Clinicopathological significance of DAPK promoter methylation in non-small-cell lung cancer: a systematic review and meta-analysis

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Background: Lung carcinogenesis is related to silencing of tumor suppressor genes and activation of oncogenes. The aim was to investigate the significance of death-associated protein kinase (DAPK) methylation in non-small-cell lung cancer (NSCLC) through a meta-analysis.

Methods: A detailed literature search was made in PubMed, Embase, and Web of Science databases. All analysis was performed with Review Manager 5.2.

Results: In total, 28 studies with a total of 2,148 patients were involved. The frequency of DAPK promoter hypermethylation was 40.50% in NSCLC, significantly higher than in non-malignant lung tissue; the pooled OR was 5.69, P<0.00001. Additionally, DAPK promoter hypermethylation was significantly correlated with poor overall survival in patients with NSCLC. However, there was no significant difference found while comparing the rate of DAPK promoter hypermethylation in adenocarcinoma and squamous cell cancer. The rate of DAPK promoter hypermethylation was similar between stage III/IV and stage I/II. In addition, the data showed that DAPK promoter hypermethylation was not associated with smoking behavior in patients with NSCLC.

Conclusion: DAPK promoter hypermethylation is correlated with risk of NSCLC and is a potential biomarker for prediction of poor prognosis in patients with NSCLC.

Keywords: DAPK, NSCLC, biomarker, methylation, adenocarcinoma, squamous cell cancer, drug target

Background

Lung cancer is the second most commonly diagnosed malignancy in men and the third most commonly diagnosed malignancy in women worldwide.1 Lung cancer can be classified into two major histological groups: small cell lung cancer and non-small-cell lung cancer (NSCLC). NSCLC accounts for more than 80% of all lung cancers, whereas 15%–20% is small cell lung cancer.2,3 NSCLC includes adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large-cell carcinoma, within them, ADC accounts for 40%, SCC for 25%–30%, and large-cell carcinoma for 10%–15%.4,5 Lung carcinogenesis is related to silencing of tumor suppressor genes and activation of oncogenes. Accumulating data indicate that hypermethylation in CpG-rich promoter regions of many suppressor genes can contribute to the development and progression of a variety of cancers.6,7

Deiss and Kimchi discovered a large group of new genes by using “technical knock-out (TKO) and rescue” screen.8 Those genes function as positive mediators...
of cell death pathways, therefore they were named “Death-
Associated Protein or DAP genes.” One of the genes isolated
by the TKO approach encoded a calcium calmodulin regu-
lated serine/threonine kinase and was named DAP kinase
(DAPk1 or DAPK). Further investigation indicated that
DAPK plays an important role in apoptotic and autophagic
cell death, tumor progression suppression, and metastasis
suppression. Last two decades, a number of studies
showed that DAPK loss by its promoter hypermethylation
was associated with the development and progression of
NSCLC. However, the results from individual studies were
inconsistent due to small size of samples. In the present study,
28 relevant studies were pooled, and a meta-analysis was
performed to evaluate the clinicopathological significance
of DAPK promoter hypermethylation in NSCLC.

Methods

Search strategy and selection criteria

The following electronic databases were screened for rele-
vant articles without any language restrictions: PubMed
We used the following keywords: “DAPK methylation”,
“NSCLC”, “Non-small-cell lung cancer”, and “lung cancer”.
A search of PubMed yielded 65 articles, Embase yielded
101, and Web Science yielded 138 articles. The included
criteria were as follows: (1) the association between DAPK
methylation and the clinicopathological significance of
NSCLC; (2) the association of DAPK and prognosis in
patients with NSCLC. After screening by titles and abstracts,
38 relevant articles were included for full text review.
The following exclusion criteria were used: (1) the same
population or overlapping database; (2) conference abstracts
containing insufficient data reviews, editorials, letters, case
reports, and expert opinion; (3) the studies utilized cell lines.
After evaluation, 28 articles fulfilled the entry criteria of
this meta-analysis. The detailed information of 28 relevant
articles was listed in Table 1.

