EGFR Mutations in US Hispanic Versus Non-Hispanic White Patients With Lung Adenocarcinoma

Wei Zhang, MD; Elizabeth B. McQuitty, MD; Randall Olsen, MD, PhD; Hongxin Fan, MD; Heather Hendrickson, MB(ASCP)^{CM}, MBA; Fermin O. Tio, MD; Keith Newton, MB(ASCP)^{CM}; Philip T. Cagle, MD; Jaishree Jagirdar, MD

• ***Context.***—**Lung cancer is the leading cause of cancer deaths worldwide. First-generation tyrosine kinase inhibitors improve progression-free survival in lung cancers with epidermal growth factor receptor (*EGFR*) mutations. *EGFR* mutations occur predominantly in exons 19 and 21 in lung adenocarcinomas of Asians (∼30%), whites (∼15%), and African Americans (∼19%). However, minimal information exists on the prevalence or type of genetic changes that occur in lung cancers in US Hispanic patients. We investigated the *EGFR* mutation frequency in primary lung adenocarcinomas in US Hispanics compared with non-Hispanic whites.**

Objective.—**To evaluate *EGFR* mutations in lung adenocarcinomas from US Hispanic patients compared with those from non-Hispanic white patients.**

Design.—**DNA samples were extracted from paraffin-embedded tissue of consecutive lung adenocarcinomas from 83 patients. Samples were collected from 40 Hispanics and 43 non-Hispanic whites. Mutations in *EGFR* were analyzed using a custom assay.**

Results.—**Fourteen of 83 patients (16.9%) had *EGFR* mutations in their tumor DNA, including 6 of 40 Hispanics (15.0%) and 8 of 43 non-Hispanic whites (18.6%). No association with age, sex, or tumor stage was identified. Smoking history could not be obtained for most of the 83 patients, although 8 of the 11 patients with *EGFR* mutations for whom smoking history was obtained were nonsmokers. Most of the tumors with *EGFR* mutations (12 of 14; 85.7%) were acinar with lepidic or papillary subtypes. *EGFR* mutations occurred in exon 19 (42.8%), exon 18 (28.6%), exon 20 (28.6%), and exon 21 (14.3%). Two cases had 2 mutations identified in different exons.**

Conclusion.—**The frequency of *EGFR* mutations is similar in US Hispanics compared with non-Hispanic whites.**

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Lung cancer is the leading cause of cancer-related deaths in the United States and worldwide. More than two-thirds of all patients with lung cancer are seen with advanced disease, and the overall 5-year survival rate of all lung cancer patients remains less than 15%.[1,2] Platinum-based chemotherapy constitutes the standard first-line treatment for stage IV non–small cell carcinoma of the lung, but 5-year survival remains approximately 2% for these patients.[3–5] First-generation tyrosine kinase inhibitors (TKIs) for epidermal growth factor receptor (*EGFR*) mutations, including gefitinib and erlotinib, significantly improve progression-free survival in stage IV lung cancer patients whose lung cancers are positive for specific driver mutations in the *EGFR* gene.[6–11] Most lung cancers that are positive for actionable *EGFR* mutations are adenocarcinoma cell type. These data recently led to the publication of an evidence-based, multidisciplinary, international Molecular Testing Guideline for Selection of Lung Cancer Patients for *EGFR* and *ALK* Tyrosine Kinase Inhibitors from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology.[12,13] The guideline provides a robust strategy for the selection of lung cancer patients for clinically validated predictive biomarker testing. According to these guidelines, *EGFR* molecular testing should be used to select patients for *EGFR*-targeted TKI therapy, and adenocarcinoma cell type is the basis for selecting lung cancers for biomarker testing.

Approximately 90% of the TKI-responsive *EGFR* mutations in lung adenocarcinomas are deletions in exon 19 and a point mutation that substitutes an arginine for a leucine at codon 858 (L858R) in exon 21. Point mutations or insertions in exons 18 and 20 are other genetic alterations commonly included.[14,15]

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From the Department of Pathology (Dr Zhang), Molecular Diagnostics Laboratory (Dr Fan), and Department of Pathology (Dr Jagirdar), The University of Texas Health Science Center at San Antonio, and Laboratory Service, Audie L. Murphy Memorial Veterans Affairs Medical Center (Dr Tio), San Antonio; and Department of Pathology and Immunology, Baylor College of Medicine (Dr McQuitty), and Department of Pathology and Genomic Medicine, The Methodist Hospital (Drs Olsen and Cagle, Ms Hendrickson, and Mr Newton), Houston, Texas.

