

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.¹ 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

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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.² 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.^{8,11–15} 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

Gene Expression Omnibus (GEO; www.ncbi.nlm.nih.gov/geo/) is a public functional genomics data repository supported by the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). Based on the GEO database for NSCLC, the Kaplan–Meier plotter global portal site (<http://kmplot.com/analysis/index.php?p=service&cancer=lung>) provides combined data of mRNA expression of independent genes on gene expression microarrays and survival data of patients with NSCLC.²⁴ Microarray platforms in the provided database were Affymetrix HG-U133A (GPL96), HG-U133 Plus 2.0 (GPL570), and HG-U133A 2.0 (GPL3921). These microarrays have 22,277 probe sets in common.²⁴ A total of 1,926 NSCLC patients were identified from the GEO series, Cancer Biomedical Informatics Grid (<https://github.com/NCIP/caarray>; caArray project), and The Cancer Genome Atlas (<http://cancergenome.nih.gov>) database. The data sets used in the present study are shown in Table 1.^{26–37} Characteristics of the *CEACAM* gene family members are listed in Table 2.^{2,6,7} Associations between mRNA expression profiles of nine *CEACAM* genes (*CEACAM1*, *CEACAM3*,

Table 1 Datasets of nonsmall cell lung cancer included in the analysis

Dataset	Platform	Sample size	M	F	Stage I/II/III/IV	Histology AD/SQ
GSE4573	GPL96	130	82	48	73/34/23/0	0/130
GSE14814	GPL96	89	66	23	45/44/0/0	27/52
GSE19188	GPL570	83	59	24	NA	41/24
GSE3141	GPL570	111	NA	NA	NA	58/53
GSE31210	GPL570	226	105	121	168/58/0/0	226/0
caArray	GPL96	468	240	228	NA	NA
TCGA	GPL3921	74	49	25	NA	0/71
GSE29013	GPL570	55	38	17	24/14/17/0	30/25
GSE37745	GPL570	196	107	89	130/35/27/4	106/66
GSE30219	GPL570	293	252	41	NA	85/61
GSE31908	GPL96	20	4	16	10/5/3/0	20/0
GSE50081	GPL570	181	98	83	127/54/0/0	127/42
Total		1,926	1,100	715	652/320/70/4	720/524

Abbreviations: AD, adenocarcinoma; F, females; M, males; NA, not applicable; SQ, squamous cell carcinoma.

CEACAM4, *CEACAM5*, *CEACAM6*, *CEACAM7*, *CEACAM8*, *CEACAM19*, and *CEACAM21*) in tumor tissues and OS of NSCLC patients were studied. Among the *CEACAM* genes, three (*CEACAM16*, *CEACAM18*, and *CEACAM20*) were not included in the studied microarrays.

On the Affymetrix gene expression microarrays, six *CEACAM* genes were detected by multiple different probe sets: five probes for *CEACAM1*, three for *CEACAM3* and *CEACAM7*, and two for *CEACAM5*, *CEACAM6*, and *CEACAM21*. A single reliable probe set matching each of the examined genes was determined by assessing specificity, splice isoform coverage, and robustness against transcript degradation. These selected probes are marked as Jetset probes³⁸ on the webpage.

The OS rates of two groups of patients subdivided by the median value of mRNA expression were calculated, and Kaplan–Meier survival plots were obtained from the webpage. Simultaneously, the hazard ratio of the higher expression group relative to the lower expression group, 95% confidence intervals, and log-rank *p*-values were automatically calculated on the same webpage.