Data extraction and study assessment

Two reviewers (YZ and JW) extracted data from selected
studies independently by using a standardized data extraction
form including the following items: first author’s name, year
of publication, country, number of patients, histology, stage
of NSCLC, smoking status of patients with NSCLC, method
for methylation detection. Any disagreement was discussed
and reached a consensus for all issues.

Statistical analysis

ORs with 95% confidence intervals (CIs) were calculated by
using a fixed or random effect model depending on heteroge-

enity (a fixed effect model for F<50%, a random effect model
for F>50%). The analysis was performed to compare DAPK
promoter hypermethylation between NSCLC and normal
tissue, DAPK promoter hypermethylation in different stage
of NSCLC, DAPK promoter hypermethylation in different histology
type of NSCLC, as well as in smoker and non-smoker patients with NSCLC. All P-values were two sided.
P-value less than 0.05 was considered statistically significant.
Funnel plots were used for detection of publication bias. All
analysis was performed with Review Manager 5.2.

Results

In total, 28 studies were included in the present study after
screening 304 articles by two reviewers (Figure 1). The fol-
lowing items were collected from each study: first author,
published year, country, histology of NSCLC, and DAPK
hypermethylation status, smoking status as well as patient
prognosis (Table 1).

The total number of NSCLC tumor from 28 studies is
2148, 870 of them were with DAPK promoter hypermeth-
ylated, the rate was 40.50%. Whereas the promoter hyper-
methylation rate from individual study ranged from 10.99%
to 83.13% (Table 1). The frequency of DAPK promoter
hypermethylation was significantly higher in NSCLC than
in non-malignant lung; and the pooled OR was 5.69 with
95% CI 3.44–9.39, Z=6.79, P<0.00001 (Figure 2). DAPK
promoter methylation was similar between SCC and ADC;
the pooled OR was 1.30 with 95% CI 0.96–1.74, Z=1.71,
P=0.09, F=0% (Figure 3). In addition, DAPK methylation
was not significantly correlated with stages of NSCLC; OR
was 0.78 with 95% CI 0.54–1.13, Z=1.29, P=0.20, F=0% (Figure 4).
The rate of DAPK methylation was not associ-
ated with smoking behavior in patients with NSCLC; OR
was 1.11 with 95% CI 0.80–1.54, Z=0.62, P=0.53, F=18% (Figure 5). However, DAPK promoter hypermethylation
was significantly associated with poor prognosis in patients
with NSCLC; HR was 1.25 with 95% CI 1.06–1.46, Z=2.68,
P=0.007, F=0% (Figure 6).

The quality of each study was assessed using the New-
castle Ottawa Quality Assessment Scale (NOQAS). This
scale for non-randomized case controlled studies and cohort
studies was used to allocate a maximum of nine points for the
quality of selection, comparability, exposure, and outcomes
for study participants. Of the studies, 15 scored eight points,
11 scored seven points, and two scored six points (data not shown). Hence, the studies were of a relatively high quality. A sensitivity analysis, in which one study was removed at a time, was conducted to assess the result stability. The pooled ORs were not significantly changed, indicating the stability of our analyses (data not shown). The funnel plots were largely symmetric (Figure 7), suggesting there were no publication biases in the meta-analysis of DAPK promoter hypermethylation and clinicopathological features.

**Discussion**

Aberrant methylation in tumor suppressor genes has been linked to carcinogenesis. Hypermethylation is the predominant mechanism to make tumor suppressor genes silent by promoter inactivation. DAPK gene is located on chromosome 9q34.1. It encodes a proapoptotic protein involved in apoptosis initiated by THN-α, IFN-γ, Fas, and TRAIL. DAPK promoter methylation has been observed in about 30 types of tumor including NSCLC. Moreover, aggressiveness of malignant tumors has been associated with the methylation of the promoter region of the DAPK gene and loss of DAPK expression. A number of studies evaluated the methylation rate in NSCLC, which ranged from 10.99% to 83.33% due to small size of samples. We pooled 28 studies including 2,148 NSCLC patients, 870 of them were with DAPK gene promoter hypermethylated; one in non-malignant lung tissue. Therefore, DAPK hypermethylation rate was 40.50%, 5.69 times higher than the normal control tissue.

