Human Cancer Biology

Molecular Epidemiology of EGFR and KRAS Mutations in 3,026 Lung Adenocarcinomas: Higher Susceptibility of Women to Smoking-Related KRAS-Mutant Cancers

Snjezana Dogan1, Ronglai Shen2, Daphne C. Ang1, Melissa L. Johnson3, Sandra P. D'Angelo3, Paul K. Paik3, Edyta B. Brzostowski1, Gregory J. Riely2, Mark G. Kris3, Maureen F. Zakowski1, and Marc Ladanyi1,4

Abstract

**Purpose:** The molecular epidemiology of most EGFR and KRAS mutations in lung cancer remains unclear.

**Experimental Design:** We genotyped 3,026 lung adenocarcinomas for the major EGFR (exon 19 deletions and L858R) and KRAS (G12, G13) mutations and examined correlations with demographic, clinical, and smoking history data.

**Results:** EGFR mutations were found in 43% of never smokers and in 11% of smokers. KRAS mutations occurred in 34% of smokers and in 6% of never smokers. In patients with smoking histories up to 10 pack-years, EGFR predominated over KRAS. Among former smokers with lung cancer, multivariate analysis showed that, independent of pack-years, increasing smoking-free years raise the likelihood of EGFR mutation. Never smokers were more likely than smokers to have KRAS G>A transition mutation (mostly G12D; 58% vs. 20%, P = 0.0001). KRAS G12C, the most common G>T transversion mutation in smokers, was more frequent in women (P = 0.007) and these women were younger than men with the same mutation (median 65 vs. 69, P = 0.0008) and had smoked less.

**Conclusions:** The distinct types of KRAS mutations in smokers versus never smokers suggest that most KRAS-mutant lung cancers in never smokers are not due to second-hand smoke exposure. The higher frequency of KRAS G12C in women, their younger age, and lesser smoking history together support a heightened susceptibility to tobacco carcinogens. Clin Cancer Res; 18(22); 6169–77. ©2012 AACR.

Introduction

EGFR or KRAS mutations are present in almost 50% of lung adenocarcinomas in Caucasian patients. More than 90% of EGFR mutations are small in frame deletions in exon 19 and L858R missense mutation in exon 21 (1). These mutations are associated with responsiveness to tyrosine kinase inhibitors (TKI) therapy (2–4). EGFR mutations are more frequently found in women, Asians, and in never smokers (5, 6). There is an inverse relationship between duration and intensity of cigarette smoking and frequency of EGFR mutations suggesting that smoking history has predictive value for the presence of EGFR mutations (7, 8).

Although KRAS mutations were identified in lung cancer more than 2 decades ago (9, 10), the clinical importance of KRAS mutation status became apparent only relatively recently, as lung adenocarcinomas harboring KRAS mutations were found to show lack of response to EGFR TKI therapy (11, 12). KRAS-mutated lung cancers are prognostically unfavorable when compared with EGFR-mutated (13–16). In more than 95% of cases, KRAS missense mutations are found in codons 12 and 13 (17). Unlike EGFR mutations, KRAS mutations show no sex predilection, are more frequent in white populations than Asians, and most patients are former or current cigarette smokers (18, 19). KRAS mutations known to be smoking-associated (G12C, G12V) are transversion mutations (G>T and G>C), whereas KRAS transitions mutations (G>A) are more common in lung adenocarcinomas from patients without any smoking history (20, 21).

Even though the distinctive distribution of EGFR and KRAS mutations in relation to ethnicity, sex, and smoking history suggests that patient characteristics have a significant predictive value for the presence of these mutations, the etiology of most mutations arising in never smokers remains unknown. In this study, we hypothesized that correlations between demographic, epidemiologic and clinical data, and types of EGFR and KRAS mutations could
Translational Relevance

To clarify the molecular epidemiology of EGFR and KRAS mutations in lung adenocarcinoma, we examined tumor genotyping data in 3,026 patients in relation to demographic, clinical, and smoking history data. In addition to the expected reciprocal associations of EGFR and KRAS mutations with smoking history, this showed that 11% of smokers had EGFR-mutated tumors and 6% of never smokers had KRAS-mutated tumors. Pack-years of smoking were predictive for EGFR and KRAS mutations but even in the context of a nomogram, it is difficult to identify a significant subset of smokers with an EGFR mutation likelihood of less than 1%, and therefore, our data do not support excluding any patient subset from EGFR testing. The distinct types of KRAS mutations in smokers versus never smokers suggest that most KRAS-mutant lung cancers in never smokers are not because of second-hand smoke exposure. The higher frequency of KRAS G12C in women, their younger age, and lesser smoking history support a heightened susceptibility to tobacco carcinogens.

