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Racial and Ethnic Differences in the Epidemiology of Lung Cancer and the Lung Cancer Genome

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Abstract

Background—Globally and in the United States, lung cancer has been the most common cancer for the past several decades. In addition to the well-established geographical- and sex-specific differences in lung cancer incidence, mortality and survival, there is also growing evidence for racial and ethnic differences.

Methods—Based on available published data, we present a summary of the current knowledge and substantive findings related to racial and ethnic differences in lung cancer.

Results—Although this report is not a systematic review, we summarized the current knowledge and substantive findings related to racial and ethnic differences in lung cancer with a particular focus on lung cancer statistics(incidence, mortality, and survival), cigarette smoking, prevention and early detection, and the lung cancer genome. Finally, we summarize some the systems-level and provider-related issues that likely contribute to racial and ethnic-specific health disparities and provide some suggestions for future strategies that may reduce the disproportionate burden of lung cancer.

Conclusions—Although lung carcinogenesis is a multifactorial process driven by exogenous exposures (e.g., cigarette smoking), inherited genetic variations, and an accumulation of somatic genetic events, this multifactorial process appears to have racial and ethnic differences which in turn impacts the observed epidemiologic differences in incidence, mortality, and survival.

Keywords

Lung cancer; race; ethnicity; cancer epidemiology; precision medicine; health disparities; risk factors; screening and prevention

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Burden of Lung Cancer Globally and in the United States

Incidence and Mortality

Globally, lung cancer has been the most common cancer for the past several decades[1,2]. Based on data from the GLOBOCAN project from the International Agency for Research on Cancer (IARC)[2], in 2012 there were approximately 1.8 million new lung cancer diagnoses worldwide accounting for 12.9% of the global cancer burden. Among men, lung cancer remains the most common cancer diagnosis with approximately 1.2 million cases in 2012. The highest incidence rates occur in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000), and the lowest rates in Central Africa (2.0 per 100,000) and Western Africa(1.7 per 100,000 respectively). Incidence rates are generally lower among women with approximately 583,000 new lung cancer diagnoses in 2012. The geographical variations for incidence and mortality differ between men and women, which is largely attributed to geographical differences in cigarette smoking between the two sexes[2,3]. The highest incidence rates in women are observed in North America (33.8 per 100,000) and Northern Europe (23.7per 100,000), while the lowest rates are found in Western Africa (1.1 per 100,000) and Central Africa (0.8 per 100,000)[2].

In the United States, lung cancer is the second most common cancer in men after prostate cancer and the second most common cancer in women after breast cancer[4]. In 2016 an estimated 224,390 new cases of lung cancer are expected. The incidence rate has been declining in men over the past two decades, but has recently started to decrease in the mid-2000s among women. The incidence rates from 2008 to 2012 have decreased by 3.0% per year among men and by 1.9% per year among women. During this time period, the incidence rate among men was76.7 per 100,000 and 54.1 per 100,000for women. While lung cancer is the second most common cancer among both sexes, it is the leading cause of cancer-related death and accounts for more deaths than prostate, breast, colon, and pancreatic cancer combined. In 2016 an estimated 158,080 lung cancer-related deaths are expected to occur. From 2008 to 2012 the mortality rate among men was59.8 per 100,000 and 37.8 per 100,000 for women[4].

Survival

Despite considerable improvements in patient survival over the last several decades for other cancer types including breast and prostate cancer, there have been little improvements in lung cancer survival. The lack of improvement in lung cancer survival is largely attributed to by the time a diagnosis is made, the cancer is often advanced stage and treatment options are limited. Because of the high fatality rate of this disease, there is relative lack of variability in survival in different world regions.[2] In the United States, the five-year relative survival rate for all lung cancers is 17% (i.e., non-small cell lung cancer [NSCLC] and small cell lung cancer combined [SCLC])[4].Among NSCLCs, the five-year relative survival rate is 21% for all stages combined[4] and SCLCs have an overall 5-year survival rate of approximately 6%[5]. The overall prognosis for NSCLC remains poor and prognostic factors associated with poor survival include late stage diagnosis, current smoking status, advanced age, male sex, poor pulmonary function, presence of cardiovascular disease, non-squamous cell histology, and pneumonectomy[6–10].Among SCLC patients, poor prognosis is associated with age greater

