppressor gene CDH1. This conclusion is consistent with that of a previous study.36 Since changes in CDH1 promoter hypermethylation are reversible, drug treatment promoting demethylation may be useful for delaying carcinogenesis and progression. Treatment with 5-aza-2′-deoxycytidine showed that migration of A549 cells decreased markedly upon restoration of CDH1.41 These preclinical studies show the therapeutic potential of restoration of tumor suppressor expression via...

![Table](image1.png)

**Figure 3** Clinicopathological significance of CDH1 hypermethylation rate in patients with lung cancer. Forest plots for the relationship between CDH1 methylation frequency and lung cancer. (A) Sex status, (B) smoking history, (C) pathological type, (D) clinical staging, (E) degree of differentiation, and (F) lymph node metastasis. **Abbreviations:** CI, confidence interval; M–H, Mantel–Haenszel; OR, odds ratio.

![Funnel plots](image2.png)

**Figure 4** Funnel plot analysis of CDH1 hypermethylation rate in patients with lung cancer. Funnel plot for assessment of publication bias in the meta-analysis. (A) Cases versus control, (B) sex status, (C) smoking history, (D) pathological type, (E) clinical staging, (F) degree of differentiation, and (G) lymph node metastasis, respectively. **Abbreviations:** OR, odds ratio; SE, standard error of the mean.
epigenetic modulation. This approach may bring hope for patients with cancer through gene-targeted therapy.

We further determined the clinicopathological significance of $CDH1$ promoter hypermethylation in patients with lung cancer. For smoking history, the summary OR was 0.97 (95% CI 0.53–1.79) in the 65 cases and 27 controls. The results show that methylation level of $CDH1$ is not associated with smoking history. Lung cancer is a complicated disease with different genetic and epigenetic profiling. Smoking is not the only risk factor for lung cancer. Smoking may target other specific genes for methylation or mutation, for example, methylenetetrahydrofolate reductase.33 Other subgroup meta-analysis was performed, including for sex status (OR 0.78, 95% CI 0.41–1.50), pathological type (OR 0.97, 95% CI 0.59–1.60), clinical stage (OR 1.48, 95% CI 0.81–2.68), lymph node metastasis (OR 0.68, 95% CI 0.13–3.63), and degree of differentiation (OR 1.01, 95% CI 0.34–3.02). $CDH1$ methylation determined by clinical staging shows a slightly more significant association than the other subgroups. Interestingly, $CDH1$ methylation was detected much more frequently in stages III and IV than in stages I and II. However, $CDH1$ methylation itself does not correlate with pathological type, sex status, lymph node metastasis, or degree of differentiation. Possible reasons for this finding might be the widely heterogeneous results for the subgroups or the lack of cases and controls in the subgroups. Other potentially significant factors may need to be investigated, such as patient age, tumor size, and biopsy sample control.42

Conclusion

$CDH1$ promoter methylation is associated with lung cancer based on this meta-analysis. $CDH1$ methylation might be a biomarker of lung cancer, with potential value in predicting the prognosis of the disease, and warrants further studies involving more clinical cases for meta-analysis in the future. In addition, the potential variables on $CDH1$ methylation from different group database are still not clear due to the limitation of the statistical power of meta-analysis.

Disclosure

The authors have no financial involvement with any organization or entity with a financial interest in the subject matter or materials discussed in this paper.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43–66.
2. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008;359:1367–1380.
3. Yanaihara N, Caplen N, Bowman E, et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell. 2006;9:189–198.
4. Aberle DR, Adams AM, Berg DR, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
5. Cho YH, Yazici H, Wu HC, et al. Aberrant promoter hypermethylation and genomic hypomethylation in tumor, adjacent normal tissues and blood from breast cancer patients. Anticancer Res. 2010;30:2489–2496.
6. Esteller M, Sanchez-Cespedes M, Rosell R, Sidransky D, Baylin SB, Herman JG. Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients. Cancer Res. 1999;59:67–70.
7. Herman JG, Baylin SB. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med. 2003;349:2042–2054.
8. Palmisano WA, Divine KK, Saccomanno G, et al. Predicting lung cancer by detecting aberrant promoter methylation in sputum. Cancer Res. 2000;60:5954–5958.
9. Guo D, Wu B, Yan J, Li X, Sun H, Zhou D. A possible gene silencing mechanism: hypermethylation of the Kcpla1 promoter abrogates binding of the transcription factor Sp1 in lung cancer cells. Biochem Biophys Res Commun. 2012;428:80–85.
10. Kurzawa E, Shimamoto T, Utsumi K, Hirano T, Kato H, Ohyashiki K. Hypermethylation of p16 (INK4a) and p15 (INK4b) genes in non-small cell lung cancer. Int J Oncol. 2001;19:277–281.
11. Gao T, Wang S, He B, et al. The association of RAS association domain family Protein1A (RASSF1A) methylation states and bladder cancer risk: a systematic review and meta-analysis. PLoS One. 2012;7:e48300.
12. Son JW, Kim YJ, Cho HM, et al. Promoter hypermethylation of the CFTR gene and clinical/pathological features associated with non-small cell lung cancer. Respirolgy. 2011;16:1203–1209.
13. Bussemakers MJ, van Bokhoven A, Mee S, Kemler R, Schalken JA. Molecular cloning and characterization of the human E-cadherin cDNA. Mol Biol Rep. 1993;17:123–128.
14. Takeichi M. Cadherins: a molecular family important in selective cell–cell adhesion. Annu Rev Biochem. 1990;59:237–252.
15. Karayiannakis AJ, Syrigos KN, Chatzigianni E, et al. Aberrant E-cadherin expression associated with loss of differentiation and advanced stage in human pancreatic cancer. Anticancer Res. 1998;18:4177–4180.
16. Zheng Z, Pan J, Chu B, Wong YC, Cheung AL, Tsoa SW. Down-regulation and abnormal expression of E-cadherin and beta-catenin in nasopharyngeal carcinoma: close association with advanced disease stage and lymph node metastasis. Hum Pathol. 1999;30:458–466.
17. Oka H, Shiozaki H, Kobayashi K, et al. Expression of E-cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis. Cancer Res. 1993;53:1696–1701.
18. Altman DG, McMahan L, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. BMC Med. 2012;10:51.
19. Sculier JP, Ghisdal L, Berghmans T, et al. The role of mitomycin in the treatment of non-small cell lung cancer: a systematic review with meta-analysis of the literature. Br J Cancer. 2001;84:1150–1153.
20. Shao D, He S. [Meta-analysis of clinical randomized controlled trials comparing refractive with diffractive multifocal intraocular lenses in cataract surgery]. Zhonghua Yan Ke Za Zhi. 2014;50:109–120. Chinese.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–560.
22. DerSimonian R. Meta-analysis in the design and monitoring of clinical trials. Stat Med. 1996;15:1237–1248.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088–1101.
24. Zochbauer-Muller S, Fong KM, Virmani AK, Geradts J, Gazdar AF, Minna JD. Aberrant promoter methylation of multiple genes in non-small cell lung cancers. Cancer Res. 2001;61:249–255.
Yanagawa N, Tamura G, Oizumi H, Takahashi N, Shimazaki Y, Motoyama T. Promoter hypermethylation of tumor suppressor and tumor-related genes in non-small cell lung cancers. Cancer Sci. 2003;94:589–592.

