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Journal Title: Cancer
Volume: Volume 122, Number 5
Publisher: Wiley: 12 months | 2016-03-01, Pages 766-772
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1002/cncr.29812
Permanent URL: https://pid.emory.edu/ark:/25593/rx7z6

Final published version: http://dx.doi.org/10.1002/cncr.29812

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Accessed January 14, 2018 8:08 AM EST
The Role of Race in Oncogenic Driver Prevalence and Outcomes in Lung Adenocarcinoma: Results from the Lung Cancer Mutation Consortium (LCMC)

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Abstract

BACKGROUND—The discovery of oncogenic drivers has ushered in a new era for lung cancer, but the role of these mutations in different racial/ethnic minorities is understudied. The Lung Cancer Mutation Consortium 1 (LCMC1) database was investigated to evaluate the frequency and impact of oncogenic drivers in lung adenocarcinomas in the racial/ethnic minority patient population.

PATIENTS AND METHODS—Patients with metastatic lung adenocarcinomas from 14 United States sites enrolled in the LCMC1. Tumor samples were collected from 2009 through 2012, with multiplex genotyping performed on 10 oncogenic drivers (KRAS, EGFR, ALK rearrangements, ERBB2 (formerly HER2), BRAF, PIK3CA, MET amplification, NRAS, MEK1, AKT1). Patients were classified as Caucasian, Asian, African-American (AA), and Latino. Driver mutation frequency, treatments, and survival from diagnosis were determined.
**RESULTS**—1007 patients were included. Caucasians represented the majority with N=838, AA N=60, Asians N=48, and Latinos N=28. Asian patients had the highest rate of oncogenic drivers with 39 (81%), followed by Latinos 19 (68%), Caucasians 511 (61%) and AA 32 (53%). In AA, EGFR mutation frequency was 22%, KRAS 17%, and ALK 4%. Asian patients were most likely to receive targeted therapies (51%), compared to 27% in AA. There were no significant differences in overall survival.

**CONCLUSIONS**—Differences are observed in the prevalence of oncogenic drivers in lung adenocarcinomas and consequent treatments among racial groups. The lowest frequency of drivers was seen in AA patients; however, over half of AA patients had a driver and those treated with targeted therapy outcomes similar to those of other races.

**Keywords**
Lung Cancer; Targeted Therapy; Genomics; Race; Disparities

**Introduction**
The treatment of patients with non-small cell lung cancer (NSCLC), particularly adenocarcinomas, has evolved in recent years because of the ongoing definition of oncogenic drivers and the increasing ability to effectively target these drivers. The success of this approach is most apparent in the development of small molecule tyrosine kinase inhibitors (TKI) targeting the activating mutations in the epidermal growth factor receptor (EGFR) gene and the anaplastic lymphoma kinase (ALK). The TKIs targeting EGFR and ALK have shown striking efficacy in clinical trials, and are currently the standard of care in the clinic.

Since research has focused primarily on Caucasian and Asian populations, little is known about the genomics of NSCLC in minority populations, including African Americans (AA). The definition of the molecular pathogenesis of NSCLC in AA is crucial, as this population continues to have both a higher incidence of NSCLC as well as an increased mortality from the disease as compared to Caucasians. While socio-economic and smoking status differences have been thought to be major contributing factors, potential differences in genomic characteristics may play a role as well. Current research indicates that race plays a role in the genomics of NSCLC. For example, the estimated prevalence of EGFR mutations in Asians with pulmonary adenocarcinoma is about 50-60 percent, while it is only 15-20 percent in Caucasian patients with pulmonary adenocarcinoma. The limited research in the role of oncogenic drivers in AA and Latinos consists of relatively small studies, examining the prevalence of mutations in EGFR and KRAS.

To better define the genomic characteristics of ethnic/racial minority patient populations with lung adenocarcinoma, we analyzed the dataset from the Lung Cancer Mutation Consortium (LCMC1). The LCMC1 was a multi-institutional collaborative effort that used multiplexed assays to determine the prevalence of 10 known oncogenic drivers in lung adenocarcinoma and used the results to guide treatment decisions and measure survival outcomes. Utilizing this dataset, our goal was to study whether race was associated with
differences in oncogenic driver prevalence, targeted therapy usage, and overall survival in patients with lung adenocarcinoma.

