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Lung Cancer Mutations and Use of Targeted Agents in Hispanics

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Abstract

Hispanic/Latinos (H/L) are expected to grow to over 24% of the USA population by 2050 and lung cancer is the number one cause of cancer death among H/L men. Due to the information that is becoming available *via* genetic testing, lung cancer molecular profiling is allowing for increasing application of personalized lung cancer therapies. However, to benefit the most people, development of these therapies and genetic tests must include research on as many racial and ethnic groups as possible. The purpose of this review is to bring attention to the fact that the mutations driving lung cancer in H/Ls differ in frequency and nature relative to the non-Hispanic White (WNH) majority that dominate current databases and participate in clinical trials that test new therapies. Clinical trials using new agents targeting genetic alterations (*driver mutations*) in lung cancer have demonstrated significant improvements in patient outcomes (for example, gefitinib, erlotinib or crizotinib for lung adenocarcinomas harboring *EGFR* mutations or *EML4-ALK* fusions, respectively). The nature and frequencies of some lung cancer driver mutations have been shown to be considerably different among racial and ethnic groups. This is particularly true for H/Ls. For example, several reports suggest a dramatic shift in the mutation pattern from predominantly *KRAS* in a WNH population to predominantly *EGFR* in multiple H/L populations. However, these studies are limited, and the effects of racial and ethnic differences on the incidence of mutations in lung cancer remain incompletely understood. This review serves as a call to address this problem.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

PATIENT CONSENT

Declared none.

Keywords

Hispanic; latino; lung cancer; mutations; targeted agents

INTRODUCTION

Lung cancer is the third most commonly diagnosed cancer among Hispanic/Latino (H/L) men and women, and the number one cause of cancer death among H/L men [1]. The word Hispanic refers to persons of Spanish origin and unlike African American (AA), persons of Hispanic origin may be of any race(s) and Latino or Hispanic are self-identified terms of ethnicity. For the purpose of this review, we will use the abbreviation H/L to refer primarily to Hispanics living in the USA, Latin America (LA) and the Caribbean.

The majority of lung cancers (~85%) are classified as non-small cell lung cancer (NSCLC). The two most common histological subtypes of NSCLC are lung adenocarcinomas (LUAD) and lung squamous cell carcinomas (LUSC). Before 2005, a “one size fits all approach” utilizing platinum-based chemotherapeutic doublets was the standard of care for stage IV NSCLC; however, the identification of driver mutations in genes that encode proteins important for cell proliferation has resulted in a paradigm shift in the treatment of stage IV NSCLC. More than 50% of NSCLC express at least one of 12 known driver mutations, including mutations in *KRAS*, *EGFR*, *ALK*, *MET*, *HER2*, *BRAF*, *AKT1*, *PIK3CA*, *MAP2K1*, *MEK*, *ROS1* and *RET* [2, 3]. Although practice varies significantly from one treatment center to the next, it is now standard of care in the US to determine the molecular status of a subset of these genes to select optimal therapy for stage IV NSCLC adenocarcinomas, and understanding the pathologic and molecular characteristics of the tumors is becoming increasingly important to improve patient outcomes.

The incidence rates and mortality of lung cancer is not the same among the different racial and ethnic groups in the USA. For example, AA patients with NSCLC have an increased incidence and decreased survival of NSCLC when compared to WNH. Research in NSCLC has focused on AA, Asians and White non-Hispanic (WNH) patients, but surprisingly few studies have focused on H/Ls given their impact on the USA’s economy and health care system. According to the USA census, H/L presently comprise 11% of the USA population and are expected to grow to 24% of the total USA population by 2050. Studies have reported that H/L have a 50% lower lung cancer mortality rates than WNHs; despite being less likely to receive treatment and more likely to be diagnosed at advanced stages (this “*Hispanic Paradox*” was reviewed recently in Patel *et al.* [4]). Due to the amount of genetic information already available and rapid generation of new data using the high-throughput next generation sequencing platforms, informed lung cancer molecular profiling will allow for personalized lung cancer therapies based on the patient’s mutation profile. These analyzes have revealed that lung cancer has a high mutation burden [5–9] with broad-spectrum mutational patterns that may differ significantly in different populations [10]. Because of this it becomes very important that the development of therapies considers ethnicity and geographical differences in planning future clinical trials, and the generation of a genomic landscape of H/L NSCLC.

Recently, high-throughput genomic platforms and bioinformatics tools have expedited the advancement of genomic research, allowing for personalized lung cancer molecular profiling. The most frequently mutated genes in lung cancer are *TP53* (53.6%), *KRAS* (16.1%), *STK11* (9.8%), *EGFR* (7.2%), *KEAP1* (6.6%), and *NFE2L2* (4.5%). First-generation tyrosine kinase inhibitors (TKIs) targeting 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. The frequency of *EGFR* mutations has been extensively studied in some groups and determined to be approximately 30% for Asian populations, 15% for WNH, and 19% for AA in well-powered studies of over 100 cases considered [11–17]. However, only very small studies (less than 50 cases) have examined the rate of EGFR mutations in USA H/Ls [18].

