

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

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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 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 $< 1 \times 10^{-4}$.

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*,

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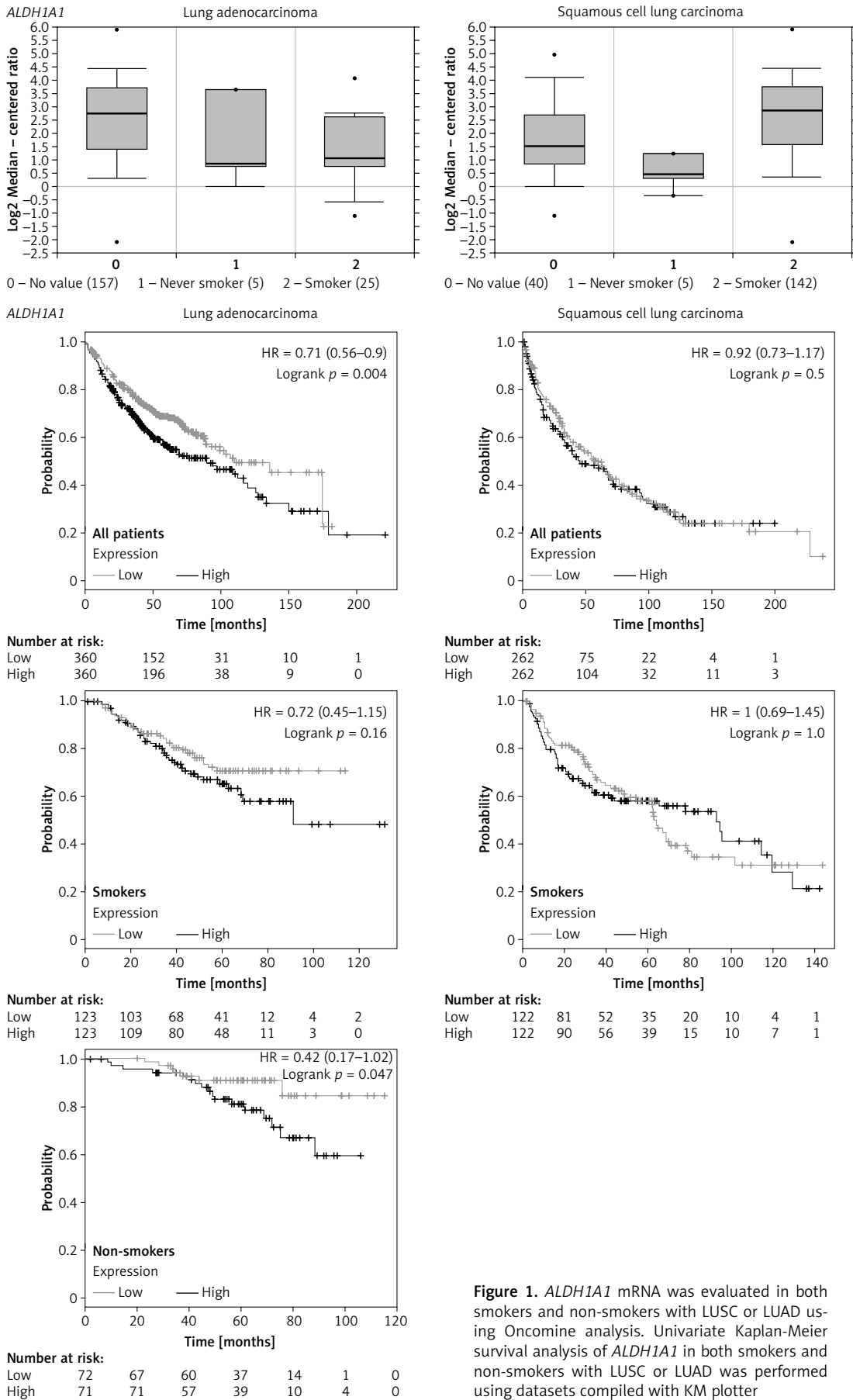


Figure 1. *ALDH1A1* mRNA was evaluated in both smokers and non-smokers with LUSC or LUAD using OncoPrint analysis. Univariate Kaplan-Meier survival analysis of *ALDH1A1* in both smokers and non-smokers with LUSC or LUAD was performed using datasets compiled with KM plotter

