Differential prognostic values of mRNA expression of CEACAM gene family members in nonsmall cell lung cancer

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Abstract: Serum carcinoembryonic antigen (CEA) is widely used as a representative marker of various malignant tumors. CEA-related cell adhesion molecules (CEACAMs), including CEACAM5, are encoded in the human genome by 12 independent genes and can be potential targets for future cancer treatments. In nonsmall cell lung cancer, serum CEA levels have been reported to predict patient survival. However, associations between mRNA expression of CEACAM gene family members in tumor tissues and patient prognosis remain unclear. To clarify this point, we used the Kaplan–Meier plotter global portal site, which collects the results of Affymetrix gene expression microarray analyses from the publicly accessible Gene Expression Omnibus database and combined it with survival data of patients. A total of 1,926 nonsmall cell lung cancer patients were identified from the Gene Expression Omnibus series, Cancer Biomedical Informatics Grid, and The Cancer Genome Atlas databases. We found statistically significant associations between mRNA expression of several CEACAMs and overall survival (OS) in patients with nonsmall cell lung cancer and lung adenocarcinoma (n=720) but not squamous cell carcinoma (n=524). In adenocarcinoma, higher expression levels of CEACAM6 and CEACAM8 were significantly associated with better OS, whereas higher expression levels of CEACAM3, CEACAM4, CEACAM19, and CEACAM21 were associated with worse OS. Conflicting results among multiple probe sets for the same gene were found for CEACAM1, CEACAM5, and CEACAM7. The findings of this study indicated that CEACAMs play important roles in tumor progression and impact OS of patients with adenocarcinoma. As the impact on OS differed based on the gene family members or the probe set used, the individual CEACAMs seem to function through complicated mechanisms. Further studies are necessary to resolve the problems encountered in our present study.

Keywords: mRNA, microarray, survival, nonsmall cell lung cancer, CEACAM, CEA

Introduction
Approximately 50 years ago, carcinoembryonic antigen (CEA) was identified as an oncofetal antigen in colorectal cancer in addition to normal human fetal organs, including the gut, liver, and pancreas. Further studies revealed the presence of CEA and numerous CEA cross-reacting antigens in human sera, normal tissues, and various cancers other than colorectal cancer.2-5 A family of CEA-related cell adhesion molecules (CEACAMs), including CEACAM5, is known to be encoded in the human genome by 12 independent genes on chromosome 19q13.2,6,7 These CEACAM proteins belong to the immunoglobulin supergene family, and the molecules contain one or two variable-like domains with or without constant 2-like domains.2 CEA is widely used as a representative serum tumor marker of various malignant tumors and elevated serum
CEA levels are reported to be frequently associated with a poor clinical outcome in cancer patients presumably through a variety of mechanisms, including the promotion of invasion, dissemination, metastasis, and immune suppression. Serum CEA concentrations are increased in both nonsmall cell lung cancer (NSCLC) and small cell lung cancer.\(^8\)\(^{-10}\) In NSCLC, elevated serum CEA levels have been reported to be associated with histological types, advanced disease stages, and worse prognoses.\(^5\)\(^{11\text{-}15}\) More recently, vaccination therapy, antibody therapy, and small interfering RNA therapy targeting CEACAMs have been developed as new therapies for several solid tumors, including lung cancer.\(^16\)\(^{-22}\) Thus, CEA and related molecules are important not only for diagnoses but also for future therapeutic targets in various malignant tumors.\(^23\)

In spite of many reports regarding associations of serum CEA levels and prognosis of NSCLC, information about mRNA expression in tumor tissues and its relationship to patient survival is quite limited. Thus, we studied associations between mRNA expression detected by gene expression microarrays and overall survival (OS) in NSCLC patients by accessing an online public database.\(^24\)\(^{25}\) To the best of our knowledge, this is the first report focusing on associations between mRNA expression of the CEACAM gene family members and OS in NSCLC patients.