HISPANICS/LATINOS AND LUNG CANCER

H/Ls are usually classified together as one broad ethnic group; however, H/Ls are diverse from a cultural, social, economical, and genetic perspective. The heterogeneity among H/Ls, defined by geographic origin (*e.g.*, Argentina, Puerto Rico, Mexico, Peru), has not been taken into consideration when examining cancer incidence and morbidity. Genetically H/L populations are a mixture of 3 ancestral populations (African, European and Indigenous American), and the ratio of each ancestral population can vary considerably [19] among different H/L groups. For example, previous studies using Ancestry Informative Markers (AIMs) have shown that Puerto Ricans carry more European and African ancestry, but significantly less Indigenous American ancestry when compared to Mexicans [20]. The contribution of each of these ancestral genetic backgrounds could explain discrepancies in disease susceptibility between different H/L groups. For instance, in a study of Latinas from the San Francisco Bay area, higher European ancestry correlated with higher breast cancer risk [21].

U.S. H/Ls have been shown to have a lower cancer incidence than USA WNHs for some common cancer sites, (breast, colorectal, prostate, and lung cancers), and a higher incidence of cancers associated with infections and lower socioeconomic status, such as cervical, liver, and stomach cancers [1]. It has been reported previously that H/Ls have a lower incidence of lung cancer compared with both AAs and WNHs, despite a socioeconomic status that would predict otherwise. However, the impact of Hispanic ethnicity on the survival of patients with NSCLC is less clear. In a recent study by Saeed *et al.* [22], data from 172,398 NSCLCs from the SEER database were used to determine the impact of race/ethnicity on overall survival. Compared with WNH patients, H/L NSCLC patients were found to have a statistically significant better overall survival, and AA patients had worse survival. Interestingly, within the bronchioalveolar carcinoma (BAC) subtype, H/L patients tend to be over represented (8.1% H/L vs 5.5% WNH vs 3.7% AA). This led the authors to hypothesize that the overall survival advantage of H/L NSCLC patients may be because of their tendency toward developing histologic subtypes of NSCLC associated with better prognosis.

Alterations in Lung Cancer Targetable Genes

As stated before, different signaling pathways are altered in NSCLC that can be impacted considerably by molecularly targeted therapy. As the number of genes and alterations identified continues to grow at a rapid pace, racial and ethnic differences are being found (reviewed in El-Telbany *et al.* [23]). These differences provide important information for the development of targeted therapies in this era of personalized medicine. Below, we summarize some of the reports on incidence and type of driver mutations in H/L. It should be noted that except for the study by Arrieta *et al.* [24], most of these studies include a small number of H/L patients (less than 200 cases) and in general, information about alterations in H/L is based on ethnicity self-reporting (no ancestry informative marker studies), and using PCR and sequencing of areas where mutations have already been described (“hotspots”).

EGFR

The *EGFR* mutation database has grown exponentially following several large clinical trials, which accrued thousands of patient tumor samples. *EGFR* mutations that exist in NSCLC are predominantly somatic, although rare germline mutations including the T790M (“gatekeeper”) mutation [25] are observed. Exons 19 and 21 within the *EGFR* tyrosine kinase domain are the most frequently sequenced regions, and are generally covered by clinical *EGFR* mutation assays as they contain the mutational hot spots. The majority of the currently identified *EGFR* kinase mutations can be attributed to the L858R missense mutation in exon 21 and in-frame deletions in exon 19, both being sensitive to EGFR TKIs. There is also evidence that different *EGFR* mutants may have different properties with respect to sensitivity to TKIs [26]. There are other *EGFR* mutations outside these hot spot exons, some having an effect on TKI sensitivity, but they occur at a lower frequency and are found primarily in Exons 18 and 20 [12].

Interestingly, as mentioned earlier, the frequency of *EGFR* mutations differs among different racial and ethnic groups. *EGFR* mutations are frequent (30%) in East Asian NSCLC patients compared to 10% in WNH [23]. The *EGFR* mutation frequency was found to be higher among Asian never smokers at a rate fluctuating between 48% to 75.3% [27, 28]. *EGFR* mutations are associated with adenocarcinoma histology, older age, nonsmokers and absence of *KRAS* mutations. Several studies with gefitinib and erlotinib as first-line therapy led to first-line EGFR TKI use among NSCLC patients with *EGFR*-sensitizing mutations in a targeted therapy paradigm [29]. However, with increasing experience with EGFR TKIs, it became evident that clinically acquired resistance develops in the majority of patients. Several molecular alterations have been proposed to explain the acquired TKI resistance, such as MET amplification, Her2 amplification, PTEN loss and changes in histology. However, the predominant resistance mechanism was found to be acquisition of the *EGFR* T790M mutation in exon 20, which is part of the “gatekeeper” residue within the kinase domain [30]. To date, the acquired genetic resistance has not been found to be exclusive to any racial group.

Until recently, few studies have addressed genomic differences in NSCLC patients from LA, and the information regarding lung cancer in the H/L population was mostly based on evidence obtained from the H/Ls in the USA. However, a few studies aimed at

