Published in final edited form as:
J Thorac Oncol. 2013 January ; 8(1): 123–125. doi:10.1097/JTO.0b013e31827914ea.

Lungs don't forget: Comparison of the KRAS and EGFR mutation profile and survival of "collegiate smokers" and never smokers with advanced lung cancers

Anna M. Varghese, M.D., **Camelia S. Sima, M.D.**, **Jamie E. Chaft, M.D.**, **Melissa L. Johnson, M.D.**, **Gregory J. Riely, M.D., PhD**, **Marc Ladanyi, M.D.**, and **Mark G. Kris**

Abstract

HYPOTHESIS—We hypothesize that among patients with lung cancers the *KRAS*/*EGFR* mutation profile and overall survival of "collegiate smokers" (former smokers who smoked between 101 lifetime cigarettes and 5 pack years) are distinct from those of never smokers and former smokers with ≥ 15 pack years.

METHODS—We collected age, sex, stage, survival, and smoking history for patients evaluated from 2004 to 2009 with advanced stage lung cancers and known *KRAS*/*EGFR* status. Mutation profile and overall survival were compared using Fisher's exact test and log-rank test, respectively.

RESULTS—Data were available for 852 patients with advanced stage lung cancers with known *KRAS*/*EGFR* status. 6% were "collegiate smokers", 36% were never smokers, and 30% were former smokers with ≥ 15 pack years. The mutation profile of "collegiate smokers" (15% *KRAS* mutations, 27% *EGFR* mutations) was distinct from those of never smokers ($p < .001$) and former smokers with ≥ 15 pack years ($p < .001$)and not significantly different from those of former smokers with 5 to 15 pack years ($p = 0.9$). Median overall survival for "collegiate smokers" was 25 months, compared to 32 months for never smokers ($p = 0.4$), 33 months for former smokers with 5–15 pack years ($p = 0.48$),and 21 months for former smokers with ≥ 15 pack years ($p = 0.63$).

CONCLUSIONS—"Collegiate smokers" with advanced stage lung cancers represent a distinct subgroup of patients with a higher frequency of *KRAS* mutations and lower frequency of *EGFR* mutations compared to never smokers. These observations reinforce the recommendation for routine mutation testing for all patients with lung cancers and that no degree of tobacco exposure is safe.

Keywords

Collegiate Smokers; non-small cell lung cancers; epidermal growth factor receptor mutation; *KRAS* mutation

INTRODUCTION

The discovery of driver lesions in epidermal growth factor receptor (*EGFR*), *KRAS*, and anaplastic lymphoma kinase (*ALK*) has led to the identification of distinct genetic sub-types of lung cancers. This information is revolutionizing the treatment of lung cancer. We have demonstrated that the frequency of *KRAS* mutations increases and *EGFR* mutation decreases with greater tobacco exposure, and *EGFR* mutations are less common in patients

Corresponding Author: Mark G. Kris, krism@mskcc.org.

who smoked greater than 15 pack years.[1, 2] These *EGFR* mutations predict sensitivity to EGFR tyrosine kinase inhibitors.[3–5] By contrast, lung cancers harboring *KRAS* mutations are found in patients with a variety of tobacco exposures ranging from never smokers to heavy smokers, while patients whose tumors harbor *ALK* rearrangements are more likely never or light smokers compared to those patients whose tumors do not harbor *ALK* rearrangements.[6, 7]

For patients with advanced lung cancers, we have shown that cigarette smoking is associated with worse survival after a diagnosis.[8] We have also demonstrated that patients with advanced lung cancers harboring *KRAS* mutations have a shorter survival compared to those of patients with tumors harboring *EGFR* mutations and patients whose tumors are wild-type for *KRAS* and *EGFR*.[9]

Whether the tobacco exposure of “collegiate smokers”, individuals who are former smokers with a lifetime exposure between 101 cigarettes and 5 pack years, is sufficient to impact their prognosis is unknown. We hypothesize that the *KRAS* and *EGFR* mutation profile and overall survival of “collegiate smokers” will be distinct from never smokers and former smokers with ≥ 15 pack year smoking histories. The ≥ 15 pack year number was chosen as we had previously determined that that *EGFR* mutation frequency above that amount of cigarette exposure was significantly different than the frequency seen in never smokers. [1]

MATERIALS AND METHODS

This cohort includes patients evaluated at Memorial Sloan-Kettering Cancer Center between 2004 and 2009 with known *KRAS* and *EGFR* status and advanced stage lung cancers (stage IIIB/IV by the *American Joint Committee on Cancer Staging Manual,* sixth edition) at the time of initial diagnosis or at the time of recurrent disease after prior surgery or radiation. Patients with squamous and small cell lung cancers did not undergo *EGFR*/*KRAS* analysis. Patients with lung cancers evaluated at MSKCC complete a prospective, self-administered smoking questionnaire at the time of their initial visit. The history of smoking, number of pack years smoked, and years since stopping smoking were determined using the smoking questionnaire. We obtained demographic and clinical information regarding gender, race, age, stage, and survival. *EGFR* exon 19 deletions and *EGFR* exon 21 L858R amino acid substitutions were identified by previously reported mutation-specific PCR-based methods.[10–12] *KRAS* codon 12 and 13 mutation identification was performed by both mass-spectrometry (Sequenom)-based genotyping and direct sequencing. *ALK* testing was not available for patients prior to 2009 and was not evaluated in this cohort. Medical record review was performed with a waiver of authorization approved by our Institutional Review Board. Mutation profile was compared across groups using the Fisher’s exact test. Overall survival following diagnosis with advanced stage lung cancer was estimated using Kaplan-Meier method and compared across groups using the log-rank test. Patients alive at the end of the study were censored at the time of the last available follow-up.