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Reprints: Jaishree Jagirdar, MD, Department of Pathology, University of Texas Health Science Center, Mail Code 7750 7703, Floyd Curl Drive, San Antonio, TX 78229-3900 (e-mail: Jagirdar@UTHSCSA.edu).

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Sex	Age at Diagnosis, y	Race/Ethnicity	Smoking Status	*EGFR* Mutation	Growth Pattern
Female	43	Non-Hispanic white	No	Exon 19 E746_A750del	Acinar and papillary
Female	62	Non-Hispanic white	No	Exon 19 E746_A750del	Acinar
Female	46	Non-Hispanic white	No	Exon 20 S768I	Lepidic and focal acinar and papillary
Male	79	Non-Hispanic white	No	Exon 20 H773>NYP	Acinar, bronchioloalveolar carcinoma
Male	88	Non-Hispanic white	No	Exon 18 E709K, exon 20 S761I	Acinar and papillary
Male	63	Non-Hispanic white	Yes	Exon 18 E709K, exon 21 L861Q	Acinar
Male	58	Non-Hispanic white	Yes	Exon 21 L861Q	Acinar
Male	64	Non-Hispanic white	Yes	Exon 18 E709K	Acinar
Female	63	Hispanic	Unknown	Exon 19 del NOS	Acinar
Female	61	Hispanic	No	Exon 19 E746_A750del	Acinar and solid
Male	69	Hispanic	No	Exon 19 del NOS	Lepidic and acinar
Male	83	Hispanic	No	Exon 18 E709K	Acinar
Male	69	Hispanic	Unknown	Exon 20 H773>NYP	Solid with signet ring feature
Male	63	Hispanic	Unknown	Exon 19 del NOS	Solid

Abbreviations: *EGFR*, epidermal growth factor receptor; NOS, not otherwise specified.

for Molecular Pathology guidelines,[13] clinical criteria such as racial/ethnic group, sex, or smoking status are not recommended as a basis for selecting patients for *EGFR* TKI therapy. That is, these criteria exclude too many patients who might benefit from targeted therapy. However, the frequency of actionable *EGFR* mutations in racial/ethnic groups is important to assess because of its possible clinical impact on specific communities. The frequency of *EGFR* mutations is approximately 30% in Asian populations, 15% in whites, and 19% in African Americans.[16,17] However, data on the frequency of *EGFR* mutations in lung adenocarcinoma among Hispanics in the United States is not currently available, to our knowledge. Of note, the frequency of *EGFR* mutations in non–small cell carcinoma of the lung has been reported to be 33.2% in Latin American countries overall, which is similar to the Asian population.[18,19] The objective of this study was to determine the prevalence and type of *EGFR* mutations that occur in adenocarcinomas among the US Hispanic population.

MATERIALS AND METHODS

With approval by the institutional review board (IRB HSC20110421H), lung adenocarcinoma tumor tissue samples from 83 patients (40 patients who self-identified as Hispanic and 43 non-Hispanic white patients) were retrieved from the surgical pathology archives at The University of Texas Health Sciences Center at San Antonio and the Audie L. Murphy Memorial Veterans Affairs Medical Center in San Antonio. Demographic information was collected by medical record review and included sex, age and tumor stage at diagnosis, and smoking status. In 2 cases, a second sample was obtained from the adenocarcinoma, providing a total of 85 samples.

Formalin-fixed, paraffin-embedded tumor tissue was cut in 10-μm sections onto uncharged glass slides. One slide from each case was reviewed by a board-certified pathologist (JJ) and marked for macrodissection to enrich the sample for tumor cells compared with benign cells. A minimum of 50% tumor cells in the sample was sought. The number of sections used for genomic DNA extraction ranged from 5 to 10 depending on tumor volume. Tissue was deparaffinized using CitriSolv (Thermo Fisher Scientific Inc, Waltham, Massachusetts), followed by treatment in 100% ethanol. Puregene Cell Lysis Buffer (Qiagen, Germantown, Maryland) was applied, and tumor tissue was scraped from the slides and digested with proteinase K. DNA was purified using an EZ1 tissue kit (Qiagen) on an automated workstation according to the manufacturer's instructions. The quantity and quality of genomic DNA were assessed using a spectrophotometer (NanoDrop, Thermo Fisher Scientific Inc, Waltham, Massachusetts), and genomic DNA was stored at –20°C.