### Materials and methods


### Results

Differences in OS between groups with higher and lower expression levels of the investigated CEACAM genes are shown according to histological types: NSCLC, adenocarcinoma (AD), and squamous cell carcinoma (SQ; Table 3). Expression of most CEACAM family members was significantly associated with OS in patients with NSCLC (n=1,926). Similar results were obtained for patients with AD (n=720). In contrast, none of the examined CEACAM gene family members were associated with OS in patients with SQ (n=524), suggesting

<p>| Table 1 Datasets of nonsmall cell lung cancer included in the analysis |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Dataset</th>
<th>Platform</th>
<th>Sample Size</th>
<th>M</th>
<th>F</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSE4573</td>
<td>GPL96</td>
<td>130</td>
<td>82</td>
<td>48</td>
<td>I/II/III/IV</td>
</tr>
<tr>
<td>GSE14814</td>
<td>GPL96</td>
<td>89</td>
<td>66</td>
<td>23</td>
<td>I/II/III/IV</td>
</tr>
<tr>
<td>GSE19188</td>
<td>GPL570</td>
<td>83</td>
<td>59</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>GSE3141</td>
<td>GPL570</td>
<td>111</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>GSE31210</td>
<td>GPL570</td>
<td>226</td>
<td>105</td>
<td>121</td>
<td>16/58/0/0</td>
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<tr>
<td>caArray</td>
<td>GPL96</td>
<td>468</td>
<td>240</td>
<td>228</td>
<td>NA</td>
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<td>TCGA</td>
<td>GPL3921</td>
<td>74</td>
<td>49</td>
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<td>GSE29013</td>
<td>GPL570</td>
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<td>24/14/17/0</td>
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<td>GSE37745</td>
<td>GPL570</td>
<td>196</td>
<td>107</td>
<td>89</td>
<td>130/35/27/4</td>
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<tr>
<td>GSE30219</td>
<td>GPL570</td>
<td>293</td>
<td>252</td>
<td>41</td>
<td>NA</td>
</tr>
<tr>
<td>GSE31908</td>
<td>GPL96</td>
<td>20</td>
<td>4</td>
<td>16</td>
<td>10/5/3/0</td>
</tr>
<tr>
<td>GSE50081</td>
<td>GPL570</td>
<td>181</td>
<td>98</td>
<td>83</td>
<td>127/54/0/0</td>
</tr>
<tr>
<td>Total</td>
<td>1,926</td>
<td>1,100</td>
<td>715</td>
<td>652/320/70/4</td>
<td>720/524</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD, adenocarcinoma; F, females; M, males; NA, not applicable; SQ, squamous cell carcinoma.
that the significant differences in OS among NSCLC patients were mainly due to OS differences in AD patients.

The prognostic value of mRNA expression of CEACAM genes in AD tissues according to the individual probe sets of the microarrays are summarized in Table 4. Higher expression of CEACAM6 and CEACAM8 was associated with better OS, whereas higher expression of CEACAM3, CEACAM4, CEACAM19, and CEACAM21 was associated with worse OS. Conflicting results among multiple probe sets for the same gene were found in CEACAM1, CEACAM5, and CEACAM7.

Table 2 Full-length structure, number of splice variants, and function of the CEACAM family members