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

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

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

Note: ^aNumber 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

CEACAM family	Probes Affymetrix ID	NSCLC (n=1,926) HR (95% CI) high expression	p-Value	AD (n=720) HR (95% CI) high expression	p-Value	SQ (n=524) HR (95% CI) high expression	p-Value
CEACAM1	209498_at ^a	0.67 (0.59–0.76)	<0.0001	0.78 (0.62–0.98)	0.034	0.94 (0.74–1.19)	0.61
	206576_s_at	0.99 (0.87–1.12)	0.83	1.35 (1.07–1.7)	0.011	0.95 (0.75–1.2)	0.66
	210610_at	0.84 (0.74–0.95)	0.007	0.76 (0.6–0.97)	0.024	0.94 (0.74–1.19)	0.58
	211883_x_at	0.92 (0.82–1.05)	0.23	1.09 (0.87–1.38)	0.44	0.97 (0.76–1.22)	0.78
	211889_x_at	0.92 (0.82–1.05)	0.23	1.27 (1.01–1.6)	0.042	0.95 (0.75–1.2)	0.65
CEACAM3	208052_x_at	1.29 (1.14–1.47)	<0.0001	1.66 (1.32–2.1)	<0.0001	1.07 (0.84–1.36)	0.59
	210789_x_at	1.23 (1.09–1.4)	0.0012	1.46 (1.16–1.84)	0.0014	1.09 (0.86–1.38)	0.49
	217209_at	1.14 (1–1.29)	0.047	1.54 (1.22–1.95)	0.00026	1.03 (0.81–1.31)	0.8
CEACAM4	207205_at ^a	1.24 (1.09–1.4)	0.001	1.65 (1.31–2.09)	<0.0001	1.02 (0.8–1.3)	0.87
CEACAM5	201884_at ^a	0.98 (0.87–1.11)	0.77	1.04 (0.82–1.31)	0.77	0.88 (0.69–1.11)	0.28
	217291_at	1.27 (1.12–1.44)	0.00022	1.45 (1.15–1.83)	0.0019	1.21 (0.96–1.54)	0.11
CEACAM6	211657_at ^a	0.7 (0.62–0.79)	<0.0001	0.68 (0.54–0.85)	0.00097	0.97 (0.77–1.23)	0.83
	203757_s_at	0.67 (0.59–0.77)	<0.0001	0.66 (0.52–0.83)	0.00039	1.06 (0.83–1.34)	0.66
CEACAM7	206198_s_at	1.1 (0.97–1.25)	0.14	1.33 (1.06–1.68)	0.015	0.93 (0.74–1.18)	0.57
	206199_at ^a	1.16 (1.02–1.31)	0.025	1.03 (0.81–1.3)	0.81	1.06 (0.84–1.35)	0.62
	211848_s_at	0.99 (0.87–1.12)	0.84	1.12 (0.89–1.41)	0.34	0.92 (0.73–1.17)	0.52
CEACAM8	206676_at ^a	0.77 (0.67–0.87)	<0.0001	0.71 (0.56–0.9)	0.0038	0.82 (0.65–1.04)	0.11
CEACAM19	230504_at ^a	1.27 (1.08–1.5)	0.0043	1.6 (1.25–2.05)	0.00017	0.99 (0.73–1.35)	0.97
CEACAM21	214907_at ^a	1.11 (0.98–1.26)	0.097	1.6 (1.27–2.02)	<0.0001	1 (0.79–1.27)	0.99
	216605_at	1.07 (0.94–1.21)	0.3	1.4 (1.11–1.77)	0.0047	0.97 (0.77–1.23)	0.81

Notes: ^aJetset 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.

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 4 Prognostic significance of higher mRNA expression of the CEACAM gene family members in lung adenocarcinoma based on individual probes

CEACAM family	Better OS	Worse OS	NS
CEACAM1	209498_at ^a 210610_at	206576_s_at 211889_x_at	211883_x_at
CEACAM3		208052_x_at 210789_x_at 217209_at	
CEACAM4		207205_at ^a	
CEACAM5		217291_at	201884_at ^a
CEACAM6	211657_at ^a 203757_s_at		
CEACAM7		206198_s_at	206199_at ^a 211848_s_at
CEACAM8	206676_at ^a		
CEACAM19		230504_at ^a	
CEACAM21		214907_at ^a 216605_at	

Note: ^aJetset probe.

Abbreviations: CEACAM, carcinoembryonic antigen-related cell adhesion molecule; OS, overall survival; NS, no significant difference in OS.

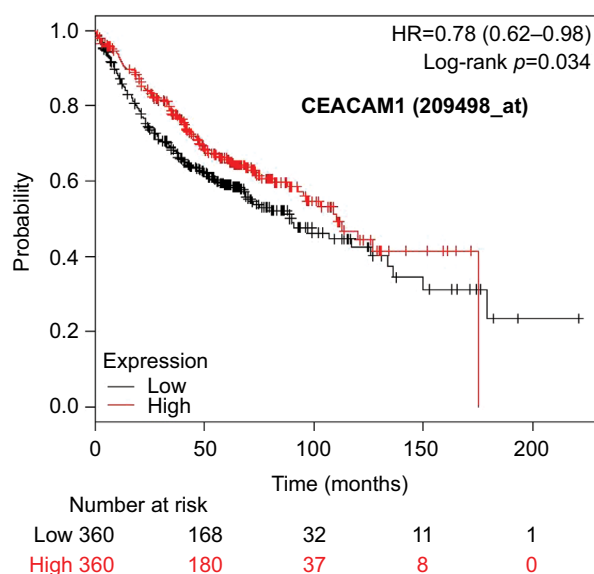


Figure 1 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM1* (Jetset probe, 209498_at) in patients with adenocarcinoma.