characterizing lung cancer genetic alterations in LA have recently been reported (Table 1). The most thorough study so far characterized *EGFR* and *KRAS* mutation nature and frequency in NSCLC patients from Argentina, Colombia, Mexico, and Peru [24]. The average frequency of *EGFR* mutations in all 4 countries was 32.5%, with similar frequencies of 19.3% in Argentina, 24.8% in Colombia and 31.2% in Mexico. Interestingly, the frequency of *EGFR* mutations in Peru is particularly high (67%), perhaps due to the Asian migration. In this LA cohort, 48.4% of the mutation positive patients had exon 19 deletions, and 49% had the L858R mutation in exon 21, similar to what has been reported in Asian and European populations. Also similar was the association with LUAD histology, non-smokers and older patients. Similar results were reported at the recent Latin American Lung Conference (LALCA) meeting in Lima, Peru (August 2014), with *EGFR* mutation rates of 26% and 35.3% in Costa Rican patients [31, 32], and 24.8% in Panamanian patients [33]. In contrast, several studies have reported a lower incidence of *EGFR* mutations among H/L (Table 1), but only one of these studies is from LA [34], where they found 8.1% frequency in Argentinian patients, and it can be speculated that this could be related to the high European/Caucasian migration to Argentina, which is in contrast to the Japanese migration to Peru. The other studies reporting no difference between H/L and WNH in the incidence of *EGFR* mutations are either from H/L living in the USA [18, 35], or in Spain [36, 37]. It is important to note, that in more recent studies looking at *EGFR* mutations in Spain, the rate of mutations is 24.6% [38]. It is important to point out that the information in some of these papers looking at Spanish patients is what is frequently used to report the rate of mutations in Hispanics (e.g. [39]), yet this does not take into consideration the genetic diversity of the Hispanic population in LA. There is little hard evidence regarding the use and benefit of *EGFR* targeted drugs in H/Ls, but it would be predicted that H/L populations would proportionately benefit from testing and targeted treatment. The overall response rate to TKIs of H/L patients with *EGFR* mutations has been reported to be between 62.5% [24] and 70% [33], which is similar to the rate observed in other selected patient groups [29].

KRAS

KRAS gene mutations are present in approximately 15% to 25% of LUAD in WNH, and the most common mutations are missense mutations in codons 12 and 13 of exon 1. In most cases, *KRAS* mutations are found in *EGFR* wild-type tumors; hence, *EGFR* and *KRAS* mutations are considered to be mutually exclusive. Most reports support the notion that *KRAS* mutations are less frequent in Asians compared to WNH. In two studies in populations of Chinese NSCLC patients, the *KRAS* mutation frequency was found to range between 3.8% and 8%. This is extremely low compared to NSCLC WNH patients where the prevalence ranges between 18% and 26%. The incidence of *KRAS* mutations in LA has been examined and reported to be between 7% to 16% (Table 1), comparable to the lower rate found in the Asian population [24, 34, 40]. *KRAS* mutations tend to be less common in never smokers compared to former or current smokers.

ALK Rearrangements

The frequency of *EML4-ALK* oncogenic rearrangement has also been found to be different among diverse racial and ethnical groups. The rate of the *EML4-ALK* rearrangement in WNH is between 1% and 3%, and in Asian cohorts the frequency of the oncogenic

translocation is in the 2.3% to 6.7% range. Interestingly, In H/L cohorts of NSCLC the incidence rate was found to be more similar to the Asian cohort at 4.2 to 10.5% [41, 42]. In most cases, *EML4-ALK* fusions were non-overlapping with other oncogenic mutations of *EGFR* or *KRAS*.

Other Mutations Associated With Lung Cancer

Few studies have looked at other driver gene mutations in H/L (Table 1). *BRAF* status has been examined in 3 different studies and no differences have been found to what has been reported for WNH [34, 35, 40]. Other genes (*MET*, *PI3KCA*, *PTEN*, *ROS1*) have also been examined in a limited number of studies, and no differences have been found [34, 35, 40, 43].

Single Nucleotide Polymorphisms (SNPs)

A higher incidence of lung cancer among relatives of lung cancer patients [44] suggest that inherited factors are involved in the development of this disease. Several polymorphisms have been associated with an increase in lung cancer risk in genes involved in the metabolism of tobacco [45], as well as in genes involved in other pathways such as DNA repair [46]. Comprehensive meta-analyses have been done of specific SNPs [47, 48], as well as a recent review of the existing literature on SNPs in lung cancer [49]. In some of these studies, an association with higher lung cancer risk was found in H/L [50, 51]. Although several studies have published data assessing the association between SNPs and lung cancer risk in H/L [46, 52, 53] these studies do not distinguish among different Hispanic groups, nor do they take into consideration that Hispanics are genetically a very diverse group. These studies, as well as recent studies of lung cancer polymorphisms correlated to ancestry markers [53] have only included Mexican Americans, and data on other Hispanic groups is lacking. Interestingly, mutations in the *CHEK2* gene have been associated with a decreased risk of lung cancer in European populations [54], and it could be speculated that the decreased risk in some Hispanic groups could be due to the fact that they “carry more European and African ancestry, but significantly less Indigenous American ancestry when compared to other Hispanic groups” [19, 20]. For example, in the Genetics of Asthma in Latino Americans (GALA) study, a polymorphism of the CD14 gene was associated with IgE levels and asthma phenotypes only in individuals exposed to environmental tobacco smoke [55]. This observation stresses the need to study the effect of genetic polymorphisms in disease risk in the context of environment exposures.

SNPs associated with acquired resistance to TKI in NSCLC have been described in *EGFR* and *BIM*, but these are understudied in the H/L population. Specifically, *EGFR* is highly polymorphic, and intron 1 polymorphisms have been associated with EGFR activity and drug responses [56]. The frequency of this polymorphism has been studied in WNH, AA, and Asians, and found to vary between these groups [57], but it has not been studied in the H/L population. Also, it has recently been reported that in the pro-apoptotic BIM, which belongs to the BH3-only subgroup of the Bcl-2 family, a *BIM* deletion polymorphism is involved in resistance to TKIs in several cancer types [58, 59]. The *BIM* deletion polymorphism involves the deletion of a 2903 bp fragment and results in a *BIM* isoform that lacks the BH3 domain. In a recent study of Colombian NSCLC patients, the *BIM* deletion

was found in 15.3% of patients, and was associated with a worse clinical response [60]. This is similar to what has been described in the Asian population [59].