<table>
<thead>
<tr>
<th>CEACAM family members</th>
<th>N-domain</th>
<th>C2-like Ig domain</th>
<th>Membrane anchorages</th>
<th>Splice variants</th>
<th>Known or speculated functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEACAM1</td>
<td>I</td>
<td>3</td>
<td>Transmembrane</td>
<td>13</td>
<td>CEACAM1-L/CEACAM-S ratio may be associated with metastasis and shorter survival in several malignant tumors</td>
</tr>
<tr>
<td>CEACAM3</td>
<td>I</td>
<td>0</td>
<td>Transmembrane</td>
<td>7</td>
<td>Phagocytosis of specific bacterial pathogens</td>
</tr>
<tr>
<td>CEACAM4</td>
<td>I</td>
<td>0</td>
<td>Transmembrane</td>
<td>2</td>
<td>Phagocytosis of specific bacterial pathogens, expressed in medullary thyroid carcinoma cells</td>
</tr>
<tr>
<td>CEACAM5</td>
<td>I</td>
<td>6</td>
<td>GPI-linkage</td>
<td>9</td>
<td>Connecting adjacent epithelial cell membranes in both embryonic intestine and colon cancer, inhibition of differentiation, suppression of tumor immunity</td>
</tr>
<tr>
<td>CEACAM6</td>
<td>I</td>
<td>2</td>
<td>GPI-linkage</td>
<td>1</td>
<td>Tamoxifen resistance in breast cancer, inhibition of differentiation in colon cancer</td>
</tr>
<tr>
<td>CEACAM7</td>
<td>I</td>
<td>1</td>
<td>GPI-linkage</td>
<td>3</td>
<td>Downregulated in colon cancer, lower expression may be predictive of rectal cancer recurrence</td>
</tr>
<tr>
<td>CEACAM8</td>
<td>I</td>
<td>2</td>
<td>GPI-linkage</td>
<td>2</td>
<td>Myelofibrotic transformation, released from human granulocyte</td>
</tr>
<tr>
<td>CEACAM16</td>
<td>2</td>
<td>2</td>
<td>Free</td>
<td>1</td>
<td>Hearing in the inner ear</td>
</tr>
<tr>
<td>CEACAM18</td>
<td>I</td>
<td>2</td>
<td>Transmembrane</td>
<td>0</td>
<td>No information</td>
</tr>
<tr>
<td>CEACAM19</td>
<td>I</td>
<td>2</td>
<td>Transmembrane</td>
<td>8</td>
<td>Progression of breast cancer</td>
</tr>
<tr>
<td>CEACAM20</td>
<td>I</td>
<td>6</td>
<td>Transmembrane</td>
<td>5</td>
<td>Downregulated in prostate cancer, tubule formation</td>
</tr>
<tr>
<td>CEACAM21</td>
<td>I</td>
<td>1</td>
<td>Transmembrane</td>
<td>6</td>
<td>Candidate gene for schizophrenia</td>
</tr>
</tbody>
</table>

Note: *Number of variants were obtained from Ensemble (http://asia.ensembl.org/index.html).

Abbreviations: CEA, carcinoembryonic antigen; CEACAM, CEA-related cell adhesion molecule; Ig, immunoglobulin; GPI, glycosylphosphatidylinositol.

Table 3 Overall survival differences in patients with nonsmall cell lung cancer based on mRNA expression of the CEACAM gene family members