than 70 year, male sex, relapsed disease, extensive-stage disease, weight loss greater than 10% of body weight at diagnosis, and poor performance status[11–15].Despite the poor patient outcomes associated with a lung cancer diagnosis, the emergence of immunotherapy/ immune checkpoint inhibitors have demonstrated durable long-term survival in some patients[16,17]. As such, these therapies may hold the key in improving lung cancer survival and possibly making lung cancer curable in the early-stage setting and/or a chronic disease for patients with metastatic disease[18].

In addition to the well-established geographical- and sex-specific differences in lung cancer incidence, mortality, and survival, there are also racial and ethnic differences for which this review will present and discuss. Although this report is not a systematic review, we present a summary of the current knowledge and substantive findings related to racial and ethnic differences in lung cancer.

Racial and Ethnic Differences in Lung Cancer

Definition of Race and Ethnicity

Although the definitions of *race* and *ethnic* background are often applied inconsistently[19], acommonly used definition describes race as a social construct that incorporates beliefs about language, history, and culture[20] and forms the basis on which social identity, traditions, and politics are built[19]. In the United States, the race classification scheme used in the2000 U.S. Census, which is often used in biomedical research, includes five major groups: White, Black or African American, Asian, Native Hawaiian or other Pacific Islander, and American Indian or Alaska native[21]. Broadly, this classification scheme emphasizes the geographic region of origin of a person's ancestry. Ethnicity background is a broader construct that takes into consideration cultural tradition, common history, religion, and often a shared genetic heritage[20]. In all cited studies, we use race and ethnicity as reported in the original study to describe the population.

Incidence and Mortality

Although race and ethnicity are complex social and cultural constructs, they are also often associated with socioeconomic status. Racial and ethnic differences in disease burden can reveal specific issues of a particular population or subpopulations. Racial and ethnic differences in lung cancer incidence, mortality, and survival are well-documented. The most comprehensive report[22] in the United States are based on data from Surveillance, Epidemiology, and End Results Program (SEER) revealed that Blacks have a higher incidence and mortality rates than any other racial or ethnic group. A report from the Disease Control and Prevention (CDC)[23] assessed potential racial and ethnic disparities and geographic differences in lung cancer incidence from 1998 to 2006 using data from SEER and CDC's National Program of Cancer Registries (NPCR). In this report, the annual incidence of lung cancer was highest among Blacks (76.1 per 100,000), followed by Whites (69.7 per 100,000), American Indians/Alaska Natives (48.4 per 100,000), and Asian/Pacific Islanders (38.4 per 100,000). Hispanics had lower lung cancer incidence (37.3 per 100,000) than non-Hispanics (71.9 per 100,000). Regionally in the United States, the highest incidence was found in the South (76.0 per 100,000) and the lowest incidence was in the

West (58.8 per 100,000). Among Whites, the highest lung cancer incidence was in the South (76.3 per 100,000). The highest incidence among Blacks (88.9 per 100,000), American Indians/Alaska Natives (64.2 per 100,000), and Hispanics (40.6 per 100,000) were in the Midwest, and the highest incidence among Asian/Pacific Islanders was in the West (42.5 per 100,000). The identification of geographical differences in incidence among racial/ethnic populations presents novel opportunities for targeted efforts in primary prevention and early detection[23].

