Impact of Smoking History on the Real-World Effectiveness of Immune Checkpoint Inhibitors in Previously Treated Non-Small Cell Lung Cancer: A Nationwide Population-Based Study

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INTRODUCTION

- Smoking is a well-established risk factor of lung-cancer mortality.

- However, meta-analysis of randomized clinical trials (RCTs) have shown that immune checkpoint inhibitors (ICIs) were more effective in non-small cell lung cancer (NSCLC) patients with a smoking history.

OBJECTIVE

To estimate the impact of smoking history on the real-world effectiveness of ICIs as second or later line of treatment in previously treated NSCLC patients.

METHOD

- **Study design**: Retrospective cohort study
- **Data source**: The Cancer Public Library Data under the K-CURE project, covering all registered cancer patients in Korea. (2012-2020)
- **Study population**: NSCLC patients diagnosed between 2013 and 2019 who received pembrolizumab, nivolumab, or atezolizumab as second or later-line treatments, with at least 1 NHI medical check-up record before ICI initiation.

Index date – Date of ICI initiation

Ever-smokers vs. Never-smokers

Covariate assessment:
- Day [-365, -1] : Comorbidities (CVD, DM, AID, respiratory, renal, other cancer)
- Day [-3years, -1] : Drinking (≥3/week), Obesity (BMI ≥ 25kg/m^2)

Baseline characteristics: Day [0,0]
- Demographic: Age, Sex, Income level
- Clinical: Stage, Histology, Primary Site, Initial Treatments

Follow-up period: Day [0, end of data]
- **All cause-mortality, NSCLC-specific mortality**
- **Time to treatment discontinuation (TTD)**

Multivariate Cox regression, Fine-Gray model

Jan 2012 ———————— **Cohort entry : 2013-2019 (NSCLC diagnosis)** ———————— **Dec 2020**

RESULTS

- After adjusting for baseline covariates, ever-smokers who initiated ICIs experienced a significantly longer treatment duration than never-smokers (HR 0.87; 95% confidence interval [CI] 0.81-0.95).

- Age, histology, primary tumor site and comorbidity with other malignancies were significant effect modifiers for TTD between the two groups.

- Despite longer treatment durations in ever-smokers, smoking history showed no significant impact on all-cause mortality (HR 0.93; 95% CI 0.85-1.03) or NSCLC-specific mortality (Sub-distribution HR 0.94; 95% CI 0.85-1.04).

Table 1. Baseline characteristics of 2L+ ICI patients

Characteristics	Never-smoker N=1,981	Ever-smoker N=5,632	P-value
Male, n (%)	510 (25.7)	5,430 (96.4)	<.0001
Age group, n (%)			
Under 60	687 (34.7)	1,321 (23.5)	
60-69	676 (34.1)	2,310 (41.0)	<.0001
70-79	526 (26.6)	1,793 (31.8)	
Over 80	92 (4.6)	208 (3.7)	
SEER stage, n (%)			
Local	129 (6.5)	476 (8.4)	
Regional	424 (21.4)	1,734 (30.8)	<.0001
Distant	1,339 (67.6)	3,152 (56.0)	
Unknown	89 (4.5)	270 (4.8)	
Histology, n (%)			
Adenocarcinoma	1,529 (77.2)	2,575 (45.7)	
Squamou cell	250 (12.6)	2,250 (40.0)	<.0001
Large cell	25 (1.3)	120 (2.1)	
Others	177 (8.9)	687 (12.2)	
Primary Site, n (%)			
Upper lobe	853 (43.0)	2,817 (50.0)	
Middle lobe	154 (7.8)	249 (4.4)	<.0001
Lower lobe	830 (41.9)	2,061 (36.6)	
Others	144 (7.3)	505 (9.0)	
Initial Treatment[2]			
Surgery, n(%)	406 (20.5)	1,208 (21.5)	0.3715
Radiation, n(%)	435 (22.0)	1,602 (28.4)	<.0001
Chemotherapy,n(%)	1,526 (77.0)	4,337 (77.0)	0.9816
Drinking[3], n (%)	110 (5.6)	1,324 (23.5)	<.0001
Obesity[4], n (%)	722 (36.5)	1,809 (32.1)	0.0004

