Spectrum of *ALDH1* mRNA in smokers and non-smokers with adenocarcinoma or squamous cell lung carcinoma

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Abstract

Introduction: Non-small cell lung carcinoma (NSCLC), which includes large cell lung cancer, lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD), is the leading cause of cancer-related death. Higher expression of ALDH1 family members (ALDH1A1-3) has been confirmed in many cancers, including lung cancer.

Material and methods: In this study, we used Oncomine database analysis and Kaplan-Meier plotter analysis to evaluate the expression levels and the prognostic roles of *ALDH1* mRNA in smokers and non-smokers with LUSC or LUAD.

Results: We found that *ALDH1A1* mRNA was higher in the LUSC tissues of smokers than that in non-smokers. *ALDH1A3* mRNA was significantly lower in the LUSC tissues of smokers than that in non-smokers. Kaplan-Meier analysis revealed that *ALDH1A1* mRNA was a benign indicator of non-smokers with LUAD.

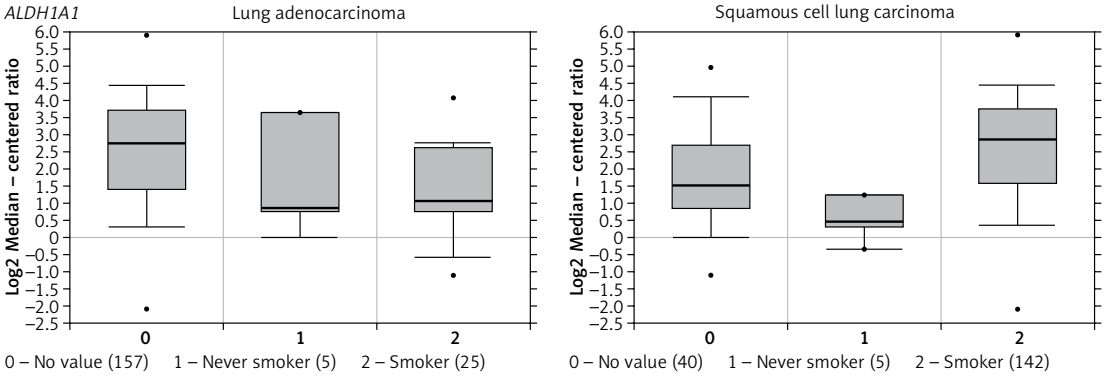
Conclusions: *ALDH1A1* mRNA could be used as a favorable marker of non-smokers with LUAD.

Key words: lung cancer, *ALDH1A1*, smoker.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Non-small cell lung carcinoma (NSCLC) includes two main types: lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) [2]. Although many factors can affect the occurrence and development of lung cancer [3, 4], we all know the basic fact that smoking causes lung cancer. A comprehensive molecular profile is needed to elucidate tumorigenesis of smokers and non-smokers with lung cancer.

The ALDH1 family of enzymes (namely ALDH1A1, ALDH1A2 and ALDH1A3) is a cytosolic detoxifying enzyme responsible for the oxidation of (retin)aldehydes into retinoids [5]. It has been widely used to isolate cancer stem cells [6]. ALDH1 is involved in cell proliferation, differentiation, and drug resistance [7]. Ginestier *et al.* [8] found that ALDH1A1 expression detected by immunostaining correlated with poorer breast cancer patient prognosis. However, Neumeister *et al.* [9] found that ALDH1A1 expression alone does not significantly predict the therapeutic outcome of breast cancer patients. So, it is hard for a single study to assess the