Note: Overall survival was better in the higher expression group ($p=0.034$).

Abbreviation: HR, hazard ratio.

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

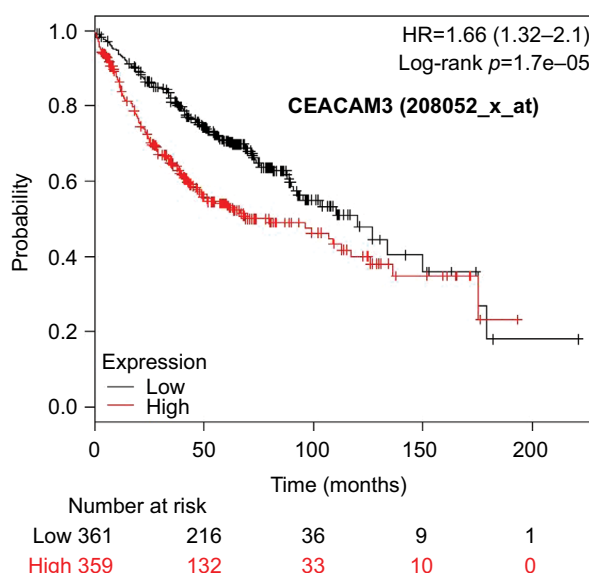


Figure 2 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM3* (probe, 208052_x_at) in patients with adenocarcinoma.

Note: Overall survival was worse in the higher expression group ($p<0.0001$).

Abbreviation: HR, hazard ratio.

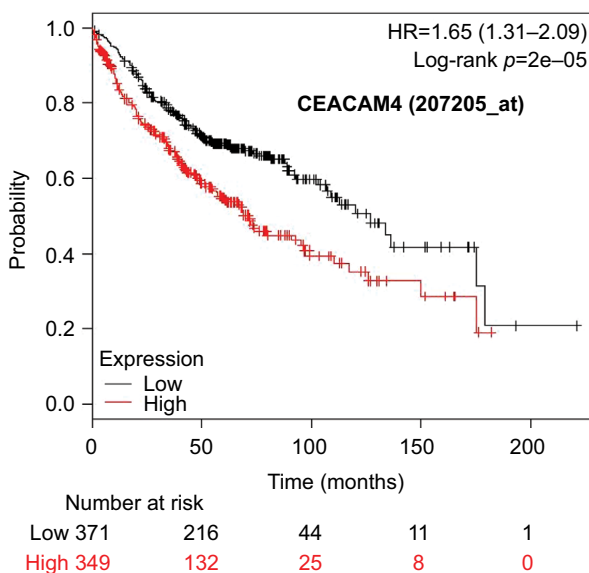


Figure 3 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM4* (Jetset probe, 207205_at) in patients with adenocarcinoma.

Note: Overall survival was worse in the higher expression group ($p<0.0001$).

Abbreviation: HR, hazard ratio.

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

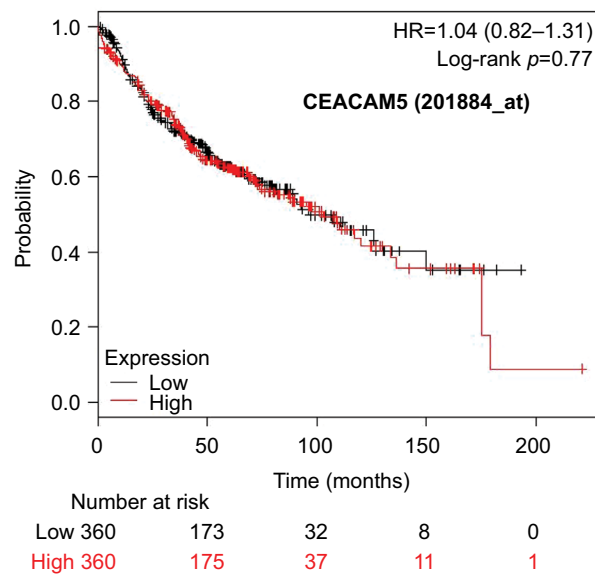


Figure 4 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM5* (Jetset probe, 201884_at) in patients with adenocarcinoma.