<table>
<thead>
<tr>
<th>CEACAM family</th>
<th>Probes</th>
<th>Affymetrix ID</th>
<th>NSCLC (n=1,926) HR (95% CI) high expression</th>
<th>p-Value</th>
<th>AD (n=720) HR (95% CI) high expression</th>
<th>p-Value</th>
<th>SQ (n=524) HR (95% CI) high expression</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEACAM1</td>
<td>209498_at</td>
<td>0.67 (0.59–0.76)</td>
<td>&lt;0.0001</td>
<td>0.78 (0.62–0.98)</td>
<td>0.034</td>
<td>0.94 (0.74–1.19)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>206576_s_at</td>
<td>0.99 (0.87–1.12)</td>
<td>0.83</td>
<td>1.35 (1.07–1.7)</td>
<td>0.011</td>
<td>0.95 (0.75–1.2)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>210610_at</td>
<td>0.84 (0.74–0.93)</td>
<td>0.007</td>
<td>0.76 (0.6–0.97)</td>
<td>0.024</td>
<td>0.94 (0.74–1.19)</td>
<td>0.58</td>
<td></td>
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<tr>
<td></td>
<td>211883_x_at</td>
<td>0.92 (0.82–1.05)</td>
<td>0.23</td>
<td>1.09 (0.87–1.38)</td>
<td>0.44</td>
<td>0.97 (0.76–1.22)</td>
<td>0.78</td>
<td></td>
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<tr>
<td></td>
<td>211889_x_at</td>
<td>0.92 (0.82–1.05)</td>
<td>0.23</td>
<td>1.27 (1.0–1.6)</td>
<td>0.042</td>
<td>0.95 (0.75–1.2)</td>
<td>0.65</td>
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</tr>
<tr>
<td>CEACAM3</td>
<td>208052_x_at</td>
<td>1.29 (1.14–1.47)</td>
<td>&lt;0.0001</td>
<td>1.66 (1.32–2.1)</td>
<td>&lt;0.0001</td>
<td>1.07 (0.84–1.36)</td>
<td>0.59</td>
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<tr>
<td></td>
<td>210789_x_at</td>
<td>1.23 (1.09–1.4)</td>
<td>0.0012</td>
<td>1.46 (1.16–1.84)</td>
<td>0.0014</td>
<td>1.09 (0.86–1.38)</td>
<td>0.49</td>
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<tr>
<td></td>
<td>217209_at</td>
<td>1.14 (1–1.29)</td>
<td>0.047</td>
<td>1.54 (1.22–1.95)</td>
<td>0.00026</td>
<td>1.03 (0.81–1.31)</td>
<td>0.8</td>
<td></td>
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<tr>
<td>CEACAM4</td>
<td>207205_at</td>
<td>1.24 (1.09–1.4)</td>
<td>0.001</td>
<td>1.65 (1.31–2.09)</td>
<td>&lt;0.0001</td>
<td>1.02 (0.8–1.3)</td>
<td>0.87</td>
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<tr>
<td>CEACAM5</td>
<td>201884_at</td>
<td>0.98 (0.87–1.11)</td>
<td>0.77</td>
<td>1.04 (0.82–1.31)</td>
<td>0.77</td>
<td>0.88 (0.69–1.11)</td>
<td>0.28</td>
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<tr>
<td></td>
<td>217291_at</td>
<td>1.27 (1.12–1.44)</td>
<td>0.000022</td>
<td>1.45 (1.15–1.83)</td>
<td>0.0019</td>
<td>1.21 (0.96–1.54)</td>
<td>0.11</td>
<td></td>
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<tr>
<td>CEACAM6</td>
<td>211657_at</td>
<td>0.7 (0.62–0.79)</td>
<td>&lt;0.0001</td>
<td>0.68 (0.54–0.85)</td>
<td>0.00097</td>
<td>0.97 (0.77–1.23)</td>
<td>0.83</td>
<td></td>
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<tr>
<td></td>
<td>203757_s_at</td>
<td>0.67 (0.59–0.77)</td>
<td>&lt;0.0001</td>
<td>0.66 (0.52–0.83)</td>
<td>0.00039</td>
<td>1.06 (0.83–1.34)</td>
<td>0.66</td>
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</tr>
<tr>
<td>CEACAM7</td>
<td>206198_s_at</td>
<td>1.1 (0.97–1.25)</td>
<td>0.14</td>
<td>1.33 (1.06–1.68)</td>
<td>0.015</td>
<td>0.93 (0.74–1.18)</td>
<td>0.57</td>
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<tr>
<td></td>
<td>206199_at</td>
<td>1.16 (1.02–1.31)</td>
<td>0.025</td>
<td>1.03 (0.81–1.3)</td>
<td>0.81</td>
<td>1.06 (0.84–1.35)</td>
<td>0.62</td>
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<tr>
<td></td>
<td>211848_s_at</td>
<td>0.99 (0.87–1.12)</td>
<td>0.84</td>
<td>1.12 (0.89–1.41)</td>
<td>0.34</td>
<td>0.92 (0.73–1.17)</td>
<td>0.52</td>
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</tr>
<tr>
<td>CEACAM8</td>
<td>206676_at</td>
<td>0.77 (0.67–0.87)</td>
<td>&lt;0.0001</td>
<td>0.71 (0.56–0.9)</td>
<td>0.0038</td>
<td>0.82 (0.65–1.04)</td>
<td>0.11</td>
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<tr>
<td>CEACAM9</td>
<td>230504_at</td>
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<td>0.0043</td>
<td>1.6 (1.25–2.05)</td>
<td>0.00017</td>
<td>0.99 (0.73–1.35)</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>CEACAM21</td>
<td>214907_at</td>
<td>1.11 (0.98–1.26)</td>
<td>0.097</td>
<td>1.6 (1.27–2.02)</td>
<td>&lt;0.0001</td>
<td>1 (0.79–1.27)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>216605_at</td>
<td>1.07 (0.94–1.21)</td>
<td>0.3</td>
<td>1.4 (1.11–1.77)</td>
<td>0.0047</td>
<td>0.97 (0.77–1.23)</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Jetset probe. Statistically significant p-values are indicated in bold.