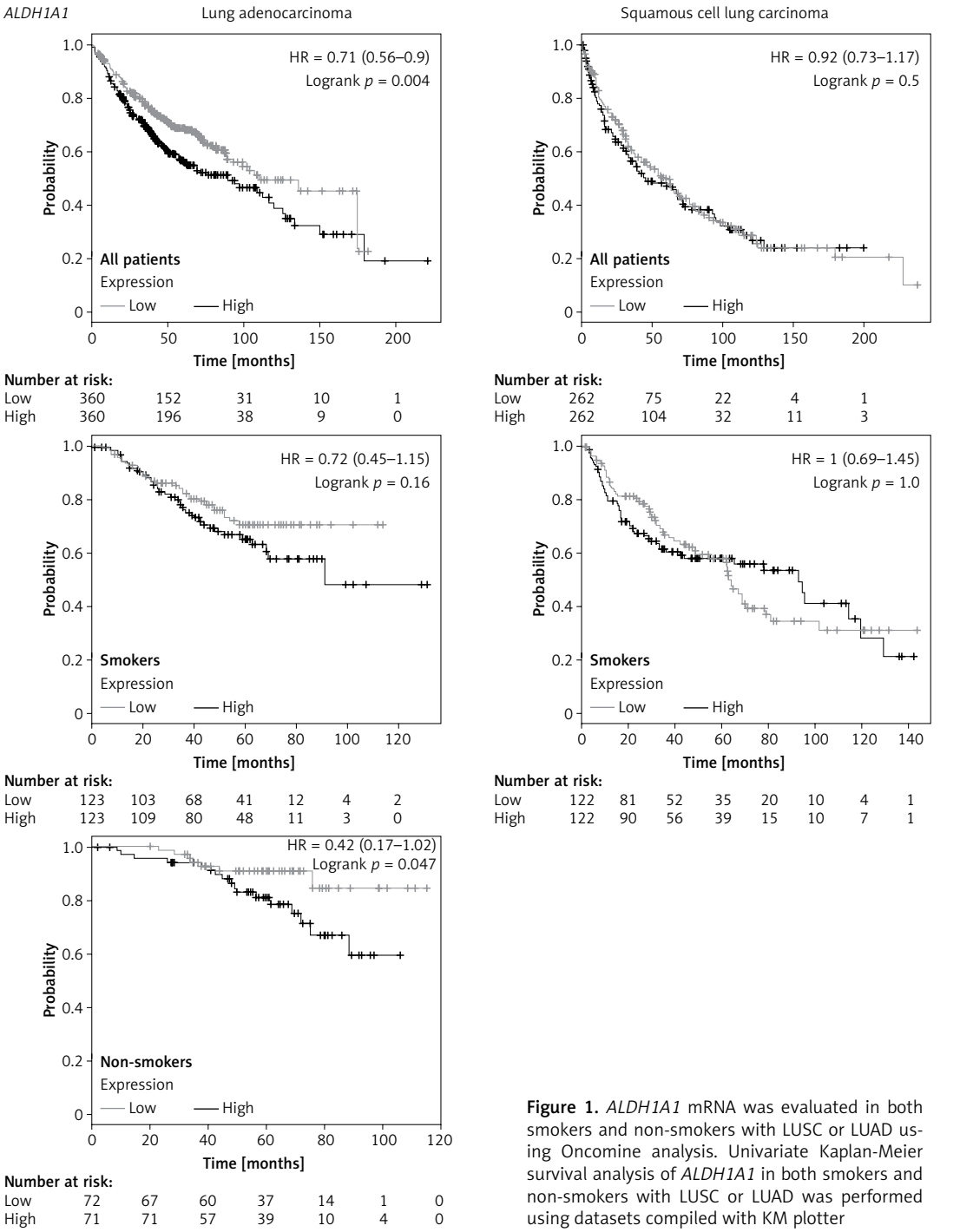
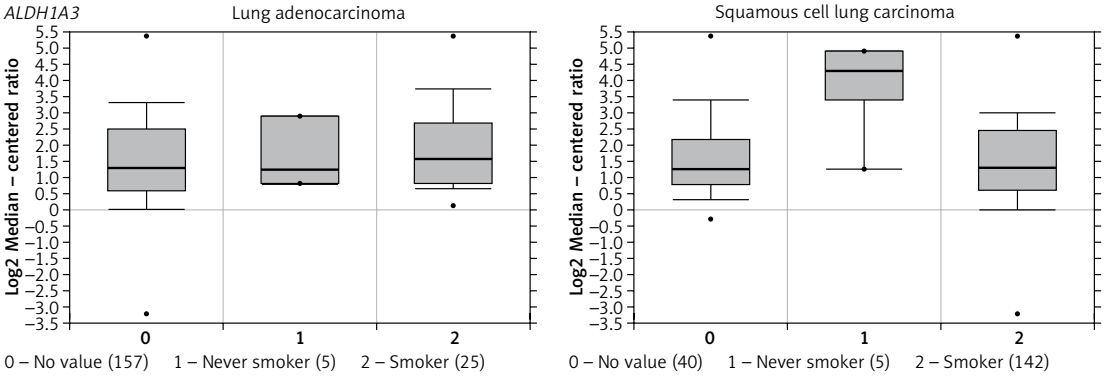
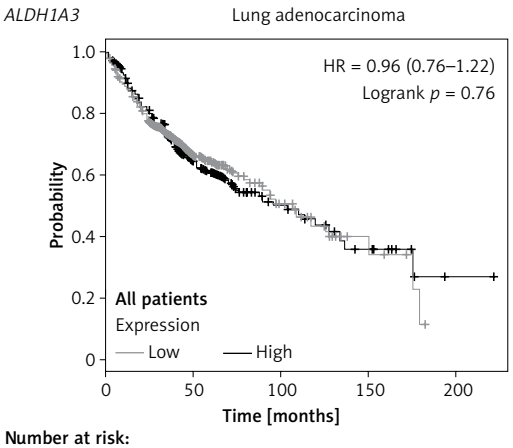