**Table 1 Main characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Sample size (M/T)</th>
<th>DAPK methylation rate (%)</th>
<th>Histology</th>
<th>Stage (TNM)</th>
<th>Smoking status</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali et al</td>
<td>2017</td>
<td>India</td>
<td>133/160</td>
<td>83.13</td>
<td>49/70</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jin et al</td>
<td>2016</td>
<td>China</td>
<td>120/199</td>
<td>60.30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Guo et al</td>
<td>2015</td>
<td>China</td>
<td>35/202</td>
<td>17.33</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kontic et al</td>
<td>2012</td>
<td>Serbia</td>
<td>11/47</td>
<td>23.40</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fuji et al</td>
<td>2011</td>
<td>Japan</td>
<td>6/46</td>
<td>13.04</td>
<td>0/25</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>2011</td>
<td>China</td>
<td>120/200</td>
<td>61.00</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>2010</td>
<td>China</td>
<td>11/78</td>
<td>14.10</td>
<td>3/78</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jin et al</td>
<td>2010</td>
<td>China</td>
<td>88/150</td>
<td>58.67</td>
<td>15/150</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Peng et al</td>
<td>2010</td>
<td>China</td>
<td>48/82</td>
<td>58.54</td>
<td>0/25</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Niklinska et al</td>
<td>2009</td>
<td>Japan</td>
<td>22/61</td>
<td>36.07</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Han et al</td>
<td>2009</td>
<td>USA</td>
<td>8/14</td>
<td>57.14</td>
<td>4/20</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lichesi et al</td>
<td>2008</td>
<td>USA</td>
<td>7/19</td>
<td>36.8</td>
<td>0/46</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Katayama et al</td>
<td>2007</td>
<td>Japan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Liu et al</td>
<td>2007</td>
<td>China</td>
<td>40/122</td>
<td>32.79</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Belinsky et al</td>
<td>2007</td>
<td>USA</td>
<td>22/72</td>
<td>30.56</td>
<td>5/25</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Fischer et al</td>
<td>2007</td>
<td>Germany</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kim et al</td>
<td>2005a</td>
<td>Korea</td>
<td>23/72</td>
<td>31.94</td>
<td>4/72</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>de Fraipont et al</td>
<td>2005</td>
<td>France</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Safar et al</td>
<td>2005</td>
<td>USA</td>
<td>12/32</td>
<td>37.50</td>
<td>6/32</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Russo et al</td>
<td>2005</td>
<td>USA</td>
<td>22/49</td>
<td>44.90</td>
<td>1/27</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kim et al</td>
<td>2005b</td>
<td>Korea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fujiwara et al</td>
<td>2005</td>
<td>Japan</td>
<td>10/91</td>
<td>10.99</td>
<td>5/100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Divine et al</td>
<td>2005</td>
<td>USA</td>
<td>72/206</td>
<td>34.95</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lu et al</td>
<td>2004</td>
<td>USA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Toyooka et al</td>
<td>2003</td>
<td>USA</td>
<td>14/38</td>
<td>36.8</td>
<td>1/15</td>
<td>8/20</td>
<td>6/18</td>
<td>–</td>
</tr>
<tr>
<td>Soria et al</td>
<td>2002</td>
<td>USA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zöchbauer-Müller et al</td>
<td>2001</td>
<td>Australia</td>
<td>20/107</td>
<td>18.69</td>
<td>6/104</td>
<td>7/45</td>
<td>9/43</td>
<td>–</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADC, adenocarcinoma; COBRA, combined bisulfite restriction analysis; DAPK, death-associated protein kinase; M, number of NSCLC with methylation; MSP, methylation-specific PCR; NCT, normal control tissue; NSCLC, non-small-cell lung cancer; SCC, squamous cell cancer; T, total number of NSCLC.
Figure 2 Forest plot for DAPK promoter hypermethylation in NSCLC and non-malignant lung tissue.

Notes: The squares represent the weight of individual study in the meta-analysis, the line width indicates the corresponding 95% CI, the diamond represents the pooled OR, and the width of diamond indicates 95% CI.