Environmental Factors

An estimated 15% of lung cancer cases occur in lifetime never smokers [61, 62] for whom risk factors are poorly understood. Some suggested factors are second hand smoke [63], and environmental and occupational exposures, such as asbestos [64, 65]. In H/L, an indication of a possible role for environmental, social and lifestyle components is the difference in lung cancer incidence among H/L living in their country of origin versus mainland USA. H/L living in their country of origin have a lower incidence of lung cancer than WNH living in the USA [66, 67]. For example, studies comparing lung cancer incidence and mortality of Puerto Ricans living in Puerto Rico (PR) to those living in the USA found that that lung cancer incidence is lower in Puerto Ricans living in PR (19.5 per 100,000) compared to first generation Puerto Ricans living in Florida (FL) (45.8 per 100,000) [67], suggesting that lifestyle and environmental factors might play a partial role in this difference. In addition, Puerto Ricans living in FL have a lower incidence than WNH in FL suggesting that in addition to environmental factors, there might be a genetic component for the lower incidence of lung cancer in Puerto Ricans. A similar relationship has been found when comparing Puerto Ricans on the island to Puerto Ricans and WNH in the Northeast USA [66].

The reasons for the differences in cancer incidence and mortality between H/L and WNH are not completely understood, but different hypothesis have been proposed. For instance, smokers have a higher risk of developing tumor types associated with a poor prognosis (*e.g.* Squamous and Large Cell Carcinoma (LCC)), and nonsmokers are more likely to develop tumor types associated with a better prognosis (*e.g.* LUAD and BAC). H/L in the USA have lower rates of cigarette smoking than WNH and AAs, which likely contribute to the lower incidence of lung cancer in this population, and also, BACs were more common in H/L patients than in WNH and AA patients [22]. While smoking histories probably play a role in the survival differences reported in some H/L cohorts, studies that examined H/L and WNH smokers described a decreased frequency of lung cancer among H/L smokers, suggesting that other factors could also play a role. These other factors include other environmental factors, as well as genetic factors.

Environmental exposures specifically associated with lung cancer in H/L include exposure to wood-smoke, asbestos, asphalt and tar [68, 69]. For example, heating and cooking with open fires in poorly ventilated places, can cause high indoor smoke levels. Data from several *in vitro* and *in vivo* models provide evidence that wood smoke and its byproducts can be carcinogenic and promote tumor growth [70, 71]. For example, one study from Mexico reported that wood-smoke exposure was associated with LUAD in non-smoking women, and the authors suggest that wood-smoke exposure might explain the high rates of *EGFR*-mutated lung cancer in some regions of LA [72]. These associations require further investigation, as they rely on self-reported data, and the number of H/Ls in some of the studies is small.

HISPANIC PARADOX?

It has been reported that for several diseases (*e.g.* cardiovascular disease, breast cancer and prostate cancer) H/L patients have improved survival compared with WNH patients and AAs. This finding, termed the “Hispanic paradox,” was first proposed in 1986 [73] to describe the lower mortality rate that H/Ls in the USA tend to have in spite of having less access to care and fewer resources than WNH, and having a poverty rate similar to that of AAs. Several explanations for the “Hispanic Paradox” have been proposed; including increased family support, lower smoking rates, an increased propensity for healthy individuals to migrate to the USA, and a tendency for sick immigrants to return to their country of birth [4, 74–76].

Therefore, some question whether a Hispanic Paradox exists, given the data and methodological concerns surrounding mortality data in H/L groups. Specifically, the study of cancer in H/L has been hindered by the following issues [4, 74–76]: (a) Hispanic ethnicity (*i.e.*, whether someone is Hispanic or not) is usually assessed through self-identification; (b) misclassification of Hispanics as non-Hispanic; (c) practice of aggregating the diverse H/L subgroups into a general Hispanic category; (d) the “healthy immigrant” effect, which proposes that there is a selective pressure for healthier and fitter individuals to immigrate to the USA; (e) the “salmon bias,” which proposes that sick immigrants tend to return to their country of birth to live out their lives (and therefore their mortality data is not captured in the databases in the USA); (f) “data linkage” problems described by Pinheiros *et al.* [74], where cancer deaths are being missed in immigrants because of issues such as not having a social security number. All of these factors contribute to a gap in cancer mortality data that may impact the study of cancer incidence and mortality in H/Ls, which may have been underestimated thus far.

CONCLUSION

It has been suggested that for some cancer types the incidence is lower among H/L than WNH; however, it is not clear if the reported differences are due to environmental and genetic factors, or if they are due to study limitations. For lung cancer specifically, Hispanics smoke less, but it is well established that not all smokers develop lung cancer; reinforcing the fact that non-environmental factors, such as genetic variability play an important role in the development of this disease. Recent studies targeting the H/L population point to the fact that they are more likely to develop certain subtypes of lung cancer, and that the frequency of driver gene mutations is significantly different from the WNH, resembling more the Asian population. This might be the reason why the incidence of lung cancer in Hispanics is more similar to the Asian population than to WNH or AA [77].