Survival

Published data has also demonstrated that the survival of lung cancer patients also differs significantly based on race and ethnicity. For examples, studies have reported Black patients are less likely to receive surgical resection than Whites patients[24–26] which likely contributes to data that shows Black patients lower survival for early-stage NSCLC[27]. Using SEER data linked to Medicare claims data during the time period of 1995 to 1999, Shugarman *et al*[26] reported that Black patients were 66% less likely to receive timely and appropriate treatment than Whites patients, and Black men were least likely to receive resection (22% for Black men versus 43.7% for White men). The authors also reported that Black patients were 34% less likely to receive timely surgery, chemotherapy, or radiation for stage III disease and were 51% less likely to receive chemotherapy in a timely fashion for stage IV disease relative to White patients. Additionally, Howington *et al* reported that Native American Indians and Native Alaskans have worse survival than non-Hispanic Whites[28]. With regard to potential ethnic difference, a study by Lin *et al*[29] compared rates of stage-appropriate treatment among Blacks, Hispanics, and non minority patients and did not observe treatment disparities among Hispanic patients. However, the authors did find that Blacks were less likely than non-minorities to receive stage-appropriate treatment as other studies reported[30–32].

Cigarette Smoking

Unequivocally, tobacco smoking is the most important and prevalent lung cancer risk factor[33–35]. Lung cancer is one of the first chronic diseases to be causally linked to tobacco smoking. Approximately 90% of lung cancer diagnoses in the United States are attributed to tobacco smoking[8,9]. Cigarette smoke contains more than 7,000 chemicals including over 60 established carcinogens and other toxicants associated with chronic diseases[36]. Although only around one in nine smokers develops lung cancer, the relative risk of lung cancer in long-term smokers is estimated to be between 10- and 30-fold higher than that of a lifetime never smoker[8].

The percentage of cigarette smoking among adults in the United States has been a steady decline over the last several decades from 20.9% in 2005 to 16.8% in 2014[37]. In 2014, prevalence of smoking was higher among males (18.8%) than females (14.8%). By racial and ethnic groups, smoking prevalence was highest among American Indian/Alaska Natives (29.2%) and multiracial adults (27.9%), and lowest among Asians (9.5%). For other racial and ethnic groups, smoking prevalence was 18.2% for Whites, 17.5% for Blacks, and 11.2% for Hispanics. As described above, the annual incidence is highest among Blacks compared

to any other race, yet the prevalence of smoking among Blacks is lower than American Indian/Alaska Natives, multiracial adults, and Whites. Moreover, data from the Multiethnic Cohort Study[38] reported significant differences in the association between cigarette smoking and the risk of lung cancer among five ethnic and racial groups. Interestingly, among those who smoked no more than 30 cigarettes per day, African Americans and Native Hawaiians had significantly greater risks of lung cancer than did the other groups. As such, these data provide further support for ethnic and racial differences, which could be attributed to innate genetic difference, in the smoking-associated risk of lung cancer.

Other established and putative risk factors lung cancer risk factors, that will not be reviewed here, include exposure to secondhand smoke (i.e., passive smoke), history of chronic obstructive pulmonary disease (COPD), family history of lung cancer, radon exposure, and occupational exposures such as asbestos, arsenic, diesel exhaust, and chromium[8,39,40]. There is conflicting evidence regarding the impact of exogenous hormones among women, diet, and BMI, on lung cancer risk[40–47]. Moreover, there are limited studies that have assessed potential racial and ethnic differences for these established and putative risk factors lung cancer risk factors.