Abbreviations: DAPK, death-associated protein kinase; M–H, Mantel–Haenszel; NSCLC, non-small-cell lung cancer.
Clinicopathological significance of DAPK promoter methylation in NSCLC

Figure 4 Forest plot for DAPK promoter hypermethylation in NSCLC stage III/IV and stage I/II.

Notes: The squares represent the weight of individual study in the meta-analysis, the line width indicates the corresponding 95% CI, the diamond represents the pooled OR, and the width of diamond indicates 95% CI.

Abbreviations: DAPK, death-associated protein kinase; M–H, Mantel–Haenszel; NSCLC, non-small-cell lung cancer.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Stage III–IV Events Total</th>
<th>Stage I–II Events Total</th>
<th>Weight</th>
<th>OR M–H, fixed, 95% CI</th>
<th>OR M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo 2015</td>
<td>20</td>
<td>91</td>
<td>13.8%</td>
<td>1.80 (0.86, 3.77)</td>
<td>1.80 (0.86, 3.77)</td>
</tr>
<tr>
<td>Jin 2016</td>
<td>65</td>
<td>104</td>
<td>28.2%</td>
<td>1.21 (0.69, 2.14)</td>
<td>1.21 (0.69, 2.14)</td>
</tr>
<tr>
<td>Kim 2005b</td>
<td>7</td>
<td>17</td>
<td>5.8%</td>
<td>1.56 (0.49, 5.01)</td>
<td>1.56 (0.49, 5.01)</td>
</tr>
<tr>
<td>Kontic 2012</td>
<td>7</td>
<td>29</td>
<td>4.9%</td>
<td>1.11 (0.27, 4.51)</td>
<td>1.11 (0.27, 4.51)</td>
</tr>
<tr>
<td>Liu 2007</td>
<td>15</td>
<td>50</td>
<td>18.8%</td>
<td>0.81 (0.37, 1.75)</td>
<td>0.81 (0.37, 1.75)</td>
</tr>
<tr>
<td>Niklinska 2009</td>
<td>17</td>
<td>41</td>
<td>5.1%</td>
<td>2.13 (0.65, 6.97)</td>
<td>2.13 (0.65, 6.97)</td>
</tr>
<tr>
<td>Toyooka 2003</td>
<td>6</td>
<td>18</td>
<td>6.6%</td>
<td>0.75 (0.20, 2.83)</td>
<td>0.75 (0.20, 2.83)</td>
</tr>
<tr>
<td>Yanagawa 2007</td>
<td>12</td>
<td>39</td>
<td>9.8%</td>
<td>1.52 (0.62, 3.76)</td>
<td>1.52 (0.62, 3.76)</td>
</tr>
<tr>
<td>Zöchbauer-Müller 2001</td>
<td>9</td>
<td>43</td>
<td>7.1%</td>
<td>1.44 (0.48, 4.28)</td>
<td>1.44 (0.48, 4.28)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.30 (0.96, 1.74)</td>
<td>1.30 (0.96, 1.74)</td>
</tr>
<tr>
<td>Total events</td>
<td>158</td>
<td>146</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=3.89, df=8 (P=0.87); I²=0%
Test for overall effect: Z=1.71 (P=0.09)

Figure 5 Forest plot for DAPK promoter hypermethylation in NSCLC patients with smoking and non-smoking behavior.

Notes: The squares represent the weight of individual study in the meta-analysis, the line width indicates the corresponding 95% CI, the diamond represents the pooled OR, and the width of diamond indicates 95% CI.