The diversity of the H/L population offers therapeutic opportunities and challenges, and characterizing the frequency of predisposing lung cancer genes, driver mutations, and molecular markers in different lung tumors in H/L in the USA and in LA is a first step to providing a personalized approach to treatment. In studies of H/L populations, several factors need to be considered: heterogeneity of the Hispanic population (ancestry), genetic factors and environmental factors. Regional efforts to achieve such characterizations have

begun as demonstrated by the number of lung genetic studies presented at LALCA [31, 33–35, 41–43, 60]. These studies address the feasibility and benefits of genetic testing, particularly for *EGFR*, and advocate for testing of other/new targets (*e.g.* *ALK*). For example, one of these studies is a literature review that found that there are no studies reporting on guidelines, economic burden or diagnosis of *ALK*+ NSCLC in LA [78]. Genotyping is necessary for patients to benefit from targeted therapeutic intervention as it has been demonstrated that genotyping alone can have a stage- and histology-independent impact on overall survival [9]. Per the College of American Pathologists, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology guidelines [39], criteria such as racial/ethnic group, sex, or smoking status are not recommended as a basis for selecting patients for EGFR TKI therapy. However, these criteria exclude too many patients who might benefit from targeted therapy, thus the frequency of actionable targetable mutations in racial and ethnic groups is important to assess because of its possible clinical impact.

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References

1. American Cancer Society. Cancer Facts & Figures for Hispanics/Latinos 2012–2014. Atlanta, GA: American Cancer Society; 2012.
2. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. *Lancet Oncol*. 2011; 12(2): 175–80. [PubMed: 21277552]
3. Luo SY, Lam DC. Oncogenic driver mutations in lung cancer. *Transl Resp Med*. 2013; 1(6):2–8.
4. Patel MI, Schupp CW, Gomez SL, Chang ET, Wakelee HA. How do social factors explain outcomes in non-small-cell lung cancer among Hispanics in California? Explaining the Hispanic paradox. *J Clin Oncol*. 2013; 31(28):3572–8. [PubMed: 23960183]
5. Pleasance ED, Stephens PJ, O'Meara S, et al. A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature*. 2010; 463(7278):184–90. [PubMed: 20016488]
6. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell*. 2012; 150(6):1121–34. [PubMed: 22980976]
7. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. 2008; 455(7216):1069–75. [PubMed: 18948947]
8. Weir BA, Woo MS, Getz G, et al. Characterizing the cancer genome in lung adenocarcinoma. *Nature*. 2007; 450(7171):893–8. [PubMed: 17982442]
9. A genomics-based classification of human lung tumors. *Sci Transl Med*. 2013; 5(209):209ra153.
10. Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell*. 2012; 150(6):1107–20. [PubMed: 22980975]
11. Leidner RS, Fu P, Clifford B, et al. Genetic abnormalities of the EGFR pathway in African American Patients with non-small-cell lung cancer. *J Clin Oncol*. 2009; 27(33):5620–6. [PubMed: 19786660]
12. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol*. 2014; 25(1):126–31. [PubMed: 24285021]
13. Reinersman JM, Johnson ML, Riely GJ, et al. Frequency of EGFR and KRAS mutations in lung adenocarcinomas in African Americans. *J Thorac Oncol*. 2011; 6(1):28–31. [PubMed: 21107288]