Methods

Patients with metastatic lung adenocarcinoma were enrolled from 14 major academic institutions in the United States. Institutional review board approval was obtained for all sites. Once enrolled, patients had their tumor tissue tested by various multiplex genotyping techniques for mutations in 10 known oncogenic drivers. These included EGFR, ALK, KRAS, NRAS, BRAF, ERBB2, PIK3CA, MEK, AKT1 and amplification of MET as previously described. These results were used to determine the frequency of the oncogenic drivers, help guide therapy decisions and enrollment into clinical trials, and overall survival data was collected. A detailed methodology for the LCMC mutation analysis has been published previously.

Race and ethnicity were self-reported in the study. Patients were grouped into four cohorts: Caucasian, AA, Asian and Latino. If patients self-identified as both Latino and another race, they were included in the study as Latino. Patients were excluded from this analysis if race was different from the four cohorts or was unknown.

Data on patient demographics, tumor pathology, mutation prevalence, receipt of targeted therapy and overall survival were analyzed. The patient characteristics were summarized and compared between the four cohorts by Kruskal-Wallis test, chi-square test or Fisher’s exact test, where appropriate. A logistic regression model was employed to examine the effect of race on mutation status. The overall survival function was estimated by the Kaplan-Meier method with 95% confidence intervals. The univariate and multivariable analyses were conducted using a Cox proportional hazards model. The proportional hazards assumption was evaluated with Schoenfeld residuals and a Kolmogorov-type supremum test. All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) and R package version 3.2.1 (The R Foundation for Statistical Computing) with a significant level of 0.05.

Results

A total of 1007 patients enrolled in the LCMC. There were 838 (83%) Caucasians, 60 (6%) AA, 48 (5%) Asians and 28 (3%) Latinos. 18 patients that self-identified as Latino also identified as Caucasian, and 1 identified as AA. 33 patients were excluded as race/ethnicity was listed as either not reported or not within the defined cohorts. Demographics including gender and ECOG performance were well balanced (Table 1). However, Caucasians and Asians were slightly older with a median age of 61 at diagnosis, and importantly the Asian population had the highest percentage of never smokers (77%), followed by Latinos (57%), AA (38%) and Caucasians (30%).

Table 2 reports the total number of patients with driver mutations by race. Asians had the highest proportion of patients with mutations at 81%. This also correlated with the observation that they had the highest percentage of patients treated with targeted therapies (51%). AA patients were least likely to harbor mutations (N=32, 53%) and to receive...
targeted therapy (N=16, 27%). For this study, if an oncogenic driver was unsuccessfully
tested, it was considered a negative result. Nonetheless, there were no significant differences
in the number of mutations successfully tested between races (p-value=0.149)
(Supplemental Table 1).

As it has been previously demonstrated that never smokers with adenocarcinoma are more
likely to have identifiable driver mutations, smoking status was adjusted for the model
examining the race effect on the presence or absence of any mutation (Table 3). Asians were
still significantly the most likely to have a mutation compared to Caucasians (OR: 2.23; 95%
CI: 1.05-4.73; p=0.036) and AA (OR: 3.22; 95% CI: 1.32-7.86; p=0.010). AA were less
likely to have a mutation (OR: 0.69; 95% CI: 0.41-1.18; p=0.176), with Caucasians as a
reference, although this did not reach statistical significance in a multivariable analysis.

We then sought to determine the prevalence of each individual oncogenic driver included in
the LCMC1. As expected, 57% of Asians and 20% of Caucasians had EGFR mutations.
Latinos had a relatively high frequency of EGFR mutations as well with 48% of patients.
Another notable difference was 27% of Caucasian patients had a KRAS mutation;
significantly higher than the 17% found in AA. The frequencies of the specific mutations in
EGFR and KRAS are shown in Supplemental Tables 2 and 3. The rest of the mutational
analysis is shown in Figure 1. Additionally, there were no significant differences seen in the
number of patients treated with targeted therapy by race for each individual mutation.