Prevention and Early Detection

Until recently, no screening method has been shown to decrease mortality rates for NSCLC. The National Lung Screening Trial (NLST) randomized 53,452 former and current cigarette smokers who were 55 to 74 years old with a 30 or more pack-year smoking history into two arms, low-dose helical computed tomography (LDCT) and standard chest radiography, for three annual screens (a baseline screen and two follow-up screens approximately 12 months apart)[48]. After a median follow-up of 6.4 years, a 20% relative reduction in lung cancer mortality was observed for LDCT compared to standard chest radiography. Screen-detected incidence lung cancers (i.e., diagnosed on the follow-up screens)accounted for 58% of all LDCT-detected lung cancers, were 2.7-fold higher in the CT arm versus the chest radiography arm, were associated with a stage shift from late stage to more early stage lung cancers, and demonstrated improved 5-year survival compared to cancers diagnosed at the baseline prevalence screen[48]. An important benefit of early detection is the ability to detect more early stage lung cancers. A meta-analysis[49] revealed that the rate of detection of stage I lung cancers was 70% with LDCT screening compared to 16% detected during routine care. Thus, screen-detected incidence lung cancers diagnosed as a result of LDCT screening have a better possibility of surgical cure and improved 5-year survival compared to prevalence- and routine care detected lung cancers that are diagnosed when patients develop symptoms from lung cancers that are associated with later stages[8]. Based on the findings from the NLST, the United States Preventive Services Task Force (USPSTF) issued a recommendation in December 2013 for annual screening for lung cancer with LDCT in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years[50].

Of the 53,452 participants in the NLST, 90.8% were White (N = 48,549), 4.4% were Black (N = 2,376), 1.7% were Asian (N = 895),2.0% were of other racial groups or reported more than one race or ethnic group (N = 1062), and 1.7% were Hispanic or Latino (N = 935).

Although the original report[48] did not provide ethnic or racial-specific results, a recent *post hoc* analysis by Tanner *et al*[51] assessed racial differences in outcomes between Blacks and White individuals who participated in the NLST. Although demographics associated with improved lung cancer survival (i.e., higher education, former smoking status, and fewer comorbidities) were less commonly found among Blacks in the NLST, their analysis revealed that screening with LDCT reduced lung cancer mortality in all racial groups but more so in Black individuals (hazard ratio [HR] = 0.61 for Blacks vs. HR = 0.86 for Whites). The authors also noted that among all racial groups, current smokers had worse lung cancer-specific mortality; however, the risk was two-fold higher in Black current smokers compared to White current smokers. Additionally, all-cause mortality was 1.35-times higher in Blacks versus White, but black individuals screened with LDCT had a statistically significant reduction in all-cause mortality when compared with White individuals. As such, the authors note that screening for lung cancer is beneficial in Black individuals but that different strategies will be needed to achieve a significant reduction in lung cancer mortality in this population[51]. On-going disparities in access to screening and resolution of abnormal results underscore the importance of delivering lung cancer screening within the context of health care systems that offer screening and resolve abnormal findings quickly.

In a separate *post hoc* analysis of the NLST, Kumar *et al*[52] examined racial differences in smoking behaviors among White and Black participants in the NLST who were current smokers at screening. They analyzed data from a follow-up survey on 24-hour and 7-day quit attempts,6-month continuous abstinence, and the use of smoking cessation programs and aids at 12 months after screening. The authors reported that Blacks were more likely than Whites to have 24-hour and 7-day quit attempts; however, these attempts did not translate to increased rates of 6-month continuous abstinence among Black smokers. Specifically, at 12 months after screening, Blacks were more likely to report a 24-hour (52.7% for Blacks vs. 41.2% for Whites, $p < 0.01$) or 7-day (33.6% for Blacks vs. 27.2% for Whites, $p < 0.01$) quit attempt. However, there were no statistically significant racial differences were found in 6-month continuous abstinence (5.6% for Blacks vs. 7.2% for Whites). In multivariable analyses, Black race was statistically significant predictive of a higher likelihood of a 24- and 7-day quit attempt; however, race was not associated with 6-month continuous abstinence. Only a positive screening result for lung cancer was significantly predictive of successful 6-month continuous abstinence. Presently, there is a gap in knowledge about the efficacy of LDCT lung cancer screening in other racial and ethnic groups.