Russo AL, Thiagalingam A, Pan H, et al. Differential DNA hypermethylation of critical genes mediates the stage-specific tobacco smoke-induced neoplastic progression of lung cancer. Clin Cancer Res. 2005;11:2466–2470.

Tsou JA, Shen L, Siegmund KD, et al. Distinct DNA methylation profiles in malignant mesothelioma, lung adenocarcinoma, and non-tumor lung. Lung Cancer. 2005;47:193–204.

Kim DS, Kim MJ, Lee JY, Kim YZ, Kim EJ, Park JY. Aberrant methylation of E-cadherin and H-cadherin genes in nonsmall cell lung cancer and its relation to clinicopathologic features. Cancer. 2007;110:2785–2792.

Tan SH, Ida H, Lau QC, et al. Detection of promoter hypermethylation in serum samples of cancer patients by methylation-specific polymerase chain reaction for tumour suppressor genes including RUNX3. Oncol Rep. 2007;18:1225–1230.

Feng Q, Hawes SE, Stern JE, et al. DNA methylation in tumor and matched normal tissues from non-small cell lung cancer patients. Cancer Epidemiol Biomarkers Prev. 2008;17:645–654.

Wang G, Hu X, Lu C, Su C, Luo S, Luo ZW. Promoter-hypermethylation associated defective expression of E-cadherin in primary non-small cell lung cancer. Lung Cancer. 2008;62:162–172.

Wang Y, Zhang D, Zheng W, Luo J, Bai Y, Lu Z. Multiple gene methylation of nonsmall cell lung cancers evaluated with 3-dimensional microarray. Cancer. 2008;112:1325–1336.

Vaissiere T, Hung RJ, Zaridze D, et al. Quantitative analysis of DNA methylation profiles in lung cancer identifies aberrant DNA methylation of specific genes and its association with gender and cancer risk factors. Cancer Res. 2009;69:243–252.

Begum S, Braut M, Dasgupta S, et al. An epigenetic marker panel for detection of lung cancer using cell-free serum DNA. Clin Cancer Res. 2011;17:4494–4503.

Guzman L, Depix MS, Salinas AM, et al. Analysis of aberrant methylation on promoter sequences of tumor suppressor genes and total DNA in sputum samples: a promising tool for early detection of COPD and lung cancer in smokers. Diagn Pathol. 2012;7:87.

Zheng SY, Hou JY, Zhao J, Jiang D, Ge JF, Chen S. Clinical outcomes of downregulation of E-cadherin gene expression in non-small cell lung cancer. Asian Pac J Cancer Prev. 2012;13:1557–1561.

Machado JC, Oliveira C, Carvalho R, et al. E-cadherin gene (CDH1) promoter methylation as the second hit in sporadic diffuse gastric carcinoma. Oncogene. 2001;20:1525–1528.

Su CY, Li YS, Han Y, Zhou SJ, Liu ZD. Correlation between expression of cell adhesion molecules CD44 v6 and E-cadherin and lymphatic metastasis in non-small cell lung cancer. Asian Pac J Cancer Prev. 2014;15:2221–2224.

Ponce E, Louie MC, Sevigny MB. Acute and chronic cadmium exposure promotes E-cadherin degradation in MCF7 breast cancer cells. Mol Carcinog. May 5, 2014. [Epub ahead of print].

Schildberg CW, Abba M, Merkel S, et al. Gastric cancer patients less than 50 years of age exhibit significant downregulation of E-cadherin and CDX2 compared to older reference populations. Adv Med Sci. 2014;59:142–146.

Liu YY, Han JY, Lin SC, Liu ZY, Jiang WT. Effect of CDH1 gene methylation on transforming growth factor (TGF-beta)-induced epithelial-mesenchymal transition in alveolar epithelial cell line A549. Genet Mol Res. 2014;13:8568–8576.

Waki T, Tamura G, Sato M, Motoyama T. Age-related methylation of tumor suppressor and tumor-related genes: an analysis of autopsy samples. Oncogene. 2003;22:4128–4133.