Overall survival (OS) time was calculated from the date of diagnosis of metastatic cancer to
date of death or last follow-up. Overall, there was no significant difference in survival
between the four race groups (p=0.289) with median OS time ranging from 2.5 to 3.3 years
(Figure 2). The median survival seen for AA that received targeted therapy was 2.7 years
(95% CI: 2.4 – NA), with a 5 year overall survival of 49.0%) (95% CI: 15.9%-75.8%). There
were no differences in survival by specific mutation for each cohort, shown in Table 4.
Finally, multivariable analysis was performed after controlling for smoking status and age,
and there remained no significant difference in overall survival between the racial groups.

**Discussion**

It is clear that the field of cancer research and treatment has entered an era of personalized
medicine, utilizing biomarkers to select patients that are more likely to benefit from a
specific drug. It has been recently shown that not all NSCLC are created equal, and some
drugs that have activity in adenocarcinoma of the lung, including pemetrexed are ineffective
in squamous cell histologies, while others like bevacizumab are potentially harmful.\textsuperscript{19, 20} The personalized approach to treatment has been further advanced in adenocarcinoma where
patients are routinely tested for oncogenic drivers to select therapy. However, published
research on oncogenic drivers in minority populations has thus far been focused on
prevalence of EGFR and ALK, with limited outcome data available.\textsuperscript{10, 13, 21, 22} This issue is
not unique to NSCLC, as AA and Latinos have traditionally been underrepresented in
clinical trials.\textsuperscript{23}
The LCMC1 dataset allowed for studying the genomic characteristics among lung adenocarcinoma patients based on racial background. A prior study examined the rate of KRAS and EGFR in AA from paraffin-embedded resected tumors, and found EGFR mutations in 23/121 (19%) patients and KRAS in 21/121 (17%). When compared to Caucasians, there was no difference in the frequency of EGFR mutations, but significantly less KRAS mutations in AA (17% vs. 26%, p=0.04). This is consistent with our results, where there was a difference in prevalence of KRAS between AA and Caucasians, but not EGFR. The comparable prevalence of EGFR in Caucasians and AA has been seen in various studies. However, the difference in KRAS frequency is sparsely reported in the literature. A recently published study using genomic techniques to examine 26 genes from NSCLC from 137 AA patients, found no difference in specific gene mutations as compares to Caucasians. Interestingly, similar to our study, the authors found with their extended genomic panel that AA had overall less probability of any mutation being detected (OR: 0.582; p = 0.025), with 68% of AA NSCLC samples as compared to 59% in Caucasians not having a mutation identified. Nonetheless, in our study AA patients with a driver mutation and treated with targeted therapy had similar outcomes to other groups, and therefore patients of all races should be assessed and treated according to practice guidelines.

We found a significantly high rate of EGFR mutations in the Latino population. However, it is difficult to make broad generalizations based on his finding as there is potential bias given the small sample size. There are limited data available for this population, but rates of EGFR mutations from a US-Hispanic group were found to be 15%, and from a large cohort of 5738 Latin American NSCLC patients, the prevalence was 26%. These data, along with our own, suggest that the true frequency of EGFR mutations in the Latino population likely falls between that of Asians and Caucasians and may be related to the ethnic background of the population. We additionally present in our study the frequencies of other gene mutations between races, but this would require much larger sample sizes to determine potential differences based on race and ethnic background. Overall, it is interesting to note that even after controlling for age and smoking status, Asians still were far the most likely to have a mutation, driven largely by EGFR. While consistent with a known EGFR mutation rate of about 51%, it remains unclear why Asians have such high mutation prevalence, as compared to other races. While genetic polymorphisms, environmental factors, and other factors may all be contributing, further research is needed.

Despite the advantages that the LCMC1 dataset provides, there are several limitations to our study. Firstly, race was self-reported in the LCMC1, and classifying race in strict categories for clinical trials can be difficult as an individual’s race can be a challenge to define. Research is evolving on using genetic markers to define race, but currently self-identification is the standard. Additionally, for certain cohorts the sample sizes were relatively small, making it unclear if the findings would hold when applied to a broader population of the same ethnic group. For instance, we found no difference in overall survival between the groups, but it would be interesting to have a larger minority dataset to see if this holds true. Furthermore, the patients in our study were treated and followed on a clinical trial, but it would be important to know in non-academic settings if minority populations are being appropriately genomically tested and treated, and if there are any differences in outcomes. Prior studies have shown that minorities often receive different treatments and have worse outcomes.
outcomes than other populations.\textsuperscript{6, 7, 28} Finally, since the LCMC1 was conducted, genomic sequencing has advanced significantly and it would be important to investigate lung adenocarcinomas by race in more depth than the 10 oncogenes tested for this study.