14. Boch C, Kollmeier J, Roth A, et al. The frequency of EGFR and KRAS mutations in non-small cell lung cancer (NSCLC): routine screening data for central Europe from a cohort study. *BMJ Open*. 2013; 3(4)
15. Suzuki Y, Oonishi T, Kudo T, Doi H. LKB1, TP16, EGFR, and KRAS somatic mutations in lung adenocarcinomas from a Chiba Prefecture, Japan cohort. *Drug Discov Therap*. 2012; 6(1):24–30. [PubMed: 22460425]
16. Gao B, Sun Y, Zhang J, et al. Spectrum of LKB1, EGFR, and KRAS mutations in chinese lung adenocarcinomas. *J Thorac Oncol*. 2010; 5(8):1130–5. [PubMed: 20559149]
17. Dahabreh IJ, Linardou H, Siannis F, Kosmidis P, Bafaloukos D, Murray S. Somatic EGFR mutation and gene copy gain as predictive biomarkers for response to tyrosine kinase inhibitors in non-small cell lung cancer. *Clin Cancer Res*. 2009; 16(1):291–303. [PubMed: 20028749]
18. Zhang W, McQuitty EB, Olsen R, et al. EGFR mutations in US Hispanic versus non-Hispanic white patients with lung adenocarcinoma. *Arch Pathol Lab Medicine*. 2013; 138(4):543–5.
19. Gonzalez BE, Borrell LN, Choudhry S, et al. Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research. *Am J Public Health*. 2005; 95(12):2161–8. [PubMed: 16257940]
20. Salari K, Choudhry S, Tang H, et al. Genetic admixture and asthma-related phenotypes in Mexican American and Puerto Rican asthmatics. *Genet Epidemiol*. 2005; 29(1):76–86. [PubMed: 15918156]
21. Fejerman L, John EM, Huntsman S, et al. Genetic ancestry and risk of breast cancer among U.S. Latinas. *Cancer Res*. 2008; 68(23):9723–8. [PubMed: 19047150]
22. Saeed AM, Toonkel R, Glassberg MK, et al. The influence of Hispanic ethnicity on nonsmall cell lung cancer histology and patient survival: an analysis of the Survival, Epidemiology, and End Results database. *Cancer*. 2012; 118(18):4495–501. [PubMed: 22528551]
23. El-Telbany A, Ma PC. Cancer genes in lung cancer: racial disparities: are there any? *Genes Cancer*. 2012; 3(7–8):467–80. [PubMed: 23264847]
24. Arrieta O, Cardona AF, Federico Bramuglia G, et al. Genotyping non-small cell lung cancer (NSCLC) in Latin America. *J Thorac Oncol*. 2011; 6(11):1955–9. [PubMed: 22005474]
25. Vikis H, Sato M, James M, et al. EGFR-T790M is a rare lung cancer susceptibility allele with enhanced kinase activity. *Cancer Res*. 2007; 67(10):4665–70. [PubMed: 17510392]
26. Kancha RK, von Bubnoff N, Peschel C, Duyster J. Functional analysis of epidermal growth factor receptor (EGFR) mutations and potential implications for EGFR targeted therapy. *Clin Cancer Res*. 2009; 15(2):460–7. [PubMed: 19147750]
27. Li C, Fang R, Sun Y, et al. Spectrum of oncogenic driver mutations in lung adenocarcinomas from East Asian never smokers. *PloS one*. 2011; 6(11):e28204. [PubMed: 22140546]
28. Ren S, Kuang P, Zheng L, et al. Analysis of driver mutations in female non-smoker Asian patients with pulmonary adenocarcinoma. *Cell Biochem Biophys*. 2012; 64(2):155–60. [PubMed: 22707299]
29. Kuykendall A, Chiappori A. Advanced EGFR mutation-positive non-small-cell lung cancer: case report, literature review, and treatment recommendations. *Cancer Control*. 2014; 21(1):67–73. [PubMed: 24357744]
30. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005; 2(3):e73. [PubMed: 15737014]
31. Corrales-Rodriguez L, Abbas J, Ramos-Esquivel A, Araya M, Casco AM. Immunohistochemistry as a predictor of EGFR mutations: a retrospective case-control study. *J Thorac Oncol*. 2014; 9(9):S176.
32. Rojas-Vigott R, Ugalde-Gamboa L, Rojas-Solano J. Thoracic Oncology Clinic: Our First 200 cases. *San Jose, Costa Rica J Thorac Oncol*. 2014; 9(9):S182.
33. Castillo-Fernandez O, Arauz E, Cabreja A, et al. EGFR Mutation and outcomes in aptients with metastatic NSCLC treated with erlotinib at Instituto Oncologico Nacional. *Panama J Thorac Oncol*. 2014; 9(9):S189.
34. Recondo G, Denninhoff V, Recondo GJ, et al. Prospective study of molecular markers in patients with advanced lung adenocarcinoma. *J Thorac Oncol*. 2014; 9(9):S200.

35. Raez LE, Mourafetis J, Abrahams N, et al. Ethnic differences in non-small cell lung cancer (NSCLC) genetics. *J Thorac Oncol.* 2014; 9(9):S159.
36. Molina-Vila MA, Bertran-Alamillo J, Reguart N, et al. A sensitive method for detecting EGFR mutations in non-small cell lung cancer samples with few tumor cells. *J Thorac Oncol.* 2008; 3(11):1224–35. [PubMed: 18978556]
37. Cortes-Funes H, Gomez C, Rosell R, et al. Epidermal growth factor receptor activating mutations in Spanish gefitinib-treated non-small-cell lung cancer patients. *Ann Oncol.* 2005; 16(7):1081–6. [PubMed: 15851406]
38. Porta R, Sanchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J.* 2011; 37(3):624–31. [PubMed: 20595147]
39. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol.* 2013; 8(7):823–59. [PubMed: 23552377]
40. McQuitty E, Zhang W, Hendrickson H, et al. Lung adenocarcinoma biomarker incidence in Hispanic versus non-Hispanic white patients. *Arch Pathol Lab Med.* 2014; 138(3):390–4. [PubMed: 23802852]
41. Perez-Mesa P, Pallotta MG, De La Iglesia P, Lupinacci L, Dalurzo ML. Mono institutional experience in non-small lung cancer with EML4-ALK rearrangement. *J Thorac Oncol.* 2014; 9(9):S170.
42. Arrieta O, Cruz-Rico G, Morales-Oyarvide V, et al. Diagnosis of the ALK-EML4 translocation with FISH, immunohistochemistry, and real time-polymerase chain reaction in patients with non-small-cell lung cancer. *J Thorac Oncol.* 2014; 9(9):S188.
43. Martin C, Patane AK, Guma G, et al. Prevalence of MET expression in early stage lung cancer. Experience of a thoracic hospital in Argentina. *J Thorac Oncol.* 2014; 9(9):S188.
44. Schwartz AG, Rothrock M, Yang P, Swanson GM. Increased cancer risk among relatives of nonsmoking lung cancer cases. *Genet Epidemiol.* 1999; 17(1):1–15. [PubMed: 10323181]
45. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature.* 2008; 452(7187):633–7. [PubMed: 18385738]
46. Chang JS, Wensch MR, Hansen HM, et al. Base excision repair genes and risk of lung cancer among San Francisco Bay Area Latinos and African-Americans. *Carcinogenesis.* 2009; 30(1):78–87. [PubMed: 19029194]
47. Zhan P, Wang Q, Qian Q, Wei SZ, Yu LK. CYP1A1 MspI and exon7 gene polymorphisms and lung cancer risk: an updated meta-analysis and review. *J Exp Clin Cancer Res.* 2011; 30:99. [PubMed: 22014025]
48. Yang X, Wang Y, Wang G. Quantitative assessment of the influence of EPHX1 gene polymorphisms and cancer risk: a meta-analysis with 94,213 subjects. *J Exp Clin Cancer Res.* 2014; 33(1):82. [PubMed: 25261893]
49. Marshall AL, Christiani DC. Genetic susceptibility to lung cancer--light at the end of the tunnel? *Carcinogenesis.* 2013; 34(3):487–502. [PubMed: 23349013]
50. Gu J, Spitz MR, Yang F, Wu X. Ethnic differences in poly(ADP-ribose) polymerase pseudogene genotype distribution and association with lung cancer risk. *Carcinogenesis.* 1999; 20(8):1465–9. [PubMed: 10426793]
51. Wu X, Gwyn K, Amos CI, Maken N, Hong WK, Spitz MR. The association of microsomal epoxide hydrolase polymorphisms and lung cancer risk in African-Americans and Mexican-Americans. *Carcinogenesis.* 2001; 22(6):923–8. [PubMed: 11375900]
52. Ishibe N, Wiencke JK, Zuo ZF, McMillan A, Spitz M, Kelsey KT. Susceptibility to lung cancer in light smokers associated with CYP1A1 polymorphisms in Mexican- and African-Americans. *Cancer Epidemiol Biomarkers Prev.* 1997; 6(12):1075–80. [PubMed: 9419406]
53. Aldrich MC, Selvin S, Hansen HM, et al. CYP1A1/2 haplotypes and lung cancer and assessment of confounding by population stratification. *Cancer Res.* 2009; 69(6):2340–8. [PubMed: 19276377]