A custom assay to test for the *EGFR* mutations was designed using the MassARRAY Assay Design 3.0 software (Sequenom, San Diego, California). Molecular testing was performed at The Methodist Hospital, Houston, Texas, using a MassARRAY instrument (Sequenom). Locus-specific polymerase chain reaction and detection primers were selected, and lung tumor DNA was amplified in a multiplex polymerase chain reaction, followed by a single-base extension reaction. The resulting nucleotides were desalted and transferred to a 384-element SpectroCHIP array (Sequenom), and alleles were discriminated by mass spectrometry.

χ^2 Contingency table analysis was used to identify significant associations between mutation status and sex, age at diagnosis, race/ethnicity, smoking status, and tumor stage at diagnosis. Significance was set at $P < .05$ by Fisher exact test.

RESULTS

In total, 85 lung adenocarcinoma tissue samples collected from 83 patients (40 Hispanic and 43 non-Hispanic white) were available for testing. Of the 40 Hispanic patients, 5 were nonsmokers, 13 were smokers, and 22 had unknown smoking status. Of the 43 non-Hispanic white patients, 8 were nonsmokers, 21 were smokers, and 14 had unknown smoking status. The 14 Hispanic female patients were nonsmokers or had an unknown smoking status. Among 12 non-Hispanic white female patients, 2 were smokers, and 10 were nonsmokers or had unknown smoking history. The median ages at diagnosis were 63 years among Hispanics and 62 years among non-Hispanic whites. The average ages at diagnosis were 65 years for white men and 58 years for white women. The average ages at diagnosis were 68 years for Hispanic men and 59 years for Hispanic women. Women were younger than men at diagnosis of lung adenocarcinoma for both populations.

Fourteen of 83 patients (16.9%) had *EGFR* mutations in their tumor DNA. Six were Hispanic (15.0%), and 8 were non-Hispanic white (18.6%) (Table). No statistically significant difference in *EGFR* mutation rates was observed between Hispanic and non-Hispanic white patients in our series ($P = .66$). Similarly, no significant association between *EGFR* mutations and sex was identified ($P = .70$). Smoking history could not be obtained for most of the 83 patients, although 8 of the 11 patients with *EGFR* mutations for whom smoking history was obtained were nonsmokers. Most of the tumors with *EGFR* mutations (12 of 14; 85.7%)

were acinar with lepidic or papillary subtypes in both populations. *EGFR* mutations occurred in exon 19 (42.8%), exon 18 (28.6%), exon 20 (28.6%), and exon 21 (14.3%). Two cases had 2 mutations in different exons. In the 2 cases in which 2 samples were obtained, both samples showed identical results.

COMMENT

The frequency of the *EGFR* mutations in different populations is well documented.[16–19] For example, the mutation rate is higher in Asians and female nonsmokers.[20] However, the *EGFR* mutation rate in lung adenocarcinomas among the US Hispanic population has not been previously investigated to our knowledge. In this limited study, we demonstrate that the *EGFR* mutation rate in US Hispanics is not significantly different from that in non-Hispanic whites. Unexpectedly, we discovered that US Hispanics seem to have a lower frequency of actionable *EGFR* mutations in their lung cancers than those reported in Latin America. Arrieta et al,[18] in a study of 1150 patients in Latin America, found that the frequency of *EGFR* mutations in non–small cell carcinoma of the lung was 33.2% overall, including 19.3% in Argentina, 24.8% in Colombia, 31.2% in Mexico, and 67.0% in Peru. Of note, these authors' findings may be skewed because of the disproportionate inclusion of nonsmokers and women. The number of Hispanic women was approximately the same as the number of non-Hispanic white women in our study. Smoking history could not be obtained for most of the 83 patients herein, although 8 of the 11 patients with *EGFR* mutations for whom smoking history was obtained were nonsmokers. Also, we observed *EGFR* mutations mostly in lepidic, papillary, or acinar subtypes of adenocarcinoma, similar to previous findings.[21]

Most of the genetic alterations identified in our study were deletions in exon 19. Exon 21 mutations occurred in only 14.3% of mutation-positive tumors, with proportionately more mutations in exons 18 and 20. None had the exon 20 T790M mutation associated with acquired resistance to *EGFR* TKI treatment.[13,22,23] Arrieta et al,[18] in their Latin American patients, showed that 48.4% of mutation-positive patients had exon 19 deletions, and 49.0% had the L858R mutation (exon 21). These findings are consistent with data collected from Asian (60% exon 19 and 40% exon 21) and European (62% exon 19 and 38% exon 21) populations.[24]

In summary, our limited study found that the frequency of *EGFR* mutations in lung adenocarcinomas among US Hispanics is similar to the frequency among non-Hispanic whites. Hispanics in the United States with lung adenocarcinoma can be expected to benefit clinically from *EGFR* mutation testing.

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