Provide a better insight into specific etiology and/or biology of these mutations. Therefore, we took the advantage of our large clinical dataset and conducted an in-depth retrospective analysis of more than 3,000 consecutive lung adenocarcinoma cases subjected to routine testing for EGFR and KRAS mutations over a 5-year period.

Materials and Methods

Clinical samples/patients

From September 2004 to December 2009, 3,026 lung adenocarcinomas (including 2 adenosquamous and 1 large cell carcinoma with adenocarcinoma component) were consecutively received and clinically tested for the presence of EGFR exon 19 deletion and exon 21 L858R mutation. In January 2006, testing for KRAS mutations (codons 12 and 13) was introduced for all cases negative for EGFR mutation, and 2,529 cases were received after that time. Cases with more than 1 tumor were included if: all the tumors were either mutation negative, harbored the same mutation, or if 1 tumor harbored EGFR or KRAS mutation and the other(s) was (were) mutation negative. Twenty-three patients with more than 1 tumor harboring different KRAS or EGFR mutations were excluded from the study; some of these have been reported separately (22). Clinical samples submitted for molecular testing included surgically resected tumor samples, biopsies, and cytology specimens. Clinical data were collected with the approval of the Institutional Review Board of Memorial Sloan-Kettering Cancer Center (MSKCC, New York). Stage designated as IIIB/IV included stages IIIB, IV, and multifocal bronchioloalveolar carcinoma. Smoking status was defined as never smokers (<100 lifetime cigarettes), former smokers (quit >1 year before diagnosis), or current smokers (still smoking, or quit < 1 year before diagnosis). Pack-years of smoking was defined as average number of cigarettes per day/20 × years smoking.

Mutation detection

DNA was extracted using a kit (DNaseq; Qiagen) from frozen tumor tissue or formalin-fixed paraffin embedded tumor tissue. If necessary, manual microdissection of paraffin sections was done to ensure at least 50% tumor content. EGFR mutations were detected by sensitive PCR-specific assays as previously described (23). KRAS mutations were detected by PCR sequencing of exon 2 as described (11). In limited volume tumor samples, presence of an exuberant inflammatory response or extensive fibrosis, PCR was conducted with addition of locked nucleic acid oligonucleotide to favor the amplification of mutated allele, if present (24).

Statistical analysis

Cases were divided into 3 groups based on mutation status: EGFR-mutated, KRAS-mutated, or wild-type for EGFR/KRAS. The associations were tested between the mutation groups and the demographic or clinical characteristics, and the smoking status using Fisher exact test or unpaired t test. A P value < 0.01 was considered significant. The Bonferroni method was used to control for family-wise error rate. Univariate and multivariate logistic regression analyses were used to test the association of smoking-free years and pack-years of smoking with EGFR and KRAS mutational status.

Nomogram development and validation

A nomogram was generated for the likelihood of EGFR mutation among Caucasian smokers based on the following logistic regression model: EGFR ~ β0 + β1 smoke-free-years + β2 pack-years + β3 gender + β4 age + β5 age2. The quadratic term allows a U-shape pattern of the age association with the mutation status. All analyses were conducted using the R package Design and Hmisc. An independent data set was used for validation (25); specifically, we used 375 adenocarcinoma patients who were Caucasian smokers from the Boston cohort included in the study by Girard and colleagues (25) as the validation cohort.