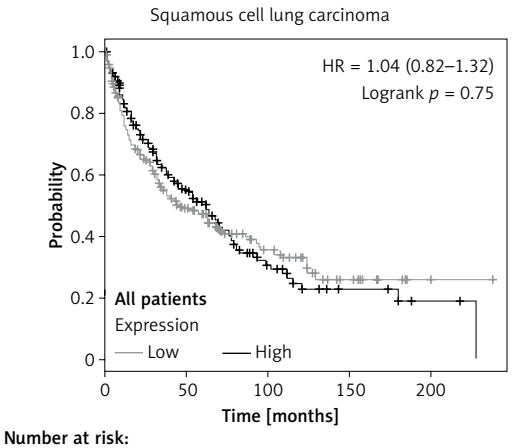
Figure 1. *ALDH1A1* mRNA was evaluated in both smokers and non-smokers with LUSC or LUAD using Oncomine analysis. Univariate Kaplan-Meier survival analysis of *ALDH1A1* in both smokers and non-smokers with LUSC or LUAD was performed using datasets compiled with KM plotter





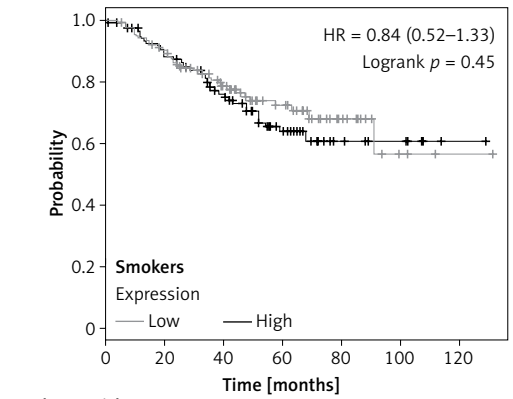
Number at risk:

Low	360	171	41	12	1
High	360	177	28	7	0



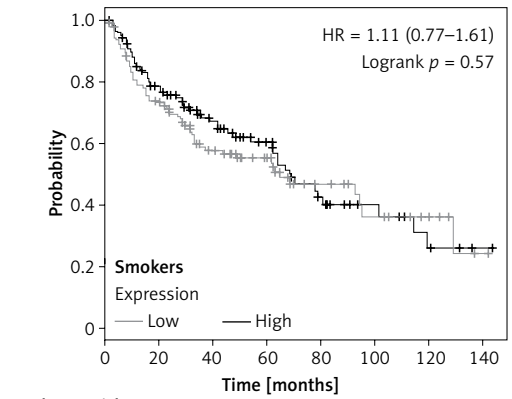
Number at risk:

Low	262	93	23	7	2
High	262	86	31	8	2



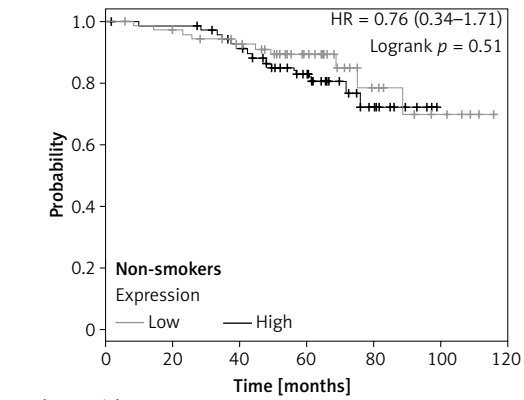
Number at risk:

Low	123	104	73	41	9	4	1
High	123	108	75	48	14	3	1



Number at risk:

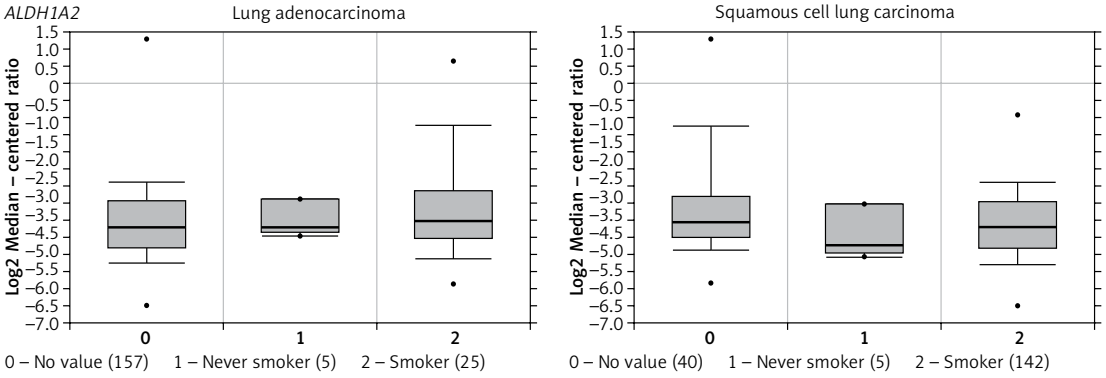
Low	122	86	55	36	18	10	5	1
High	122	85	53	38	17	10	6	1

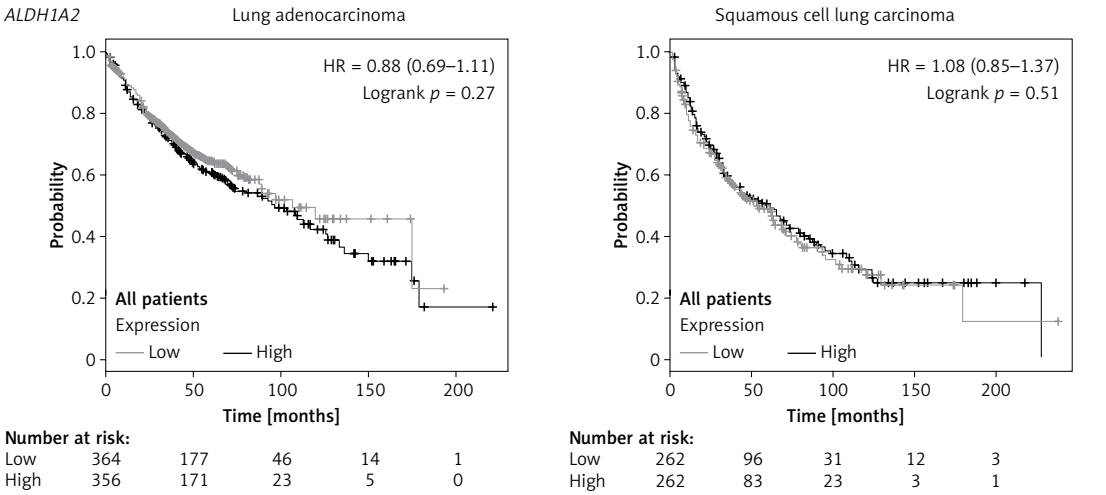


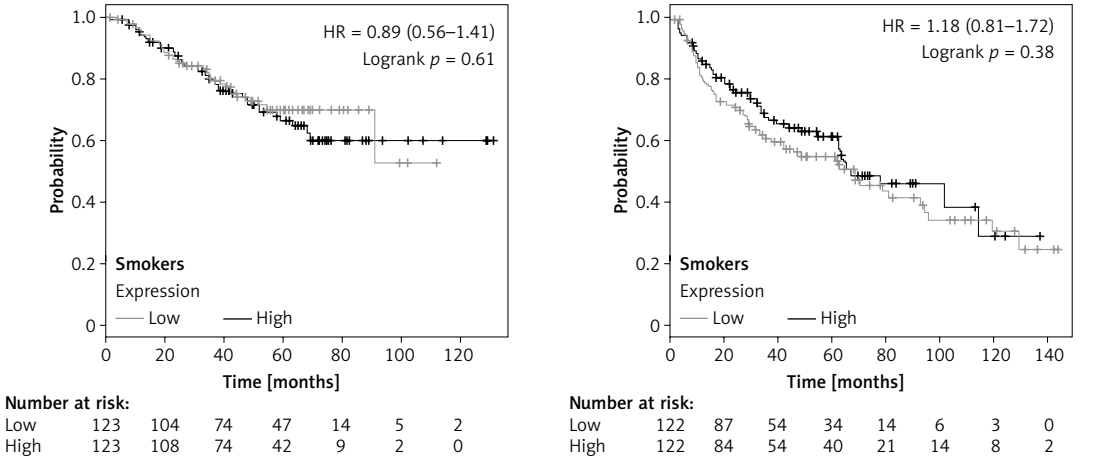
Number at risk:

Low	72	70	61	42	13	0	0
High	71	68	56	34	11	5	0

Figure 2. *ALDH1A3* mRNA was evaluated in both smokers and non-smokers with LUSC or LUAD using Oncomine analysis. Univariate Kaplan-Meier survival analysis of *ALDH1A3* in both smokers and non-smokers with LUSC or LUAD was performed using datasets compiled with KM plotter