In our study, differences exist between the genomic composition of lung adenocarcinomas between races including \textit{KRAS} and \textit{EGFR}, as well as in the overall prevalence of detectable oncogenic drivers. The causes of these differences remain unclear, but are important areas of research to improve cancer care for all patients. Conversely, it is important to note that there were actionable oncogenic drivers found in all cohorts of our study. It is therefore important that ensure that all patients with advanced adenocarcinoma of the lung be tested and treated with targeted therapies when appropriate, regardless of race. Finally, inclusion of minorities in clinical trials is important in order to generalize the results to the overall population.

\section*{Supplementary Material}
Refer to Web version on PubMed Central for supplementary material.

\section*{Acknowledgments}
Grant Number: P30 CA008748

\section*{References}


The discovery of oncogenic drivers has ushered in a new era for lung cancer and other cancers, but the prevalence and impact of these mutations in different racial/ethnic minorities in lung adenocarcinomas are understudied. We investigated the Lung Cancer Mutation Consortium 1 (LCMC1) database to evaluate the frequency and impact of oncogenic drivers in lung adenocarcinomas in the racial/ethnic minority patient population.
**Figure 1. Mutational Prevalence by Race**

This figure represents the results of the mutational analysis by race.
Figure 2. Overall Survival
This figure demonstrates the overall survival or the patients by race.
### Table 1

Patient Demographic Information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caucasian N=838</th>
<th>African American N=60</th>
<th>Asian N=48</th>
<th>Latino N=28</th>
<th>P-value *&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of metastatic disease, Median (Range)</td>
<td>61 (18 - 88)</td>
<td>57 (30 - 79)</td>
<td>61 (32 - 75)</td>
<td>56 (38 - 68)</td>
<td>0.015</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>340 (41)</td>
<td>25 (42)</td>
<td>21 (44)</td>
<td>11 (39)</td>
<td>0.972</td>
</tr>
<tr>
<td>Female</td>
<td>498 (59)</td>
<td>35 (58)</td>
<td>27 (56)</td>
<td>17 (61)</td>
<td></td>
</tr>
<tr>
<td>Performance status at enrollment *&lt;sup&gt;x&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>292 (35)</td>
<td>18 (31)</td>
<td>15 (32)</td>
<td>8 (29)</td>
<td>0.509</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>450 (55)</td>
<td>34 (58)</td>
<td>30 (64)</td>
<td>19 (68)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 2</td>
<td>83 (10)</td>
<td>7 (12)</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Ever smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoker</td>
<td>583 (70)</td>
<td>37 (62)</td>
<td>11 (23)</td>
<td>12 (43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never smoker</td>
<td>251 (30)</td>
<td>23 (38)</td>
<td>37 (77)</td>
<td>16 (57)</td>
<td></td>
</tr>
<tr>
<td>Prior chest surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>318 (42)</td>
<td>18 (33)</td>
<td>12 (30)</td>
<td>3 (14)</td>
<td>0.015</td>
</tr>
<tr>
<td>No</td>
<td>439 (58)</td>
<td>37 (67)</td>
<td>28 (70)</td>
<td>19 (86)</td>
<td></td>
</tr>
<tr>
<td>Prior chest radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>169 (21)</td>
<td>15 (26)</td>
<td>9 (19)</td>
<td>3 (12)</td>
<td>0.478</td>
</tr>
<tr>
<td>No</td>
<td>644 (79)</td>
<td>42 (74)</td>
<td>38 (81)</td>
<td>23 (88)</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>488 (60)</td>
<td>38 (64)</td>
<td>28 (58)</td>
<td>21 (78)</td>
<td>0.246</td>
</tr>
<tr>
<td>No</td>
<td>332 (40)</td>
<td>21 (36)</td>
<td>20 (42)</td>
<td>6 (22)</td>
<td></td>
</tr>
<tr>
<td>Brain met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>155 (22)</td>
<td>11 (21)</td>
<td>9 (23)</td>
<td>9 (35)</td>
<td>0.469</td>
</tr>
<tr>
<td>No</td>
<td>565 (78)</td>
<td>41 (79)</td>
<td>31 (78)</td>
<td>17 (65)</td>
<td></td>
</tr>
<tr>
<td>Liver met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>73 (10)</td>
<td>4 (8)</td>
<td>5 (13)</td>
<td>3 (12)</td>
<td>0.769</td>
</tr>
<tr>
<td>No</td>
<td>651 (90)</td>
<td>47 (92)</td>
<td>33 (87)</td>
<td>22 (88)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number of patients (%) or median (range).