Results

Table 1 summarizes characteristics of patients with lung cancer with EGFR and KRAS mutations. Our lung adenocarcinoma patient population was predominantly female (1,898/3,026, 62.7%) and this was consistent in each year from 2006 to 2009 (1,624/2,620, 62%) reflecting the routine reflex EGFR/KRAS testing that was initiated in 2006 (26). Only 13% of the cases (406/3,026) were submitted for testing before 2006 and these showed a slightly higher female to male ratio (274/406, 67.5%) presumably reflecting some referral bias. Of 3,026 cases tested clinically for the 2 major EGFR mutations, 593 (20%) were mutated, including 347 exon 19 deletions (59%) and 246 L858R mutations.
(41%). Patients with **EGFR** L858R tended to be older than exon 19- mutated (median age 68 vs. 64; \( P = 8.1 \times 10^{-5} \)), reflected by an exon 19 del to L858R ratio of 3.5 less than age 50 \( ( P = 0.002) \), and of 1.0 in patients aged 70 and more \( ( P = 0.004; \text{Fig. 1}) \). Men with **EGFR** mutations were more likely than women to present at late stage (i.e., IIIB/IV) of disease (118/170, 69% vs. 235/423, 56%; \( P = 0.002; \text{Fig. 1}) \). Testing of 2,529 cases for **KRAS** mutations in the present clinical data set were tested for concomitant **EGFR** mutations (codons 12 and 13) detected 670 (26%) mutations, including G12C (39%), G12V (21%), G12D (17%), G12A (11%), and other G12 and G13 mutations (12%). Although none of the **EGFR**-mutated tumors in the present clinical data set were tested for concomitant **KRAS** mutations, our more recent experience using multiplex genotyping by MALDI-TOF mass spectrometry (Sequenom) further confirm their mutually exclusive occurrence pattern (27). No significant differences in age or stage at presentation were noted between different subtypes of **KRAS** mutations (Supplementary Fig. S2).

The positive and negative associations of **KRAS** and **EGFR** mutations, respectively, with smoking are well known but had not previously been analyzed in detail in a single large dataset. Figure 2 illustrates the frequency of **EGFR** and **KRAS** mutations in relation to smoking history and smoking pack-years. **EGFR** mutations were found in 352 of 828 (43%) of never smokers and in 241 of 2,198 (11%) former and current smokers. There was no significant difference in frequency of **EGFR** exon 19 del versus **EGFR** L858R relative to smoking pack-years (data not shown). **KRAS** mutations were found in 627/1,860 (34%) of former and current smokers and in 43/669 (6%) of never smokers, the latter proportion being notably lower than in a smaller study from our center but within the confidence interval of the previously reported higher percentage (21). Although any smoking history significantly decreased the likelihood of **EGFR** mutations, no difference was noted among smokers with less than 10 pack-years smoking history. Furthermore, in smokers of more than 10 pack-years, **EGFR** mutations were 5-fold less likely to be found than in never smokers \( ( P = 0.0001) \). In contrast, the proportion of **KRAS**-mutated lung cancers was significantly higher in smokers with any smoking history than in never smokers; among smokers, we

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<th>Table 1. Demographic and clinical characteristics of patients according to the <strong>EGFR</strong> and <strong>KRAS</strong> mutation status</th>
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**NOTE:** \( P \) values compare the frequency of **EGFR** or **KRAS** mutations between men and women, between White patients and other ethnicities/races, and between never smokers and former and current smokers, respectively.
found 15 pack-years as a cut-point above which the likelihood of a lung cancer harboring KRAS mutations was 6-fold higher than in never smokers ($P = 0.0001$). Notably, even in patients with up to 10 pack-years of smoking, tumors with EGFR mutations were still more common than those with KRAS mutations.

The effect of smoking and smoking-free period on the likelihood of EGFR mutation has been previously reported in Asian patients with lung adenocarcinoma (28, 29), but the impact of these 2 smoking variables on the proportions of lung adenocarcinomas with either EGFR or KRAS mutations has not been previously investigated in a predominantly white patient population. Because smoking-free years and pack-years of smoking are partly dependent variables, we conducted a multivariate logistic regression analysis to examine the effect of these 2 parameters in current and former Caucasian smokers. Interestingly, this showed that, among patients with lung cancer, smoking-free years change the likelihood of EGFR mutation but not that of KRAS mutation (Supplementary Table S1).