Abbreviations: AD, adenocarcinoma; CEACAM, carcinoembryonic antigen-related cell adhesion molecule; CI, confidence interval; HR, hazard ratio; NSCLC, nonsmall cell lung cancer; SQ, squamous cell carcinoma.
Kaplan–Meier plots of OS using the Jetset probes for individual genes are shown in Figures 1–9. Because the online database listed no Jetset probe for CEACAM3, 208052_x_at was used as a representative probe for this gene to construct the OS curves.

**Discussion**

Quantification of serum CEA in lung cancer patients is widely performed to arrive at a diagnosis, evaluate tumor responses to various therapeutic modalities, and predict risks of postsurgical recurrences. However, evidence of prognostic values in lung cancer patients remains unclear. Because of this, there are no official guidelines or recommendations for the use of CEA as a prognostic indicator of lung cancer.

According to a recent review article regarding the prognostic significance of CEA in lung cancer, 18 studies reported statistically significant evidence for the use of CEA as a prognostic indicator of lung cancer.

**Table 4**

<table>
<thead>
<tr>
<th>CEACAM Family</th>
<th>Better OS</th>
<th>Worse OS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEACAM1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEACAM3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEACAM4</td>
<td></td>
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<td></td>
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<tr>
<td>CEACAM5</td>
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<td></td>
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<tr>
<td>CEACAM6</td>
<td></td>
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<td></td>
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<tr>
<td>CEACAM7</td>
<td></td>
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<td></td>
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<tr>
<td>CEACAM8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEACAM19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEACAM21</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: aJetset probe.

Abbreviations: CEACAM, carcinoembryonic antigen-related cell adhesion molecule; OS, overall survival; NS, no significant difference in OS.
A prognostic marker in NSCLC patients, while seven studies showed negative results. Among the 25 studies included in this review article, only one examined the relationship between immunohistochemical CEA expression in tumor tissues and prognoses of patients but found no association. A meta-analysis of 16 studies (4,296 NSCLC patients) reported that preoperative high serum CEA levels were associated with poor OS with a combined hazard ratio of 2.28. This meta-analysis concluded that preoperative serum CEA levels can predict OS in patients with NSCLC, although high heterogeneity between included studies and publication biases should be taken into consideration.