Certainly the NLST demonstrated that screening with LDCT can mitigate the risk of lung cancer via early detection. Indeed, screening with LDCT appears to be second only to primary prevention (i.e., smoking prevention/cessation) for mitigating lung-cancer mortality —and the only remaining option for those who have already quit smoking. Lung cancer risk caused by smoking is reduced following smoking cessation, but it always remains elevated compared to never-smokers.

Lung Cancer Genomics

Fundamentally cancer is a genomic disorder and racial and ethnic differences in cancer incidence, mortality, and patient outcomes can be attributed, in part, to diversity in inherited genetic variations(germline) and an accumulation of somatic genetic events including mutations, rearrangements, or amplification that lead to uncontrolled cell proliferation, evasion of apoptosis, and eventually angiogenesis. Based on data[53] from the Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM), 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%). Advances in tumor genomic profiling has resulted in a paradigm shift whereby lung cancers are characterized and classified by genetic alternations in oncogenes and tumor suppressor genes that are critical to tumor growth and survival and can be exploited with specific targeted agents[54]. Because most lung cancer harbor somatic mutations and/or alterations, targeted therapy, or *precision medicine*[55], is important to improve outcomes of this disease. Unfortunately, to date there has been limited research on the impact of race and ethnicity in targeted therapies. Additionally, the impact and frequency of tumor mutations are not as well characterized in Black and of Hispanic/Latino patients to the same extent as they are in Asian and White populations. Nonetheless, in the following section we will highlight examples of how the frequency of mutations in oncogenes and tumor suppressor differ across racial and ethnic populations (Table 1). Though there is evidence that suggests racial and ethnicity differences in markers of susceptibility[56,57], this review focused on somatic mutations because of their clinical implications and observed racial and ethnic differences, and because germline variations in lung cancer have yet to be deemed clinically actionable.

EGFR

Epidermal growth factor receptor (EGFR) is a transmembrane protein with cytoplasmic kinase activity that facilitates critical growth factor signaling from the extracellular milieu to the cell[58]. EGFR is expressed on the cell surface and EGFR tyrosine kinase inhibitors (TKIs), inhibitors that target the kinase domain of EGFR have been developed and are clinically active. TKIs are especially effective in patients whose tumors harbor activating mutations in the tyrosine kinase domain of the *EGFR* gene. Therefore, mutation testing is routinely performed to identify patients harboring targetable *EGFR* mutations, given that selection based only on clinical and pathologic characteristics is inadequate. Overall, approximately 10% of NSCLC patients in Western Countries and 35% in East Asia have a tumor that exhibit *EGFR* mutations[59,60]. The most frequent *EGFR* mutations occur in exons 18–21, which encodes a portion of the EGFR kinase domain; and, *EGFR* mutations are often heterozygous with the mutant allele also showing gene amplification[61]. Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations[62]. Irrespective of ethnicity, *EGFR* mutations are more often found in females who are never smokers with adenocarcinoma histology[59,60]. However, EGFR mutations can also be found in other subsets of NSCLC, including in former and current smokers as well as in other lung cancer histological subtypes.

In frame deletions and insertions in exon 19 and point mutation L858R in exon 21 are the most common activating *EGFR* mutations, and their prevalence is significantly higher in Japanese, Korean, and Chinese patients than White patients from the United States or Europe[63]. Based on data from the Iressa Pan-Asia Study (IPASS) study, the frequency of activating *EGFR* mutations in Asian never smokers or light smokers with advanced-stage adenocarcinoma were 59.5%. In contrast, the frequency was only 15% in non-Asian patients based on data from an early phase III trials that performed retrospective *EGFR* mutation testing on archival samples[64,65]. The IGNITE study compared *EGFR* mutations in Asian and Russian patients with advanced NSCLC and reported that the frequency of *EGFR* mutations in adenocarcinoma to be 49% East Asian patients and 18% in Russian patients. The frequency of *EGFR* mutation non-adenocarcinoma lung cancers were 14% and 4%, respectively.[66] There has also been published studies exploring whether the frequency of *EGFR* mutation differ by race and ethnicity. There have been several studies that compared the frequency of *EGFR* mutation between Black and White patients with NSCLC, but the results are conflicting. Specifically, Yang et al[67] and Leidner *et al*[68] found a lower frequency of *EGFR* mutation among Black patients, while Riely et al[69], Cote et al[70] and Reinersman *et al*[71] did not find a statistically significant difference between the two groups.