54. Cybulski C, Masojc B, Oszutowska D, et al. Constitutional CHEK2 mutations are associated with a decreased risk of lung and laryngeal cancers. *Carcinogenesis*. 2008; 29(4):762–5. [PubMed: 18281249]
55. Choudhry S, Coyle NE, Tang H, et al. Population stratification confounds genetic association studies among Latinos. *Hum Genet*. 2006; 118(5):652–64. [PubMed: 16283388]
56. Jung M, Cho BC, Lee CH, et al. EGFR polymorphism as a predictor of clinical outcome in advanced lung cancer patients treated with EGFR-TKI. *Yonsei Med J*. 2012; 53(6):1128–35. [PubMed: 23074112]
57. Liu W, Innocenti F, Chen P, Das S, Cook EH Jr, Ratain MJ. Interethnic difference in the allelic distribution of human epidermal growth factor receptor intron 1 polymorphism. *Clinic Cancer Res*. 2003; 9(3):1009–12.
58. Ng KP, Hillmer AM, Chuah CT, et al. A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. *Nat Med*. 2012; 18(4):521–8. [PubMed: 22426421]
59. Nakagawa T, Takeuchi S, Yamada T, et al. EGFR-TKI resistance due to BIM polymorphism can be circumvented in combination with HDAC inhibition. *Cancer Res*. 2013; 73(8):2428–34. [PubMed: 23382048]
60. Cardona-Cardona AF, Arrietta O, Karachliou N, et al. BIM deletion polymorphisms in Colombian patients with non-small cell lung cancer who carries EGFR mutations (CLICAP). *J Thorac Oncol*. 2014; 9(9):S174.
61. Bain C, Feskanich D, Speizer FE, et al. Lung cancer rates in men and women with comparable histories of smoking. *J Natl Cancer Inst*. 2004; 96(11):826–34. [PubMed: 15173266]
62. Freedman ND, Leitzmann MF, Hollenbeck AR, Schatzkin A, Abnet CC. Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. *Lancet Oncol*. 2008; 9(7):649–56. [PubMed: 18556244]
63. Brennan P, Buffler PA, Reynolds P, et al. Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. *Int J Cancer*. 2004; 109(1):125–31. [PubMed: 14735478]
64. Bruske-Hohlfeld I. Environmental and occupational risk factors for lung cancer. *Methods Mol Biol*. 2009; 472:3–23. [PubMed: 19107427]
65. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008; 83(5):584–94. [PubMed: 18452692]
66. Ho GY, Figueroa-Valles NR, De La Torre-Feliciano T, et al. Cancer disparities between mainland and island Puerto Ricans. *Rev Panam Salud Publica*. 2009; 25(5):394–400. [PubMed: 19695128]
67. Pinheiro PS, Sherman RL, Trapido EJ, et al. Cancer incidence in first generation U.S. Hispanics: Cubans, Mexicans, Puerto Ricans, and new Latinos. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(8):2162–9. [PubMed: 19661072]
68. Arrieta O, Martinez-Barrera L, Trevino S, et al. Wood-smoke exposure as a response and survival predictor in erlotinib-treated non-small cell lung cancer patients: an open label phase II study. *J Thorac Oncol*. 2008; 3(8):887–93. [PubMed: 18670307]
69. McClean MD, Kelsey KT, Sison JD, Quesenberry CP Jr, Wrensch MR, Wiencke JK. A case-control study of asphalt and tar exposure and lung cancer in minorities. *Am J Ind Med*. 54(11):811–8. 201. [PubMed: 21882217]
70. Barcenas CH, Delclos GL, El-Zein R, Tortolero-Luna G, Whitehead LW, Spitz MR. Wood dust exposure and the association with lung cancer risk. *Am J Ind Med*. 2005; 47(4):349–57. [PubMed: 15776474]
71. Delgado J, Martinez LM, Sanchez TT, Ramirez A, Iturria C, Gonzalez-Avila G. Lung cancer pathogenesis associated with wood smoke exposure. *Chest*. 2005; 128(1):124–31. [PubMed: 16002925]
72. Hernandez-Garduno E, Brauer M, Perez-Neria J, Vedal S. Wood smoke exposure and lung adenocarcinoma in non-smoking Mexican women. *Int J Tuberc Lung Dis*. 2004; 8(3):377–83. [PubMed: 15139478]