Little is known about the functions of CEACAMs, particularly impacts on lung cancer tumorigenesis and...
and CEACAM6, lead to undifferentiated cell growth and
CEACAM1-4S and other CEACAMs, such as CEACAM5
Disturbances in CEACAM1-4L signaling in A549 cells by
28
inhibited cell growth, and tumor suppressive functions.42
reported to play a critical role in differentiation, contact-
sion of CEACAM1-4L in A549 human lung AD cells is
investigated in several tumors. For instance, surface expres-
sion of CEACAM1, CEACAM5, and CEACAM6 have been
development. However, the functions and prognostic values
of CEACAM1, CEACAM5, and CEACAM6 have been
investigated in several tumors. For instance, surface expres-
sion of CEACAM1-4L in A549 human lung AD cells is
reported to play a critical role in differentiation, contact-
hindered cell growth, and tumor suppressive functions.42
Disturbances in CEACAM1-4L signaling in A549 cells by
CEACAM1-4S and other CEACAMs, such as CEACAM5
and CEACAM6, lead to undifferentiated cell growth and
malignant transformation. In contrast, multiple clinical
studies reported that CEACAM1 overexpression was associ-
ated with worse prognosis in melanoma,31 gastric cancer,44
thyroid cancer,45 and NSCLC,46 suggesting that CEACAM1
contributes to tumor progression. Thus, there are discrep-
ancies concerning the functions of CEACAM1 among
these studies. In colorectal cancer, immunohistochemi-
cally detected CEACAM6 overexpression in tumor tissues
independently predicted poor OS and shortened disease-
free survival, whereas CEACAM1 and CEACAM5 were
not significantly related to these outcomes.37 In epidermal
growth factor receptor mutation-negative lung AD patients,
a immunohistochemical study of tumor tissues revealed that
CEACAM6 expression was associated with worse prognoses,
whereas CEACAM3 expression was associated with better
prognoses.49 These studies indicated that CEACAM6 over-
expression was a worse prognostic factor for selected lung
cancer patients.

In the present study, none of the CEACAM gene family
members were predictive of OS in patients with SQ. The most
apparent result in this study is that CEACAM expression in
lung SQ is not useful to predict OS. In contrast, statistically
significant differences in OS were confirmed in NSCLC and
AD. Since NSCLC is mainly composed of AD and SQ, differ-
ces in OS among NSCLC patients are mostly a reflection
of OS differences in AD patients.

Associations with worse OS in patients with AD were
confirmed by higher mRNA expression of CEACAM3,
CEACAM4, CEACAM19, and CEACAM21, while
CEACAM6 and CEACAM8 were associated with better OS.
Since CEACAM6 overexpression is reportedly associated
with worse prognosis of various cancers,47–51 the results of
the present study are unique and should be confirmed in further
studies. We found no reports examining serum concentration
or expression levels of the other CEACAMs and associated
impacts on survival of cancer patients.

For some CEACAM gene family members, conflicting
results were obtained because of the use of unique probes for
each gene. This is not surprising because a given gene may
be detected by multiple probe sets on an Affymetrix micro-
array, which can result in inconsistent or even contradictory
findings. The cross-reactivity of probes to other genes and
multiple transcripts produced by alternative splicing events
are plausible reasons. In order to create simple one-to-one
mapping between genes and probe sets, a scoring system
using a specific algorithm was proposed for Jetset probes
as the most reliable, and these probes are identified on the
Kaplan–Meier plotter webpage.38 The most conflicting results
were found for the CEACAM1 probe sets. Because CEACAM1 has 13 splice variants and each may have a different function in lung cancer progression, different prognostic significance might be due to the different specificity of the probe set relative with the different variants. Jetset probe 209498_at for CEACAM1 indicated better OS. Similarly, conflicting results were found in CEACAM5 and CEACAM7. No differences in OS based on mRNA expression were found for Jetset probe sets 201884_at for CEACAM5 and 206199_at for CEACAM7.

Since there is quite limited information concerning the relationships between overexpressed CEACAMs in tumor tissues and survival of lung cancer patients, data mining using an accessible public database is both reasonable and useful. A major limitation to this study was the limited clinical information of individual patients, thus it was difficult to perform subgroup analyses. However, the total number of included patients was sufficient to obtain reliable results, if interpreted cautiously.

In conclusion, we found statistically significant associations between mRNA expression of CEACAMs and OS of NSCLC patients. These close associations were confirmed in lung cancer patients, thus it was difficult to perform subgroup analyses. However, the total number of included patients was sufficient to obtain reliable results, if interpreted cautiously.

Disclosure

The authors report no conflicts of interest in this work.

References