Until recently, few studies have addressed the frequency of lung cancer mutations among Hispanics/Latinos. Arrieta *et al*[72] analyzed 1,150 biopsies of NSCLC patients from Latin America (Argentina, Colombia, Peru, and Mexico) and found that frequency of *EGFR* mutations among all four countries was 32.5%. The frequency of mutations by country was 19.3% in Argentina, 24.8% in Colombia, 31.2% in Mexico, and 67% in Peru. Our group has previously speculated[56] that the particularly high frequency of *EGFR* mutations in Peru is attributed to Asian migration. A study presented at the Latin American Lung Conference (LALCA) found the frequency of *EGFR* mutation ranging from 26% to 35.3% in Costa Rican patients[73,74] and 24.8% in Panamanian patients[75]. However, in contrast, several studies have reported a lower frequency of *EGFR* mutations among Hispanics/Latinos while other studies found no statistically significant difference between Hispanics/Latinos and Whites (*reviewed in*[56]).

KRAS

The RAS gene family, which includes *HRAS*, *NRAS*, and *KRAS*, and encodes for membrane-bound guanosine-triphosphate-(GTP)-binding proteins that regulate cell growth, differentiation and apoptosis by interacting with mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) and signal transducer and activator of transcription (STAT) cascades[76,77]. The three *RAS* genes encode have 85% sequence identity proteins and the KRAS protein is a potent tumor initiator when aberrantly activated when a point mutation in the gene replaces an amino acid at codons 12 or 13 in Exon 2 or codon 61 in Exon 3[78]. These mutations results in impaired GTPase activity and a constitutive activation of RAS signaling[79]. Mutations in KRAS gene occur frequently in NSCLC especially in adenocarcinoma (20% to 30%) and they are less common in squamous cell carcinoma (about 7%)[80,81]. Though mutationally activated *KRAS* tumors were originally identified in 1982[78], to date there are no successful treatment strategies that target these tumors[81] and their impact on lung cancer survival and prognosis is unclear and remains controversial[82,83].

To date there have been over 50 published studies evaluating *KRAS* mutations on clinical outcome in lung cancer[82,83] and the results from individual studies vary greatly and are inconsistent. A meta-analysis of 41 studies[83] concluded that *KRAS* mutations are associated with a poor prognosis in patients with NSCLS, especially in patients with adenocarcinoma and early stage NSCLC. Published studies have suggested that the frequency of *KRAS* mutations differ by race and ethnicity. Specifically, *KRAS* mutations are less common in Asians compared White lung cancer patients[84,85]. Frequency of *KRAS* mutations ranged between 3.8% and 8% in studies comprised of Chinese NSCLC patients which is substantially lower compared to the White patients which range from 18% to 26%[57,68,86]. There are also very few studies that have assess KRAS mutational status among Black patients, and the published data are inconsistent. Three studies have reported no statistically significant difference in frequency of KRAS mutations between Whites and Blacks[68,71,87]; however, the frequency in Hispanics may be lower[72,88].