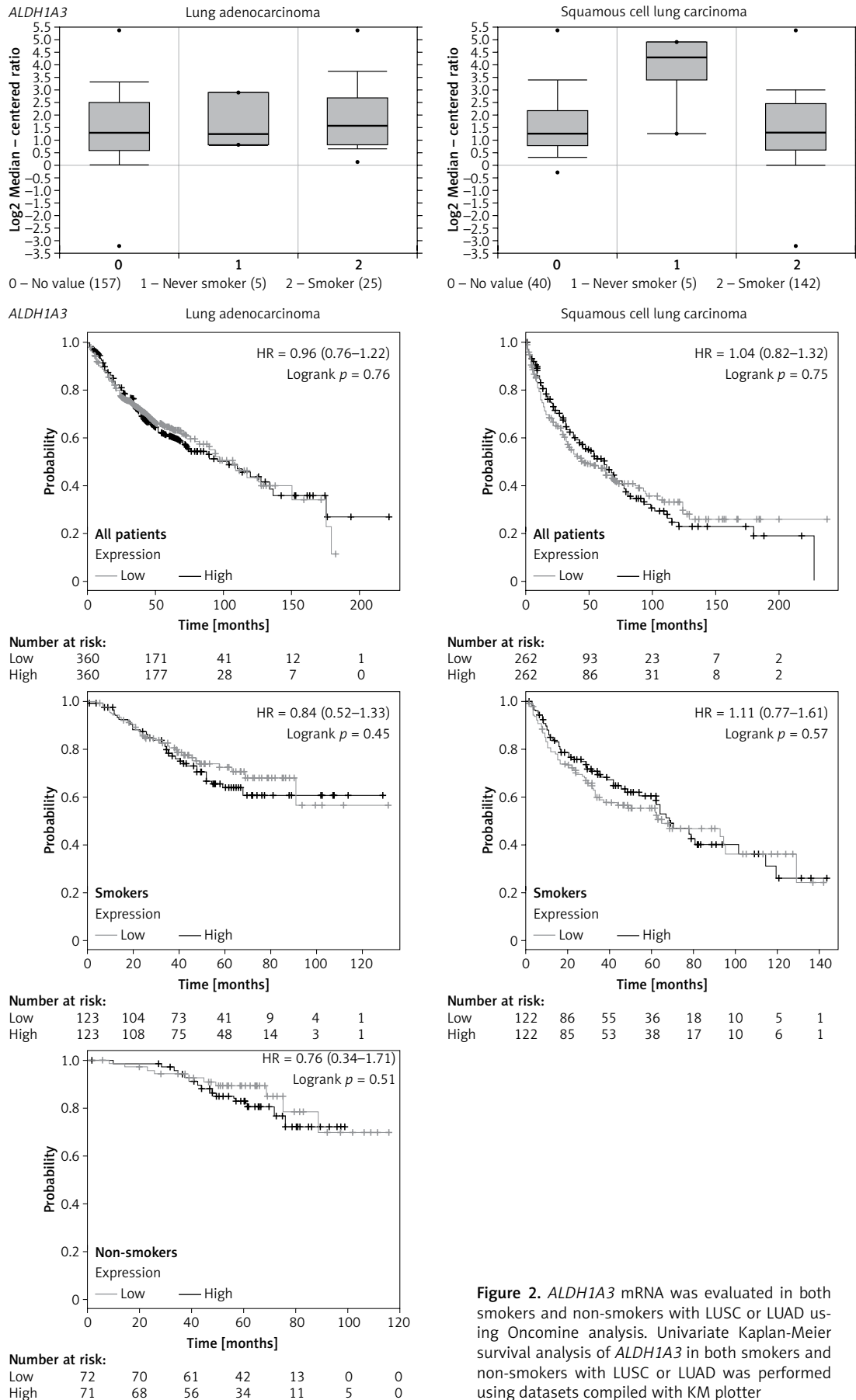


Figure 2. *ALDH1A3* mRNA was evaluated in both smokers and non-smokers with LUSC or LUAD using OncoPrint analysis. Univariate Kaplan-Meier survival analysis of *ALDH1A3* in both smokers and non-smokers with LUSC or LUAD was performed using datasets compiled with KM plotter