Given the variety of possible nucleotide substitutions leading to missense mutations of KRAS G12 and G13, we examined their association with smoking in this large dataset. Among never smokers, the most common KRAS mutation was G12D (56%), and G12C was the most frequent mutation among former and current smokers (41%; Fig. 3A). Never smokers were significantly more likely than former and current smokers to have $G > A$ transition mutations (as in G12D; 58% vs. 19% vs. 21%; $P = 0.0001$), whereas $G > T$ transversion mutations (as in G12C), a typical change associated with tobacco carcinogens, was the most common nucleotide change in former and current smokers (67% and 71%, respectively; Fig. 3B). Compared with other KRAS mutations types, G12C was more frequent in women ($P = 0.007$; Fig. 3C), who were also younger than men with the same mutation (median age 65 vs. 69; $P = 0.0008$). Intriguingly, women with $G > T$ transversions had smoked less (average 34 pack-years vs. 40 pack-years; $P = 0.001$; Supplementary Table S2) and were younger than men with the same nucleotide change.
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smoking-free years (P = 0.007). Fisher exact test, P value

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KRAS G12C was relatively more

frequent in women than in men (P = 0.007). Fisher exact test, P value

< 0.01 is considered significant.

Figure 3. KRAS mutation type as a function of smoking history. A, KRAS

G12D is the most common mutation in never smokers and KRAS G12C

is the most frequent mutation among former and current smokers. B,

never smokers are significantly more likely to have G > A transition

mutation (P < 0.0001), G > T

transversion is the most common

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KRAS G12C was relatively more

frequent in women than in men (P = 0.007). Fisher exact test, P value

< 0.01 is considered significant.

(median age 64 vs. 67; P = 0.006). As discussed below, this

pattern of findings suggests an increased susceptibility to

tobacco carcinogenesis in women.

There is continuing interest in using clinical variables to

prioritize EGFR mutation testing. Certain patient subsets,

such as Asians and never-smokers are routinely tested,

whereas other subsets, such as male Caucasian smokers,

are considered of lower priority for testing. However, it is

also becoming clear that these patient characteristics should

not be used individually to exclude patients from testing, as

shown in a recent analysis of a subset of the present data

(30). Given the significant associations of EGFR mutation

with sex (P = 0.01), pack-years of smoking (P < 0.0001), and

smoking-free years (P = 0.002), we used these variables

along with age to generate a nomogram to predict the EGFR

status specifically in Caucasian smokers (current and for-

mer). We excluded Asians and never smokers from the

nomogram dataset because it is generally agreed that

patients in these groups should be tested regardless. The

area under the receiver operating characteristic (ROC) curve was

0.70 (Fig. 4). To validate the performance of our

nomogram in an independent dataset, we used the Cauca-

sian smokers from the Boston cohorts used in the study by

Girard and colleagues (25). In this independent set of

patients, our nomogram generated an area under the ROC

curve for predicting EGFR status of 0.71 (Supplementary

Fig. S3). In the MSKCC training dataset (n = 2078), 16 had a

predicted probability of EGFR mutation of 1% or less, and

none were EGFR-mutated, and 421 had a predicted probability

of 0.05 or lower, of which 14 (3%) had EGFR

mutations. In the Boston dataset (n = 373) used for vali-

dation, 10 patients had probability below 1%, one of which

was EGFR mutated and 145 had a probability below 5%,

including 10 (7%) EGFR-mutated cases. As discussed

below, we view these results as indicating that, even in

the context of a rigorously developed nomogram, clinical
variables cannot be used to robustly identify patients with a negligible chance of harboring an EGFR-mutated lung cancer.

Discussion

To accurately and reliably determine the frequency of the major mutations in EGFR and KRAS in lung adenocarcinoma in relation to patient characteristics and different levels of smoking, a sufficiently large number of case subjects is necessary to provide statistical power for more detailed analyses. Here, we carried out a retrospective analysis of our large clinical database of lung adenocarcinomas with established EGFR/KRAS mutation status. (i) We found distinct differences in sex, age, and stage distribution of 2 most common types of EGFR mutations; (ii) we determined the likelihood of EGFR and KRAS mutations by intensity and duration of smoking; (iii) evaluated the effects of smoking-free period on the proportions of EGFR and KRAS mutations in lung cancers arising in former smokers; (iv) we designed a nomogram to predict presence of EGFR/KRAS mutation status among Caucasian smokers; (v) we noted a distinct distribution of types of KRAS mutations in smokers versus never smokers; and (vi) we observed significant sex and age differences in the frequency of G12C as the most common smoking-related KRAS mutation.