STK11

Theserine/threonine kinase 11 (*STK11*) gene encodes a tumor suppressor located on chromosome 19p13.3 that encodes the serine/threonine protein kinase also known as liver kinase β1 (LKB1). The gene spans 23 kb and is made up of nine coding exons (exons 1 to 9) and a final non-coding exon (exon 10). The *STK11* gene product regulates cellular energy metabolism and cell polarity by activating AMP-activated protein kinase (AMPK) and other members of the AMPK family[89,90]. As a multi-functional kinase, STK11 is involved in a broad spectrum of cellular activity including metabolism, polarity and epithelial-mesenchymal transition, cell cycle regulation, apoptosis, and autophagy.[91] Germline mutations in *STK11* were first identified in patients with Peutz-Jeghers syndrome[92], a rare autosomal dominant disorder which is associated with an increased risk of gastrointestinal and other malignancies[93]. Studies have also reported that STK11 somatic mutations are quite common in NSCLCs with prevalence of inactivating mutations ranging up to 50% revealing an important role of STK11 in lung tumorigenesis[91,94–100]. The frequency of STK11 mutations in these studies range from 0.6% to 44.4%. Previously published data have reported that *STK11* inactivating mutations occur in other lung cancer histology subtypes including 19% of squamous cell carcinomas, 14% of large cell carcinomas, and 25% of adenosquamous carcinomas[91,97,98,101–103]. Like *KRAS* and *EGFR*, there appear to be ethnic and racial differences in *STK11* mutations. Studies in Asian populations including Japanese, Korean, and Chinese have reported much lower *STK11* mutation rates compared to Whites, ranging from 3% to 7%[103–106]. This observation is similar to *KRAS* mutations in lung cancer, which frequently co-occur with *STK11*, where it has been noted that lung tumors in Western populations harbor a higher frequency of *KRAS* mutation compared to Asian populations. Asian populations have also been found to express an STK11 germline F354L polymorphism at approximately 10% frequency[105]. This allele has been called a nonfunctional polymorphism in lung cancer, but has also previously been reported to affect cell polarity maintenance in an AMPK-dependent manner.[107] At present there are no published data on the frequency of STK11 mutations among Blacks and Hispanics/Latinos.

BRAF

BRAF kinase is a proto-oncogene that belongs to a family of serine-threonine protein kinases that includes ARAF, BRAF, and CRAF (RAF1). Mutant *BRAF* has been implicated in the pathogenesis of several cancers and the most commonly identified *BRAF* mutation is V600E accounting for 90% of *BRAF* mutations in melanoma. By contrast, in NSCLC the frequency of *BRAF* gene mutations ranges from 1% to 3.5%[108–111]. There have been no published reports assessing racial and ethnic differences of *BRAF* mutations in lung cancer patients, likely attributed to its rarity in lung cancer.

PIK3CA

The *PIK3CA* gene belongs to a family of lipid kinases involved in many cellular processes, including cell growth, proliferation, differentiation, motility, and survival. *PIK3CA* was found to be mutated in over 30% of colorectal cancers[112]. By contrast, mutations in *PIK3CA* have been found only in 1% to 3% of all NSCLCs[112,113]. As noted with BRAF, there have been no published reports assessing racial and ethnic of *PIK3CA* mutations in lung cancer which again can attributed its rarity in this disease.

ALK

Anaplastic lymphoma kinase (ALK)is a tyrosine kinase receptor that is can be abnormally expressed by forming a fusion gene with one of several other genes, by gaining additional gene copies, or by somatic mutations. The *EML4-ALK* fusion was first documented in 2007 in NSCLC[114] as a novel potential oncogenic driver mutant kinase. Studies have reported that approximately 3% to 7% of all lung tumors harbor *ALK* fusions[114,115] and *EML4-ALK* fusions are usually found in light or never smokers of patients diagnosed at a younger age[116–118]. *EML4-ALK* rearrangements have also reported to differ across different racial groups. Studies have reported that the frequency of translocation to between 2.3% to 6.7% among Asians [119–121]. In contrast, *EML4-ALK* rearrangement was found to be much lower in Whites ranging 1% to 3%[114,117,122]. One study analyzed a cohort of NSCLC patient samples collected from Italy and Spain and found that 7.5% of the patients expressed EML4-ALK transcripts which is more similar to Asians that Whites[123].