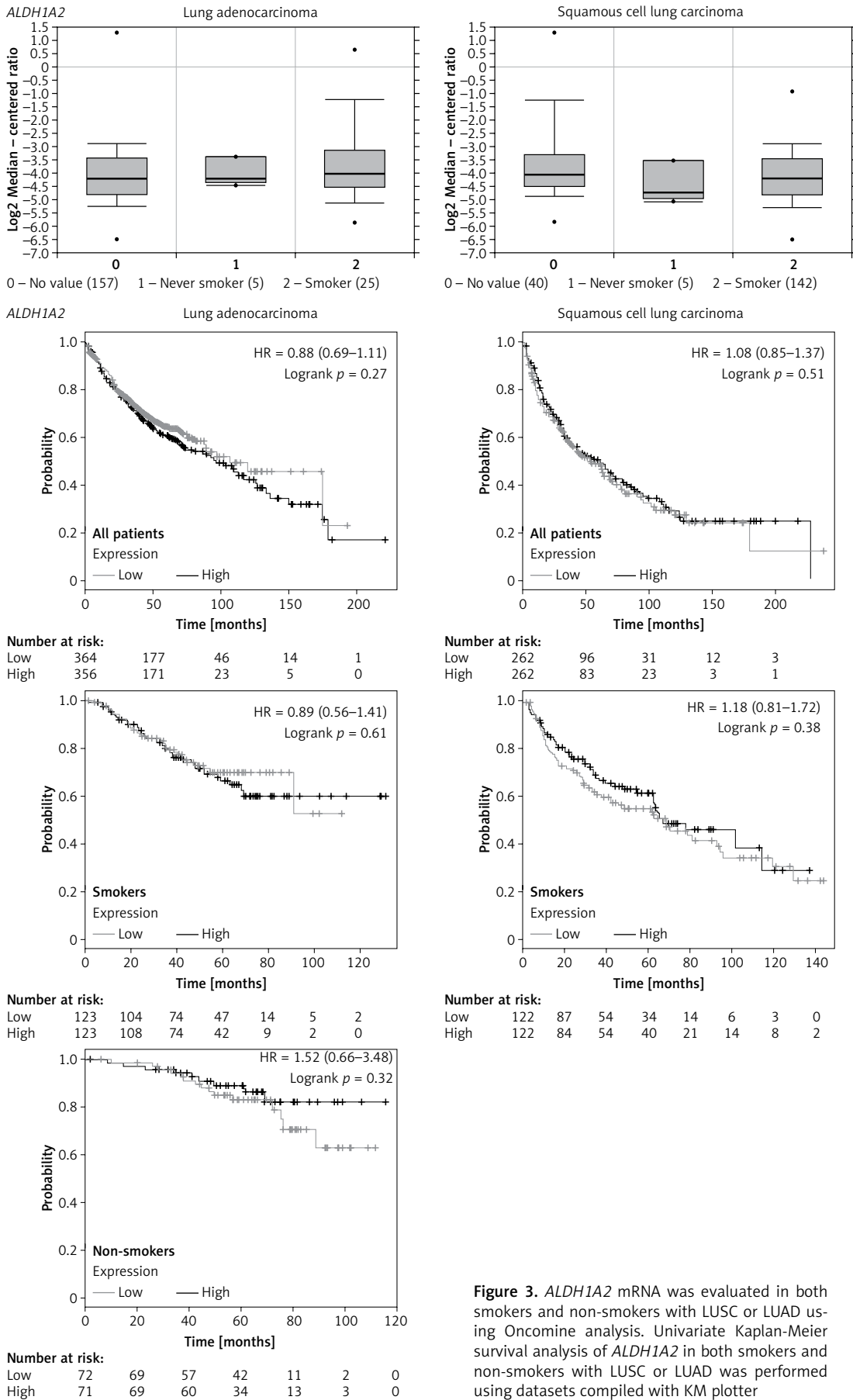


Figure 3. ALDH1A2 mRNA was evaluated in both smokers and non-smokers with LUSC or LUAD using OncoPrint analysis. Univariate Kaplan-Meier survival analysis of ALDH1A2 in both smokers and non-smokers with LUSC or LUAD was performed using datasets compiled with KM plotter

ALDH1A2 and *ALDH1A3* was shown using a Kaplan-Meier survival plot.

Results

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

Based on the OncoPrint 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 (Figures 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 ($p > 0.05$, Figures 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 conclusion, 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*.

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Conflict of interest

The authors declare no conflict of interest.

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