Association between smoking history and tumor mutation burden in an advanced non-small cell lung cancer cohort

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Background

Lung carcinogenesis is a complex process involving an accumulation of genetic mutations in oncogenic pathways via interactions with environmental factors and host susceptibility. Tobacco exposure is the leading cause of lung cancer, but its relationship to clinically relevant mutations and the composite TMB remains undefined.

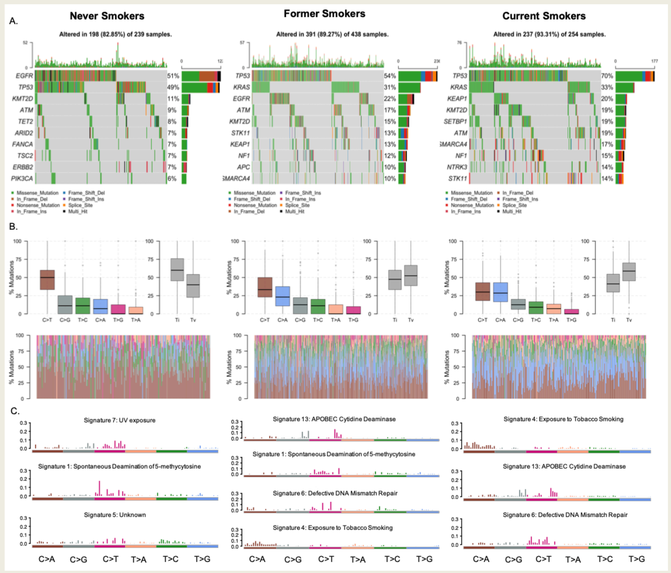
Methods

The dose-response relationship between detailed smoking history and TMB was discovered in a retrospective study of **931** patients treated for advanced-stage NSCLC between April 2013 and February 2020 at the **DFCI** and **BWH**. Patient TMB and genomic landscape were determined by the **clinical targeted NGS panel** and **detailed smoking history** were prospectively collected.

Logistic regression, generalized additive models and piecewise regression were applied to assess the association between smoking history and somatic mutations and TMB, controlling for clinical covariates.

Results

Genomic landscapes by smoking metrics

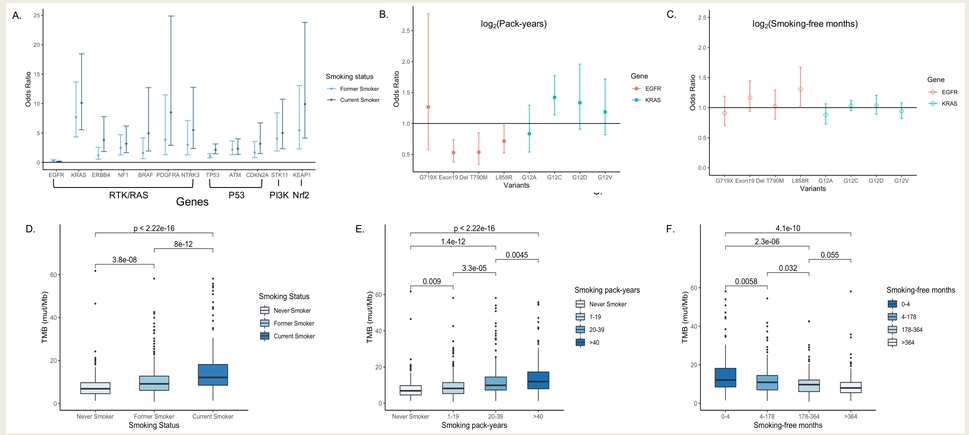


Results

Table.1 Baseline clinicopathological characteristics by smoking status

	N=931		
	Never Smoker (n = 239)	**Former Smoker (n = 438)**	**Current Smoker (n = 254)**
Age, median (SD), y	61 (13)	68 (10)	60 (9)
Gender, n (%)			
Male	151 (63)	252 (58)	139 (55)
Female	88 (37)	186 (42)	115 (45)
Pathology, n (%)			
Adenocarcinoma	219 (92)	350 (80)	195 (77)
Squamous Cell Carcinoma	12 (5)	28 (6)	17 (6)
Others	8 (3)	60 (14)	42 (17)
Stage, n (%)			
III	43 (18)	133 (30)	101 (40)
IV	196 (82)	305 (70)	153 (60)
Pack-years, median (SD)	0 (0)	24 (24)	40 (20)
Smoking-free months, median (SD)	NA	261 (170)	1 (3)

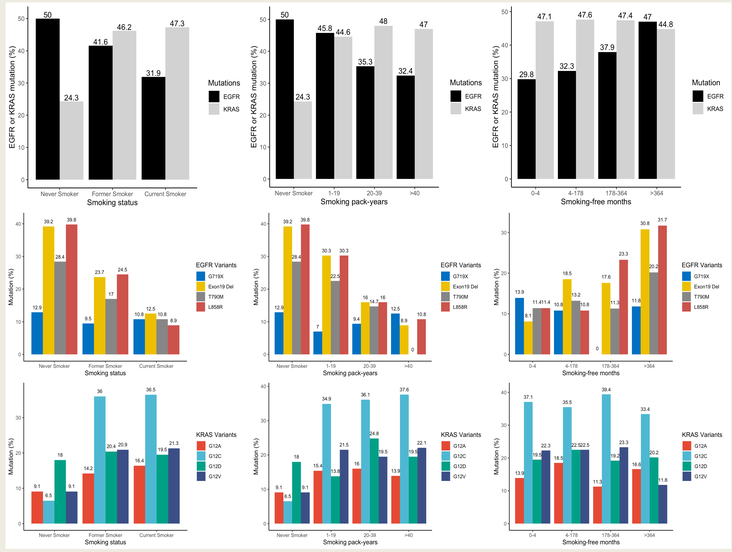
Effect of smoking metrics on certain mutations and TMB



Effect of smoking history on TMB

	All advanced NSCLC		Adenocarcinoma	
Parameters	**Estimate (95% CI)**	**P**	**Estimate (95% CI)**	**P**
Age	1.00 (1.00-1.01)	0.10	1.00 (1.00-1.01)	0.02
Male vs female	0.95 (0.85-1.05)	0.30	0.91 (0.81-1.03)	0.15
Squamous cell Carcinoma vs Adenocarcinoma	1.2 (0.97-1.49)	0.09	NA	NA
Others vs adenocarcinoma	1.1 (0.94-1.27)	0.23	NA	NA
Stage IV vs III	0.93 (0.84-1.04)	0.22	0.90 (0.79-1.02)	0.10
Doubling Smoking pack-years	1.14 (1.08-1.21)	<0.001	1.11 (1.04-1.24)	<0.001
Doubling Smoking-free months	0.96 (0.94-0.98)	<0.001	0.95 (0.92-0.99)	<0.001

Mutation rates of *EGFR* and *KRAS* by smoking metrics



Conclusions & Relevance

- There is a significant dose-response association between smoking history, and clinically relevant genes in cancer-related pathways and TMB in advanced lung adenocarcinoma.
- This significant dose-response relationship provides important insights for smoking history being a surrogate for TMB in advanced NSCLC.

Selected References

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