* Data not available in 13 Caucasians, 1 AA, and 1 Asian

*<sup>†</sup>P-value is calculated by Kruskal-Wallis test for age; chi-square test or Fisher's exact test for categorical variables where appropriate.
### Table 2

**Driver Mutation Prevalence**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caucasian N=838</th>
<th>African American N=60</th>
<th>Asian N=48</th>
<th>Latino N=28</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>511 (61)</td>
<td>32 (53)</td>
<td>39 (81)</td>
<td>19 (68)</td>
<td>0.017</td>
</tr>
<tr>
<td>No</td>
<td>327 (39)</td>
<td>28 (47)</td>
<td>9 (19)</td>
<td>9 (32)</td>
<td></td>
</tr>
<tr>
<td>Total number of mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>22 (3)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>3 (11)</td>
<td>0.043</td>
</tr>
<tr>
<td>&lt;= 1</td>
<td>816 (97)</td>
<td>60 (100)</td>
<td>46 (96)</td>
<td>25 (89)</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>216 (26)</td>
<td>16 (27)</td>
<td>24 (51)</td>
<td>10 (36)</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>616 (74)</td>
<td>43 (73)</td>
<td>23 (49)</td>
<td>18 (64)</td>
<td></td>
</tr>
</tbody>
</table>

*Oncogenic drivers that were not successfully tested were considered negative for this analysis.

†P-value is calculated by chi-square test or Fisher's exact test for categorical variables where appropriate.
Table 3
Multivariable Analysis Of The Presence of Any Mutation For Race, Controlled For Smoking

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td>0.082 *</td>
</tr>
<tr>
<td>African American</td>
<td>0.69 (0.41-1.18)</td>
<td>0.176</td>
</tr>
<tr>
<td>Asian</td>
<td>2.23 (1.05-4.73)</td>
<td>0.036</td>
</tr>
<tr>
<td>Latino</td>
<td>1.19 (0.53-2.67)</td>
<td>0.681</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Ever smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoker</td>
<td>0.64 (0.48-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Never smoker</td>
<td>1 (Ref)</td>
<td></td>
</tr>
</tbody>
</table>

970 observations were used.

* Overall p-value for race.
### Table 4

Univariate Survival Analysis For Race Within Patients With Individual Mutations

<table>
<thead>
<tr>
<th>Race</th>
<th>EGFR</th>
<th>KRAS</th>
<th>ALK</th>
<th>MET</th>
<th>NRAS</th>
<th>PIK3CA</th>
<th>ERBB2</th>
<th>BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>0.56 (0.20-1.54)</td>
<td>1.09 (0.48-2.47)</td>
<td>*</td>
<td>*</td>
<td>2.45 (0.15-39.72)</td>
<td>*</td>
<td>0.76 (0.10-6.01)</td>
<td>*</td>
</tr>
<tr>
<td>Asian</td>
<td>1.35 (0.73-2.51)</td>
<td>0.61 (0.15-2.47)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>0.41 (0.05-3.42)</td>
<td>1.36 (0.37-5.07)</td>
<td>*</td>
</tr>
<tr>
<td>Latino</td>
<td>1.00 (0.36-2.76)</td>
<td>2.08 (0.51-8.43)</td>
<td>1.14 (0.15-8.42)</td>
<td>1.53 (0.18-12.82)</td>
<td>*</td>
<td>1.03 (0.13-8.39)</td>
<td>*</td>
<td>1.01 (0.11-8.86)</td>
</tr>
</tbody>
</table>

Note: Data are presented as hazard ratio (HR) (95% CI); Caucasian was set as a reference level; No comparisons were significantly different.

* Mutation prevalence too infrequent to run analysis.