73. Markides KS, Coreil J. The health of Hispanics in the southwestern United States: an epidemiologic paradox. *Public Health Rep.* 1986; 101(3):253–65. [PubMed: 3086917]
74. Pinheiro PS, Williams M, Miller EA, Easterday S, Moonie S, Trapido EJ. Cancer survival among Latinos and the Hispanic Paradox. *Cancer Causes Control.* 2011; 22(4):553–61. [PubMed: 21279543]
75. Pinheiro PS, Sherman R, Fleming LE, et al. Validation of ethnicity in cancer data: which Hispanics are we misclassifying? *J Registry Manag.* 2009; 36(2):42–6. [PubMed: 19694116]
76. Palloni A, Arias E. Paradox lost: explaining the Hispanic adult mortality advantage. *Demography.* 2004; 41(3):385–415. [PubMed: 15461007]
77. Division of Cancer Prevention and Control. Lung Cancer Rates by Race and Ethnicity. Centers for Disease Control and Prevention; 2014. [cited 16 October 2014]. Available from: <http://www.cdc.gov/cancer/lung/statistics/race.htm>
78. Balu S, Seseña-Carrillo L, Solon C, et al. A targeted literature review on ALK+ non-small cell lung cancer (NSCLC) epidemiology, diagnostic, and economic outcomes relevant to Latin America. *J Thorac Oncol.* 2014; 9(9):S159.

Table 1

Prevalence of lung cancer driver mutations in Hispanic/Latinos

A. STUDIES TARGETING LATIN AMERICAN POPULATIONS				
Population	H/L	Gene	Findings	Ref.
Hispanic from Latin American countries *	1,150	<i>EGFR</i>	32.5% frequency of mutations Assoc. to adenocarcinoma, older age, non-smokers	[24]
Hispanics (self-identified)	40	<i>EGFR</i>	15% Hispanics 18.6% Non-Hispanics Mutations in exon 18, 19, 20 and 21.	[18]
Patients in Costa Rica Hospital *	200	<i>EGFR</i>	26% frequency of mutations. Exon 19- 53% Exon 20- 7% Exon 21- 34%	[32]
Patients in Costa Rica Hospital *	116	<i>EGFR</i>	35.3% frequency of mutations. 1 Exon 19- 48.8% Exon 21- 31.7%	[31]
Patients in Panama Hospital *	125	<i>EGFR</i>	24.8% frequency of mutations. Exon 19- 58% Exon 20- 3.2% (T790M)- 1 patient Exon 21- 29% L858R/S768I- 2 patients -6.4%	[33]
Patients in Argentina hospital *	68	<i>EGFR</i>	8.1% frequency of mutations.	[34]
Hispanic from Latin American countries *	1,150	<i>KRAS</i>	16.6% frequency of mutations.	[24]
Hispanics (self-identified)	40	<i>KRAS</i>	7% frequency of mutations.	[40]
Patients in Argentina hospital *	68	<i>KRAS</i>	15.7% (9 patients)- 7 in codon 12 and 2 in codon 3	[34]
Patients in Argentina hospital *	68	<i>BRAF</i>	None detected	[34]
Patients in Argentina hospital *	68	<i>ALK</i>	3+ in one case (1.5% of total)	[34]
Patients in Buenos Aires Hospital *	95	<i>EML4-ALK</i>	Found EML4-ALK translocation in 4.2% of patients. All had adenocarcinoma	[41]
Patients from Mexico *	95	<i>EML4-ALK</i>	10.5% of patients + by FISH	[42]
Patients in Colombia hospital *	72	<i>BIM</i>	BIM deletion in 11 patients (15.3%) Similar to what is reported in Asians	[60]
Patients in Argentina hospital *	68	<i>C-MET</i>	Overexpressed in 35 (55.5% of patients)	[34]
Patients in hospital in Argentina *	122	<i>MET</i>	MET + 10 patients (8%) MET - 112 patients (92%)	[43]
Hispanics (self-identified)	40	<i>MET, BRAF, mTOR, STAT3, JAK2, PIK3CA, AKT, PTEN</i>	PI3KCA H = 5% ; No mutations detected in other genes listed	[40]
Patients from Boca Raton Hospital *	58	<i>EGFR, ALK, MET, KRAS, ROS1, BRAF</i>	No differences- they do not report the numbers by ethnicity	[35]

B. STUDIES TARGETING SPANISH PATIENTS				
Population	H/L	Gene	Findings	Ref
Spanish Patients	83	<i>EGFR</i>	13% frequency of mutations Exon 19 – 9.6% Exon 21- 2.4%	[37]
Spanish patients	69	<i>EGFR</i>	24.6% frequency of mutations Exon 19 17.4%	[38]

B. STUDIES TARGETING SPANISH PATIENTS				
Population	H/L	Gene	Findings	Ref
			Exon 21 - 7.2%	
Spanish patients	217	<i>EGFR</i>	17% frequency of mutations Exon 19 11.5% Exon 21- 5.5%	[36]

* No other confirmation of ethnicity.

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