Patients were categorized as never smokers if they had smoked 100 or fewer lifetime cigarettes, current smokers if they continue to smoke or quit less than 12 months prior to completion of the smoking questionnaire, and former smokers if they quit smoking at least 12 months prior to completion of the smoking questionnaire. Race was reported by the patient.

RESULTS

Detailed smoking history and clinical data were available for 852 patients with advanced stage lung cancers (492women, 360 men).97% of this patient population had

adenocarcinoma, and the remaining 3% included patients with non-small cell lung cancer not otherwise specified and large cell neuroendocrine carcinoma. Demographic characteristics are summarized in Table 1. “Collegiate smokers” had stopped smoking a median of 30 years prior to diagnosis (range 1 to 60 years).

Mutation profiles are depicted in Figure 1.The mutation profile of “collegiate smokers” is different from those patients who had never smoked ($p < .001$) and of former smokers who had smoked ≥ 15 pack years ($p < .001$) but similar to that of patients who were former smokers with 5–15 pack years ($p = 0.9$). Among former smokers with smoking histories ≥ 15 pack years, 40% had *KRAS* mutations, 11% had *EGFR* mutations, and 49% were wild type for *KRAS* and *EGFR* mutations.

Median overall survival after diagnosis of advanced stage lung cancer for “collegiate smokers” was 25 months, compared to 32 months for never smokers ($p = 0.4$), 21 months for former smokers with ≥ 15 pack years ($p = 0.63$), and 33 months for former smokers with 5–15 pack years ($p = 0.48$).

DISCUSSION

Many persons with lung cancers state that they “only smoked in college” or for just a few years when they were younger. Since we prospectively collect smoking questionnaires for all patients with advanced stage lung cancers, we were in a position to assess whether the mutational profile and course of lung cancer were different from individuals who never smoked or had greater exposures to cigarette smoking. We defined “collegiate smokers” as former smokers who have smoked between 101 lifetime cigarettes and 5 pack years. Based on this data, “collegiate smokers” with advanced stage lung cancers represent a distinct group of patients with a higher percentage of *KRAS* mutations and lower percentage of *EGFR* mutations as compared to never smokers. The median overall survival of “collegiate smokers” was not significantly different from never smokers, former smokers with 5–15 pack years, and former smokers with ≥ 15 pack years but not significantly different in this relatively small cohort.

Heavier cigarette smoking history is associated with decreased survival after a diagnosis of advanced stage lung cancer.[8] Likewise, recent work has demonstrated that any amount of smoking exposure greater than 1 pack year can impact the likelihood of *EGFR* and *KRAS* mutations among patients with lung cancers.[2] Although the majority of gene expression alterations associated with smoking return to the levels associated with never smokers, expression of a subset of genes remains affected, even decades after smoking cessation.[13] Building on this work, these data serve as a reminder that the effects of even minimal amounts of cigarette smoking decades earlier influence the biology and perhaps the outcome of lung cancers. Additionally, many clinicians continue to choose *EGFR*-targeted therapy based on clinical history, including never or “collegiate” smoking history. These data reinforce the necessity of performing routine molecular testing on all patients with lung cancers. Lastly, this data remind us that no amount of cigarette smoking is safe.

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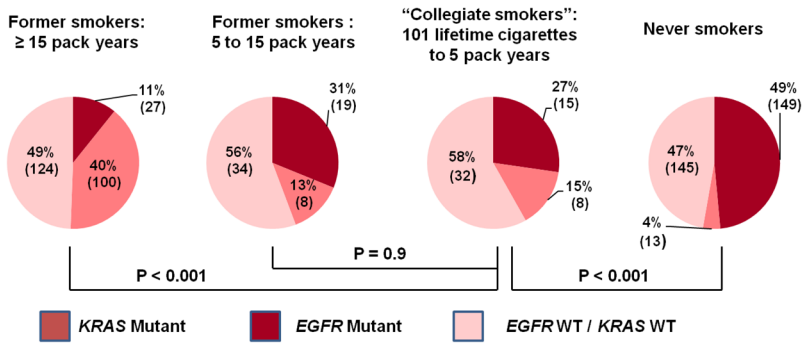

Figure 1.
Mutation Profile for Never Smokers, Collegiate Smokers, and Former Smokers with ≥ 15 pack year smoking histories

Table 1

Patient Characteristics

	N	%
Men	360	42
Women	492	58
Median Age (range), years	64 (26–92)	
Smoking History		
Never Smoker	307	36
“Collegiate” Smoker	55	6
Former Smoker with 5 to 15 pack years	61	7
Former Smoker with ≥15 pack years	251	30
Current Smoker	178	21
Race		
White	710	83
Asian	67	8
Unknown/Other	75	9