Note: There was no significant difference in overall survival between the two groups ($p=0.77$).

Abbreviation: HR, hazard ratio.

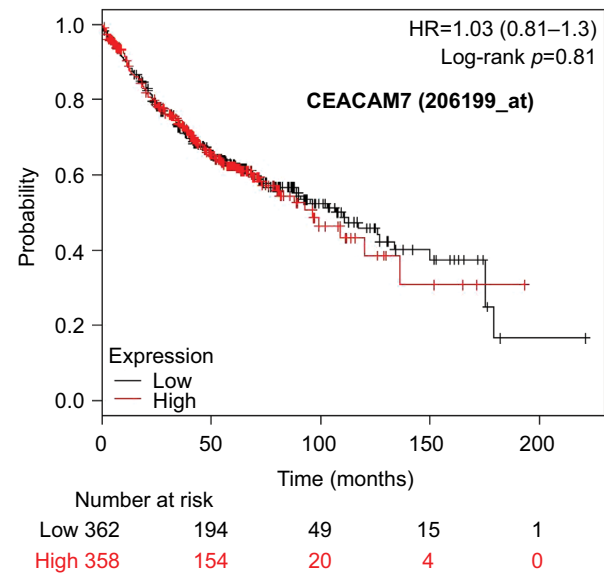


Figure 6 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM7* (Jetset probe, 206199_at) in patients with adenocarcinoma.

Note: There was no significant difference in overall survival between the two groups ($p=0.81$).

Abbreviation: HR, hazard ratio.

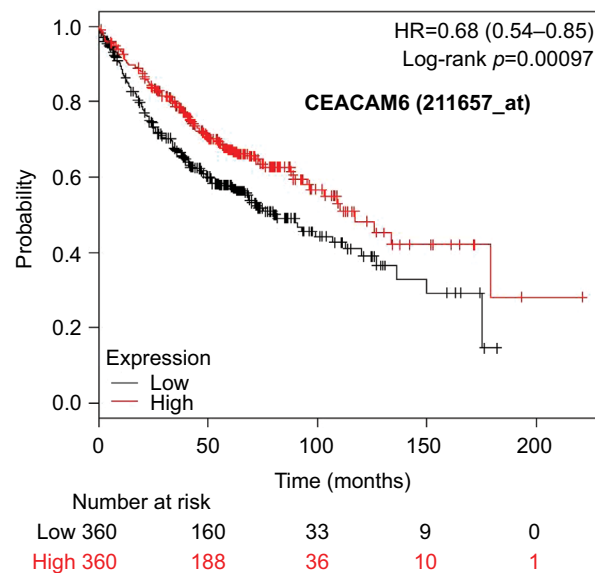


Figure 5 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM6* (Jetset probe, 211657_at) in patients with adenocarcinoma.

Note: Overall survival was better in the higher expression group ($p=0.00097$).

Abbreviation: HR, hazard ratio.

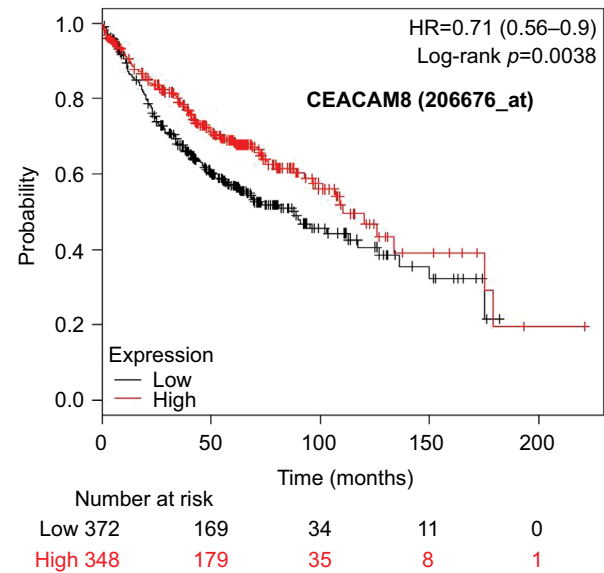


Figure 7 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM8* (Jetset probe, 206676_at) in patients with adenocarcinoma.