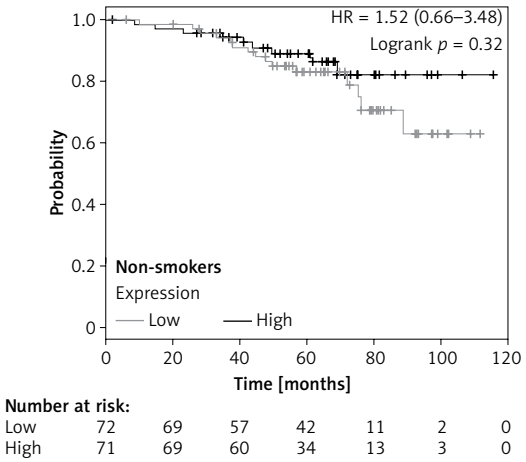


Figure 3. *ALDH1A2* mRNA was evaluated in both smokers and non-smokers with LUSC or LUAD using Oncomine analysis. Univariate Kaplan-Meier survival analysis of *ALDH1A2* in both smokers and non-smokers with LUSC or LUAD was performed using datasets compiled with KM plotter

robustness of the relationship between ALDH1A1 expression and the clinicopathologic parameters of cancer patients. The objective of this project is to explore the impact of tobacco consumption and histology type on ALDH1 expression.

Material and methods

Oncomine database analysis

The mRNA levels of *ALDH1A1*, *ALDH1A2* and *ALDH1A3* in lung cancer tissues were compared with their matched normal tissues by using TCGA datasets in the Oncomine database (http://www.oncomine.org). The threshold used to obtain the most significant probes of the queried gene for each microarray data included a two-fold difference in expression between cancers and normal tissues with a p-value < 1×10^{-4}.

Kaplan-Meier plotter analysis

The prognostic value of *ALDH1A1*, *ALDH1A2* and *ALDH1A3* in lung cancer was analyzed using the Kaplan-Meier (KM) plotter (http://kmplot.com/analysis/). Overall survival of patients with high and low levels of *ALDH1A1*, *ALDH1A2* and *ALDH1A3* was shown using a Kaplan-Meier survival plot.

Results

ALDH1A1, *ALDH1A2* and *ALDH1A3* in LUSC and LUAD tissues

Based on the Oncomine analysis of cancer vs. normal tissue, we found that *ALDH1A1* mRNA was significantly higher in the LUSC tissues of smokers than that in non-smokers (Figure 1). *ALDH1A3* mRNA was significantly lower in the LUSC tissues of smokers than that in non-smokers (Figure 2). No significant difference of *ALDH1A2* mRNA was found in LUSC tissues of smokers and non-smokers (Figure 3). *ALDH1A1*, *ALDH1A2* and *ALDH1A3* showed no significant difference in LUAD tissues of smokers and non-smokers (Figure 1–3). Kaplan-Meier analysis revealed that high *ALDH1A1* mRNA was correlated with a benign survival rate of non-smokers with LUAD (p = 0.047, Figure 1). No influence of *ALDH1A2* and *ALDH1A3* mRNA was found in either smokers or non-smokers with LUSC or LUAD (p > 0.05, Figure 1–3).

Discussion

In this brief report, we used bioinformatics analysis to describe the mRNA levels of ALDH1 family members (ALDH1A-3) in LUSC and LUAD tissues. In the study of Patel *et al.*, they found higher expression of ALDH1A1 in lung specimens from smokers when compared to non-smokers [10]. Consistent with their study, a higher ALDH1A1 mRNA level was found in the LUSC tissues of smoker in this study. Cigarette smoking seems to be an inducer of ALDH1A1. You *et al.* [11] found that *ALDH1A1* mRNA in NSCLC is associated with better prognosis. In this study, we found that high ALDH1A1 mRNA was correlated with a benign survival rate of non-smokers with LUAD using the KM plotter. In most cancers, high expression of the ALDH1A1 protein was associated with a poor prognosis, such as breast cancer [12], colorectal carcinoma [13], and gastric cancer [14]. In a meta-analysis, ALDH1 was an independent factor associated with reduced survival of lung cancer patients [13]. Based on the present data, we cannot conclude the reason for the discordance between ALDH1A1 protein and mRNA [15].

In summary, our results showed that *ALDH1A1* mRNA could be used as a favorable marker of non-smokers with LUAD. This marker should be further evaluated for its potential use in tracking lung cancer stem cells *in vivo* and *in vitro*.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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