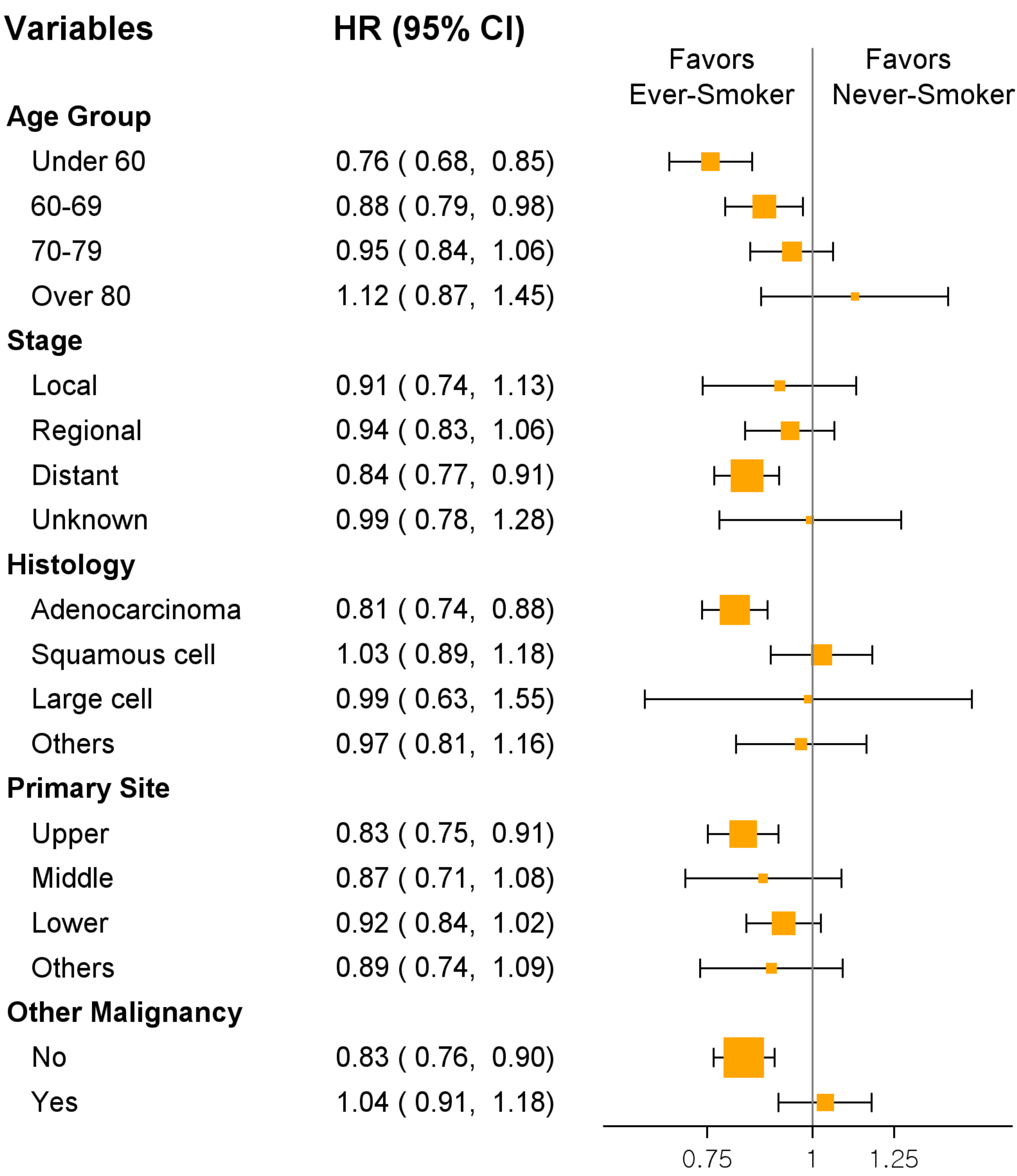| Variables	HR (95% CI)
Age Group	
Under 60	0.76 (0.68, 0.85)
60-69	0.88 (0.79, 0.98)
70-79	0.95 (0.84, 1.06)
Over 80	1.12 (0.87, 1.45)
Stage	
Local	0.91 (0.74, 1.13)
Regional	0.94 (0.83, 1.06)
Distant	0.84 (0.77, 0.91)
Unknown	0.99 (0.78, 1.28)
Histology	
Adenocarcinoma	0.81 (0.74, 0.88)
Squamous cell	1.03 (0.89, 1.18)
Large cell	0.99 (0.63, 1.55)
Others	0.97 (0.81, 1.16)
Primary Site	
Upper	0.83 (0.75, 0.91)
Middle	0.87 (0.71, 1.08)
Lower	0.92 (0.84, 1.02)
Others	0.89 (0.74, 1.09)
Other Malignancy	
No	0.83 (0.76, 0.90)
Yes	1.04 (0.91, 1.18)

Figure 1. Forest plot of HRs for TTD by smoking history, stratified by effect modifiers

1) Stage at diagnosis; 2) Treatments within 4 months from cancer diagnosis (KCCR); 3) ≥3 times per week; 4) BMI ≥ 25kg/m^2

CONCLUSIONS

In NSCLC patients treated with ICIs as second or later lines, ever-smokers experienced longer treatment durations than never-smokers. However, smoking history did not significantly affect overall or NSCLC-specific mortality.

REFERENCES

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