Summary of Lung Cancer Genomics

In the previous section we focused on specific oncogenes and tumor suppressor genes where published studies have assessed potential racial and ethnic differences. Although other genes have also been studied, including *MET, PI3KCA, PTEN*, and*ROS1*, at present the published limited data suggests there are no differences[56]

The genomic diversity of oncogenes and tumor suppressor genes across racial and ethnic groups poses unique but important challenges for therapeutic opportunities in providing personalized medicine. Molecular genomic profiling for specific alterations is necessary to identify which patients will benefit from targeted therapeutic intervention. As such, identifying novel, but actionable target able mutations that may be exclusive to specific racial and ethnic groups is critical to ensure these populations benefit from such therapies.

Conclusion

Although lung carcinogenesis is a multifactorial process driven by exogenous exposures (e.g., cigarette smoking), inherited genetic variations, and an accumulation of somatic genetic events, this multifactorial process also appears to have racial and ethnic differences. In this review, we highlighted examples of racial and ethnic differences in smoking and lung cancer genome which in turn may play a role in the observed epidemiologic differences in incidence, mortality, and survival. However, many of the observed racial and ethnic differences are attributed to underlying racial and ethnic disparities in lung cancer are not fully understood. Broadly speaking, health disparities, can also occur at the systems-level issues, such as access to care, insurance, and hospital-level factors[24,32,124]. Other potential sources of racial and ethnic disparities are derived from provider-related factors such as limited cultural sensitivity, stereotyping, and poor patient–physician communication may also be involved[125]. Studies have shown that even after controlling for these factors[126,127], treatment disparities persist, suggesting that patient-specific factors may also contribute to lung cancer differences.

The lung cancer epidemic peaked in the 20th century in the United States and most Western Nations[2], but began to decline by the century's end and continues to decline today due to successful tobacco-control efforts. In the United States smoking rates have steadily declined since the 1960s[128]; however, today nearly 17% of adults still continue to smoke cigarettes[129]. Even after smoking cessation is successfully accomplished, former smokers remain at significant risk of developing lung cancer. Certainly the NLST demonstrated that screening with LDCT can mitigate the risk of lung cancer via early detection. As such, screening with LDCT appears to be second only to primary prevention (i.e., smoking prevention/cessation) for mitigating lung-cancer mortality—and the only remaining option for those who have already quit smoking. Lung cancer risk caused by smoking is reduced following smoking cessation, but it always remains elevated compared to never-smokers. As such, lung cancer will remain a major global public health burden for the 21st century.

Although effective smoking cessation programs and early detection will reduce the overall lung cancer burden, improvements to the access of these modalities and affordability of health care is particularly important to address lung cancer-related racial and ethnic disparities. As such, identifying and addressing cultural factors may also help improve implementing racially/ethnicity-sensitive population-based interventions, such as surveillance and screening programs and smoking cessation interventions, and lung cancer treatment rates among minorities. Finally, identifying and eliminating regional and racial/ethnic differences in lung cancer may contribute to more effective preventive and treatment strategies that will ultimately reduce the disproportionate burden of lung cancer in the United States[126].

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Table 1

Estimated prevalence of the frequency mutated genes in lung cancer

Gene	Frequency (%)
EGFR	
By region	
Western populations	~10%
Asian populations	~35%
By Country	
Argentina	19.3%
Colombia	24.8%
Mexico	31.2%
Peru	67.0%
Costa Rica	26.0 to 35.3%
Panama	24.8%
KRAS	
By region	
Western populations	18.0 to 26.0%
Asian populations	3.8 to 8.0%
STK11/LKB1	
Western populations	9.0 to 17.0%
Asian populations	3.0 to 7.0%
BRAF[a]	
Overall	1.0 to 3.5%
PIK3CA[a]	
Overall	1.0 to 3.0%
ALK fusion	
Overall	3.0 to 7.0%
By region	
Western populations	1.0 to 3.0%
Asian populations	2.3 to 6.7%

[a]No published reports assessing racial and ethnic differences