EGFR exon 19 del was relatively more common than L858R mutation in younger patients. Notably, of 8 patients below the age of 40 years with EGFR-mutated lung adenocarcinoma, 7 were EGFR exon 19 del. In contrast, L858R occurred in a relatively older age distribution and the patients more often presented with stage I disease. These findings may suggest a potentially more aggressive natural history of adenocarcinomas with EGFR exon 19 del compared with tumors with the L858R mutation. Differences between EGFR exon 19 del and L858R-mutated tumors have been reported in patients treated with TKI or chemotherapy. EGFR exon 19 deletions have been associated with better response to TKI and with a longer time-to-progression (TTP) and overall survival (OS) in patients with advanced adenocarcinoma (31–34). However, the better clinical outcome of patients with EGFR exon 19 del compared with patients harboring EGFR L858R mutations remains controversial; 2 prospective randomized phase III trial studies did not confirm these observations (35, 36). A distinct age and stage distribution as well as differences in response to molecular targeted therapy may suggest subtle differences in biology and/or etiology for EGFR exon 19 del and the L858R mutation.

Although typically seen in the absence of smoking history, a significant minority (11%) of former and current smokers harbors EGFR-mutated tumors, arguing against excluding smokers from EGFR testing. Moreover, among smokers with less than 10 pack-years, EGFR mutations were more common than KRAS mutations. In a study of 265 lung adenocarcinomas, some of which are included in the current dataset, Pham and colleagues found significantly fewer EGFR mutations in people who smoked for more than 15 pack-years or stopped smoking less than 25 years ago compared with individuals who never smoked (7). Our extended dataset allowed for more accurate risk stratification by pack-years categories and showed, that any smoking history at or above one pack-year significantly decreased the likelihood of EGFR-mutated tumors with no notable difference up to 10 pack-years. Although our patient population was primarily Caucasian, the results seem generalizable, as a similar relationship of EGFR mutations to pack-
years and smoke-free years has also been reported in Asian patients with lung cancer (28, 29, 37).

As expected, most of the KRAS mutations were found among current and former smokers, and consistent with other studies (38), we identified 6% of never smokers with KRAS-mutated tumors. In our earlier study that included 102 KRAS-mutated tumors (21), we failed to show predictive value of pack-years for the presence of KRAS mutations likely due to small number of cases. Here, we have shown that any smoking history significantly increases the likelihood of a KRAS mutation being found in the lung cancer. Smoking-free years provided additional value in predicting the likelihood of EGFR mutations but not that of KRAS mutations, independent of pack-years of smoking. These multivariate results suggest a model in which KRAS mutations occur at the time of smoking and may lead to cancer eventually, explaining the lack of impact of smoke-free years. This is also supported by the observation that former and current smokers have similar proportions of KRAS-mutated lung cancers (Fig. 2A). Overall, this further supports the notion that permanent DNA damage by tobacco carcinogens acquired at the time of smoking is the major source of most KRAS-mutated lung adenocarcinomas. Thus, the likelihood that a patient with lung cancer has a KRAS mutation is determined by pack-years of smoking and does not decrease significantly over time upon smoking cessation; in contrast, because overall lung cancer incidence decreases with increasing smoke-free years, the relative proportion of nonsmoking-associated cancers (represented by EGFR-mutated tumors) increases. Importantly, these data should not be misinterpreted as supporting a “protective” effect of smoking on the risk of EGFR-mutated lung adenocarcinoma.

On the basis of the need for efficient medical resource utilization and concerns regarding health care costs and possible treatment delays due to testing, there is continuing controversy regarding routine EGFR mutation testing in certain patient subsets perceived as having a low chance of EGFR mutation in their lung cancer, such as male Caucasian smokers. Using the readily available clinical parameters of age, sex, pack-years, and smoking-free years, we developed a nomogram to predict the likelihood of EGFR mutation in Caucasian current or former smokers with lung adenocarcinoma. We should note that a similar, recently published nomogram (25) differs in 2 important ways from the one we have developed. First, it includes never smokers, a group in which the value of EGFR testing is no longer in question. Second, it includes the histologic subtype of adenocarcinoma, which usually can only be properly analyzed in resection specimens, whereas decisions regarding EGFR testing are often made to be made in advanced stage patients in whom the available small biopsies are sometimes suboptimal for histologic subtyping. The accuracy of our nomogram was 70% on the source dataset and 71% in an independent validation dataset. On the basis of clinical considerations (for instance, the fact that testing of ALK fusions present in only 3–5% of lung adenocarcinomas is now indicated to select patients for crizotinib; ref. 39), we deemed that only a probability of harboring an EGFR mutation of less than 1% was clinically negligible and therefore actionable in terms of bypassing EGFR testing. However, only a very small proportion of patients fall in this category, 0.8% in the source dataset and 2.7% in the validation dataset and the latter included one incorrect prediction (10% error rate). Overall, the 70% to 71% accuracy of nomogram prediction, along with the very low proportion of predictions below 1%, suggests that clinical variables cannot be used to robustly identify patients with a negligible chance of harboring an EGFR-mutated lung cancer. Nonetheless, our nomogram may still be helpful in situations where mutation analysis for EGFR is simply not possible and the clinical parameters and smoking history are used to direct the treatment decision.

