Examination of Targetable Lung Cancer Mutations by Smoking Status in The Cancer Genome Atlas

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BACKGROUND

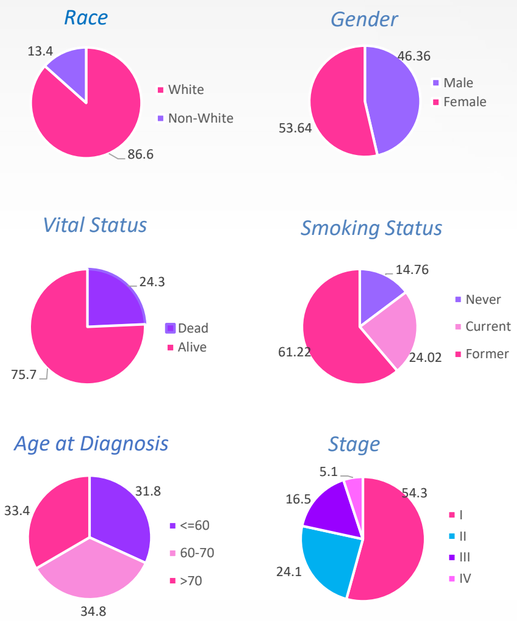
- Lung cancer is the leading cause of new cancer cases and cancer deaths in the United States. With the advent of targeted therapy it is extremely useful to identify factors that are associated with targetable driver mutations in lung cancer to better mitigate the efficacy of targeted therapy.
- Certain demographic and lifestyle risk factors, such as smoking, have shown associations with lung cancer mutations, but more research is needed to better define these relationships. The Cancer Genome Atlas (TCGA) is a comprehensive database sponsored by the National Cancer Institute, which has molecularly characterized over 20,000 primary cancers and genetic mutation samples; it provides a useful resource for research on driver mutations which has led to improvements in the ability to diagnose and treat cancer.
- The purpose of this report was to develop predictive models examining lifestyle, demographic and clinical factors, such as smoking, age, race, gender, stage, and their association with targetable driver mutations, EGFR, ALK, ROS1, KRAS and RET in lung cancer.

METHODS

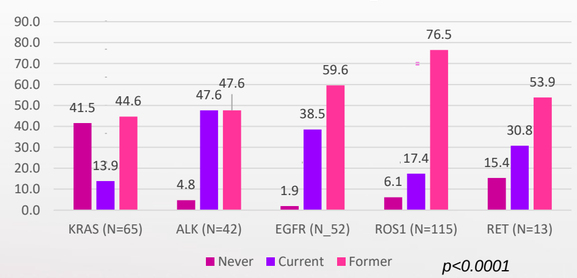
- The TCGA database was used for this analysis and provided patient-reported lifestyle, demographic and clinical information for 522 histologically confirmed adenocarcinoma lung cancer cases.
- Multiple logistic regression was used to develop predictive models that examined associations between genetic alterations in ALK, ROS1, EGFR, KRAS and ROS1 and lifestyle, demographic and clinical risk factors, including smoking, gender, race, stage and age at diagnosis.
- Odds ratios (OR) from multiple logistic regression models were used to estimate associations between risk factors and genetic driver mutations for lung cancer.

RESULTS

Patient Demographic and Clinical Characteristics (N=522)



Correlation of Smoking Status and Driver Mutations in Lung cancer



Multiple Logistic Regression Models of Clinical and Lifestyle Factors by Mutation

ALK

Multivariate	OR (95% CI)
Race (white vs nonwhite)	2.93 (1.01, 8.62)
Gender (male vs female)	1.14 (0.65, 1.99)
Stage (early vs late)	1.12 (0.82, 1.47)
Age at dx >60	1.02 (0.99, 1.05)
Nonsmoker vs current	3.99 (1.27, 12.55)
Nonsmoker vs former	3.21 (1.10. 9.35)

EGFR

Multivariate	OR(95% CI)
Race (white vs nonwhite)	1.60 (0.73, 3.51)
Gender (female vs male)	1.96 (1.06, 3.66)
Stage (late vs early)	1.47 (0.76, 2.82)
Age at dx	1.18 (0.85, 3.09)
Nonsmoker vs current	5.05 (2.13, 11.90)
Nonsmoker vs former	4.65 (2.46. 8.77)

KRAS

Multivariate	OR(95% CI)
Race (white vs nonwhite)	1.07 (0.92, 2.02)
Gender (female vs male)	1.14 (0.74, 1.76)
Stage (early vs late)	1.03 (0.61, 1.73)
Age at dx <60	1.06 (0.69, 1.63)
Current vs nonsmoker	3.08 (1.24, 7.69)
Former vs nonsmoker	5.41 (2.38. 12.20)

ROS1

Multivariate	OR(95% CI)
Race (white vs nonwhite)	1.18 (0.46, 3.00)
Gender (male vs female)	1.08 (0.58, 2.02)
Stage (early vs late)	1.01 (0.47 2.13)
Age at dx >60	1.45 (0.77, 2.73)
Current vs nonsmoker	6.58 (1.85, 23.25)
Former vs nonsmoker	2.35 (0.68, 8.13)

SUMMARY

- Of 522 lung adenocarcinoma cases, approximately 87% were white, 54% were female, 61% were former smokers and the mean age was 65 years. Mutations (%) were: KRAS (27), ALK (14), EGFR (13), ROS1 (10), RET (7).
- The multiple logistic regression model for the ALK mutation revealed a 3-fold increased odds of being white, and a 4- and 3-fold increased odds of ALK mutation for non-smokers vs current and former smokers, respectively.
- For EGFR mutations, females had 2 times increased odds vs males, and nonsmokers had a 5- and 4-fold increased odds versus current and former smokers, respectively.
- For KRAS mutations, we found that current and former smokers had a 5- and 4- fold odds, respectively, vs non-smokers.
- The ROS1 model showed a 7-fold increased chance of current vs nonsmokers having ROS1 mutations.
- There were no significant associations for RET.

CONCLUSIONS

- This study identified various patterns of association between demographic and lifestyle risk factors, especially smoking status, and driver mutations in lung cancer.
- Consistent with past findings, nonsmokers had a higher chance of developing EGFR mutant lung cancer. However, interestingly, we found that EGFR mutations are more pronounced for nonsmokers when compared to current versus former smokers.
- Interestingly, white race showed positive associations with ALK mutations. Female gender showed positive associations with EGFR mutations, as expected. Smoking was highly associated with KRAS, and was surprisingly higher for current versus former smokers. ROS1 also showed a strong positive association for current smoking but not former smoking.
- Overall, these results shed new light on race, gender, and smoking status as possible predictive factors for driver alterations, which may have diagnosis and treatment implications. These results warrants further research with more diverse populations to validate these findings.