Note: Overall survival was better in the higher expression group ($p=0.0038$).

Abbreviation: HR, hazard ratio.

prognostic marker in NSCLC patients, while seven studies showed negative results.³⁹ 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.⁴⁰ 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 2.28.⁴¹ 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

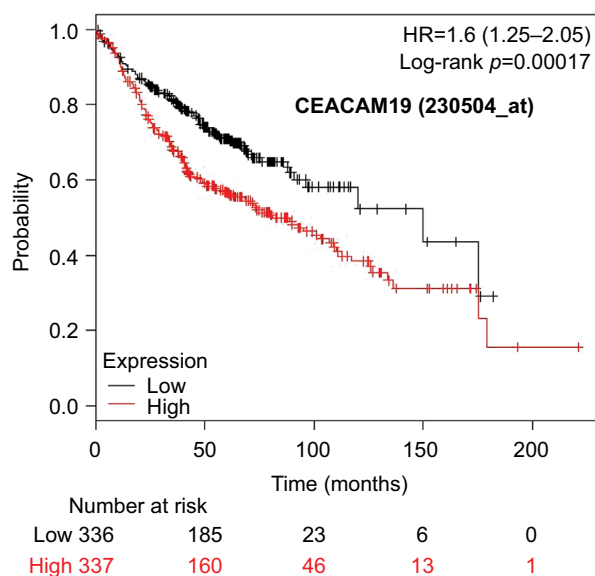


Figure 8 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM19* (Jetset probe, 230504_at) in patients with adenocarcinoma.

Note: Overall survival was worse in the higher expression group ($p=0.00017$).

Abbreviation: HR, hazard ratio.

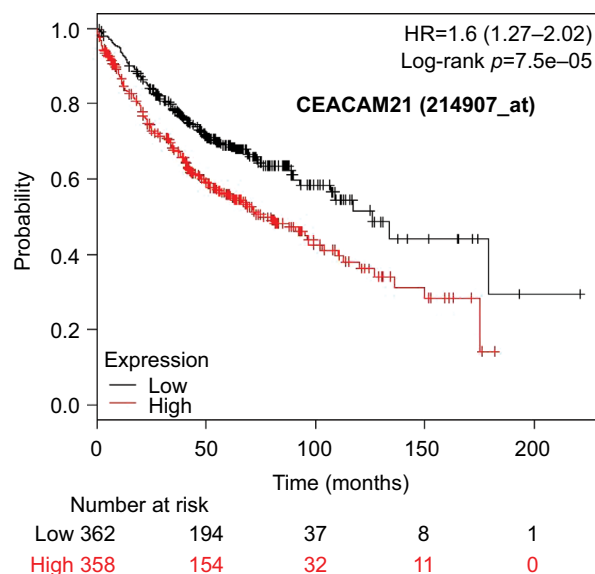


Figure 9 Kaplan–Meier survival curves of the higher and lower expression groups divided by the median value of *CEACAM21* (Jetset probe, 214907_at) in patients with adenocarcinoma.

Note: Overall survival was worse in the higher expression group ($p<0.0001$).

Abbreviation: HR, hazard ratio.

development. However, the functions and prognostic values of CEACAM1, CEACAM5, and CEACAM6 have been investigated in several tumors. For instance, surface expression of CEACAM1-4L in A549 human lung AD cells is reported to play a critical role in differentiation, contact-inhibited 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 associated with worse prognosis in melanoma,⁴³ gastric cancer,⁴⁴ thyroid cancer,⁴⁵ and NSCLC,⁴⁶ suggesting that CEACAM1 contributes to tumor progression. Thus, there are discrepancies concerning the functions of CEACAM1 among these studies. In colorectal cancer, immunohistochemically 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.⁴⁷ 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.⁴⁸ These studies indicated that CEACAM6 overexpression 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, differences 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 microarray, 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,⁴² different prognostic significance might be due to the different specificity of the probe set reactive 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 AD, but not in SQ, suggesting that CEACAMs play important roles in progression of AD. Since the impact of expression of individual CEACAMs on OS differed (better, worse, or neutral) based on the gene family members or used probe sets, each CEACAM seems to function through complicated mechanisms. Hence, further studies are necessary to resolve the problems encountered in the present study.

Disclosure

The authors report no conflicts of interest in this work.

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