In a previous smaller study, we showed that never smokers were significantly more likely than former or current smokers to have a KRAS transition mutation (G > A) rather than the transversion mutations known to be smoking-related (G>T or G>C; ref. 21). The much larger number of cases in the present series allowed us to robustly confirm these earlier findings as well as to detect sex and age differences in the frequency of the most common smoking-related G>T transversion mutation, KRAS G12C. These findings support the notion that most KRAS-mutant lung adenocarcinomas in never smokers are not likely to be caused by environmental (second-hand) tobacco smoke, a potentially important observation in assessing the level of risk posed by such exposure.

Sex differences in sensitivity to tobacco smoke have been well documented (40). Zang and Wynder have reported that the odds ratios for major lung cancer types are consistently higher in women than in men at every level of exposure to cigarette smoke and that these differences cannot be explained by differences in baseline exposure, smoking history, or body size, but are likely because of a higher susceptibility to tobacco carcinogens in women (41). Computed tomographic screening data suggest that female smokers are almost twice as likely as male smokers to have a lung cancer detected in spite of lesser smoking histories (42). Consistent with our findings in KRAS, studies of the mutational spectrum of TP53 in relation to smoking and sex showed that cancers arising in female smokers had significantly more tobacco-related mutations (G > T transversions) than in male smokers (43, 44). Therefore, taken together, the relatively higher percentage of the female patients with tumors containing KRAS G12C (because of G>T transversion), their younger age at diagnosis, and the fewer pack-years of smoking in women with this KRAS mutation, compared with men with the same KRAS mutation, provide yet another type of data supporting the hypothesis that women are more susceptible to tobacco carcinogens.

The apparent increased susceptibility of women to tobacco carcinogenesis may reflect constitutive differences in genes encoding tobacco carcinogen–metabolizing enzymes. For example, the cytochrome P450 phase 1 detoxifying enzyme CYP1A1 shows higher expression in the normal
lungs of female smokers than male smokers (45). The most common polymorphism found in cytochrome P450 phase II detoxification enzymes is the GSTM1-null genotype, which is present in 40% to 50% of the general population due to homozygosity for a deletion polymorphism and the impact of this GSTM1 genotype may be enhanced in female smokers (46).

In summary, several observations emerge from this large analysis of the molecular epidemiology of EGFR and KRAS mutations in lung adenocarcinoma. Pack-years of smoking have a significant predictive value for the presence of EGFR and KRAS mutations and smoking-free years have additional predictive value for presence of EGFR mutations but not that of KRAS mutations. However, even in the context of a rigorously developed nomogram incorporating these clinical variables, it remains difficult to reliably identify a significant subset of smokers who would have an EGFR mutation likelihood of less than 1%, and therefore our data are not supported excluding any subset of patients with lung adenocarcinoma from EGFR testing. Our results suggest a different etiology of KRAS mutations in smokers versus never smokers and firmly support earlier observations of increased susceptibility to tobacco carcinogenesis in women. More broadly, our observations strengthen the notion that careful consideration of histologic subtypes (focusing on adenocarcinoma instead of mixing all lung cancer types) and molecular subtypes defined by distinct, nonoverlapping driver mutations (EGFR, KRAS) can help to clarify epidemiologic associations that may otherwise remain elusive (47, 48). This approach, which recognizes the possible etiologic diversity represented by different histologic and molecular subtypes, has recently been termed molecular pathologic epidemiology (49).

References

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