Abbreviations: NSCLC, non-small-cell lung cancer.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Smoking Events Total</th>
<th>Non smoking Events Total</th>
<th>Weight</th>
<th>OR M–H, fixed, 95% CI</th>
<th>OR M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Fraipont 2005</td>
<td>18</td>
<td>121</td>
<td>2.4%</td>
<td>0.52 (0.05, 5.32)</td>
<td>0.52 (0.05, 5.32)</td>
</tr>
<tr>
<td>Divine 2005</td>
<td>16</td>
<td>45</td>
<td>22.4%</td>
<td>0.98 (0.48, 2.00)</td>
<td>0.98 (0.48, 2.00)</td>
</tr>
<tr>
<td>Fujiwara 2005</td>
<td>9</td>
<td>43</td>
<td>12.3%</td>
<td>0.74 (0.26, 2.08)</td>
<td>0.74 (0.26, 2.08)</td>
</tr>
<tr>
<td>Jin 2016</td>
<td>94</td>
<td>145</td>
<td>19.5%</td>
<td>1.98 (1.05, 3.74)</td>
<td>1.98 (1.05, 3.74)</td>
</tr>
<tr>
<td>Kontic 2012</td>
<td>1</td>
<td>11</td>
<td>4.8%</td>
<td>0.30 (0.03, 2.62)</td>
<td>0.30 (0.03, 2.62)</td>
</tr>
<tr>
<td>Liu 2007</td>
<td>28</td>
<td>81</td>
<td>15.2%</td>
<td>1.28 (0.57, 2.88)</td>
<td>1.28 (0.57, 2.88)</td>
</tr>
<tr>
<td>Soria 2002</td>
<td>13</td>
<td>89</td>
<td>8.9%</td>
<td>0.30 (0.08, 1.17)</td>
<td>0.30 (0.08, 1.17)</td>
</tr>
<tr>
<td>Yanagawa 2007</td>
<td>20</td>
<td>73</td>
<td>9.2%</td>
<td>1.38 (0.49, 3.91)</td>
<td>1.38 (0.49, 3.91)</td>
</tr>
<tr>
<td>Zöchbauer-Müller 2001</td>
<td>18</td>
<td>98</td>
<td>4.4%</td>
<td>0.79 (0.15, 4.11)</td>
<td>0.79 (0.15, 4.11)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>706</td>
<td>354</td>
<td>100.0%</td>
<td>1.11 (0.80, 1.54)</td>
<td>1.11 (0.80, 1.54)</td>
</tr>
<tr>
<td>Total events</td>
<td>217</td>
<td>117</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=9.75, df=8 (P=0.28); I²=18%
Test for overall effect: Z=0.62 (P=0.53)

Abbreviations: M–H, Mantel–Haenszel; NSCLC, non-small-cell lung cancer.
and stage. Although TNM staging system still remained the most powerful tool for medical decision making, it is difficult to accurately predict the prognosis for individual patient. The 5-year survival rate for patients with stage I NSCLC is about 65%–80%, therefore a more accurate tool, independent from TNM stage, is very important to predict prognosis in those patients. Our finding indicated that DAPK was correlated to worse survival in our meta-analysis, supporting the importance of epigenetic gene regulation in NSCLC progression and prognosis. Loss of apoptotic functions would compromise cell death induced by unrepaired DNA damage. In addition, DAPK
promoter hypermethylation is associated with metastatic status. Taken together, DAPK promoter hypermethylation leads to worse prognosis in patients with NSCLC. DAPK hypermethylation is a potential predictor of survival in patients with NSCLC.

Given the important role of smoking in the development of lung cancer and the fact that DNA methylation is an early event in carcinogenesis, several biomarker such as Wnt inhibitory factor-1 (Wif1), Phosphatase and tensin homologue deleted on chromosome 10 (PTEN), and TP53 were associated with smoking behavior. However, no correlation was found between DAPK promoter hypermethylation and the smoking behavior in the present study. Further confirmation needs to be finished in future when more relative studies are available.

Our findings should be interpreted in view of certain limitations. First, most of the included studies were retrospective, 26 out of 28 were of sufficient quality (NOQAS ≥ 7). Hence, the studies were of a relatively high quality. Although the possibility of selection, sample, and publication bias could not be excluded, no obvious bias was detected by the funnel plots. Second, present findings were based on individual unadjusted ORs and further confirmation needs to be finished by evaluation adjusted with other potential risk factors.

**Conclusion**

In summary, present findings suggested that DAPK promoter hypermethylation was correlated with the risk of NSCLC; and DAPK is a promising drug target for development of new therapy strategy. Additionally, DAPK promoter hypermethylation was a potential predictor of poor prognosis in patients with NSCLC.

**Data sharing statement**

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

**Author contributions**

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. The corresponding author had full access to all data and the final responsibility for the decision to submit the article for publication. All authors read and approved the final manuscript.

**Disclosure**

The authors report no conflicts of interest in this work.
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