Lung carcinogenesis is a multifactorial process that can affect racial and ethnic groups differently.

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

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Background: Lung cancer is the most common cancer in the world. In addition to the geographical and sex-specific differences in the incidence, mortality, and survival rates of lung cancer, growing evidence suggests that racial and ethnic differences exist.

Methods: We reviewed published data related to racial and ethnic differences in lung cancer.

Results: Current knowledge and substantive findings related to racial and ethnic differences in lung cancer were summarized, focusing on incidence, mortality, survival, cigarette smoking, prevention and early detection, and genomics. Systems-level and health care professional–related issues likely to contribute to specific racial and ethnic health disparities were also reviewed to provide possible suggestions for future strategies to reduce the disproportionate burden of lung cancer.

Conclusions: Although lung carcinogenesis is a multifactorial process driven by exogenous exposures, genetic variations, and an accumulation of somatic genetic events, it appears to have racial and ethnic differences that in turn impact the observed epidemiological differences in rates of incidence, mortality, and survival.

Introduction

Lung cancer is the most common cancer worldwide. In 2012, new diagnoses of lung cancer reached approximately 1.8 million worldwide, accounting for 13% of the global cancer burden. Among men, lung cancer remains the most common cancer diagno-

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racial and ethnic disparities in lung cancer are not fully understood. Health disparities can also occur as a result of systems-level issues, such as access to care, insurance, and hospital-level factors. Other potential sources of racial and ethnic disparities are derived from health care professional–related factors, such as limited cultural sensitivity, stereotyping, and poor doctor–patient relationships. Studies have shown that, even after controlling for these factors, treatment disparities persist, suggesting that patient-specific factors may also contribute to lung cancer differences.

In addition to the established geographical and sex-specific differences in the incidence, mortality, and survival rates of lung cancer, certain racial and ethnic differences exist. Although the terms race and ethnicity are often inconsistently applied, a commonly used definition describes race as a social construct that incorporates beliefs about language, history, and culture, forming the basis on which social identity, traditions, and politics are built. In the United States, the race classification scheme used in the 2000 census, which is often used in biomedical research, includes 5 major groups: white, black/African American, Asian, Native Hawaiian/Pacific Islander, and American Indian/Alaska Native. Broadly, this classification scheme emphasizes the geographical region of origin of an individual’s ancestry. Ethnicity is a broader construct that takes into consideration cultural tradition, common history, religion, and, oftentimes, a shared genetic heritage. Thus, to avoid confusion, we will use the terms race or ethnicity as reported in the originally cited work to describe the population studied.

Epidemiology

Incidence

The incidence rates of lung cancer are generally lower among women (583,000 new lung cancer diagnoses in 2012). The highest incidence rates occur in eastern and Central Europe as well as eastern Asia; by contrast, the lowest rates occur in western and Central Africa. The geographical variations for incidence and mortality differ between men and women, largely attributed to geographical differences in cigarette smoking between the 2 sexes. The highest incidence rates in women are observed in North America and northern Europe, whereas the lowest rates are found in western and Central Africa.

In the United States, the incidence rates have been declining in men in the past 20 years and in women since the mid-2000s: From 2008 to 2012, they annually decreased by 3.0% among men and 1.9% among women. During this time period, the incidence rate among men was 76.7 per 100,000 and 54.1 per 100,000 persons for women.

Race and ethnicity are complex social and cultural constructs, but they are also often associated with socioeconomic status. Racial and ethnic differences in disease burden can reveal specific issues of a particular population or subpopulation. Racial and ethnic differences in rates of incidence, mortality, and survival of lung cancer are well documented. The most comprehensive report in the United States is based on data from the Surveillance, Epidemiology, and End Results (SEER) program, which revealed that blacks have higher rates of incidence and mortality than any other racial or ethnic group.

A report from the Centers for Disease Control and Prevention assessed potential racial/ethnic disparities and geographical differences in incidence rates of lung cancer from 1998 to 2006 using data from SEER and the National Program of Cancer Registries. In this report, the annual incidence rate of lung cancer was highest among blacks, followed by whites, American Indians/Alaska Natives, and Asian/Pacific Islanders. Hispanics had lower rates of lung cancer incidence than non-Hispanic whites. In the United States, the highest rate of lung cancer incidence was found in the South and the lowest rate of incidence was in the West. Among whites, the highest rate of lung cancer incidence was in the South; the highest incidence rates among blacks, American Indians/Alaska Natives, and Hispanics were in the Midwest; and the highest incidence among Asian/Pacific Islanders was in the West. The identification of geographical differences in incidence rates among racial and ethnic populations presents novel opportunities for targeted efforts in primary prevention and early detection.

Survival

Despite considerable improvements in patient survival during the past several decades for breast and prostate cancers, few improvements have been seen in survival rates of lung cancer. Improvements in survival are lacking because the majority of lung cancers are at an advanced stage by the time a diagnosis is made and treatment options are limited. Because of its high mortality rate, variability in survival is lacking in different world regions. In the United States, the 5-year relative survival rate for all lung cancers is 17%.

Among all stages of non–small-cell lung cancer (NSCLC) and small-cell lung cancer, the combined 5-year relative survival rates are 21% and 6%, respectively. 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, nonsquamous cell histology, and pneumonectomy. Among individuals with small-cell lung cancer, poor prognosis is associated with age older than 70 years, male sex, relapsed disease, extensive disease, weight loss of more than 10% of total body weight at diagnosis, and poor per-
formance status. 22-26 Despite the poor outcomes associated with a diagnosis of lung cancer, the emergence of immunotherapy and immune checkpoint inhibitors has demonstrated durable rates of long-term survival in select patients. 27,28 As such, these therapies may lead to improved survival rates and, in the early stage, possibly curable disease. 29

Published data have demonstrated that the survival rates of those with lung cancer also differ based on race and ethnicity. 30-33 Blacks are less likely to receive surgical resection than whites, a finding that likely contributes to data that show blacks have lower rates of survival for early-stage NSCLC. 31-32 Using SEER data linked to Medicare claims data during 1995 and 1999, Shugerman et al 31 reported that blacks were 66% less likely to receive timely and appropriate treatment than whites, and black men were least likely to receive resection (22.0% for black men vs 43.7% for white men). The authors also reported that blacks were 34.0% less likely to receive timely surgery, chemotherapy, or radiotherapy for stage III disease and were 51.0% less likely to receive chemotherapy in a timely fashion for stage IV disease relative to whites. 33 Howington et al 33 reported that American Indians and Alaskan Natives have worse survival rates than non-Hispanic whites. With regard to potential ethnic differences, a study by Lin et al 34 compared rates of stage-appropriate treatment among blacks, Hispanics, and nonminority patients and did not observe treatment-related disparities among Hispanics. However, the authors did find that blacks were less likely than nonminorities to receive stage-appropriate treatment, similar to data reported in previous studies. 5,34-36

**Risk Factors**

Tobacco smoking is the most important and prevalent risk for lung cancer. 37-39 Lung cancer is one of the first chronic diseases to be causally linked to tobacco smoking, and approximately 90% of lung cancer diagnoses in the United States are attributed to tobacco smoking. 19,20 Cigarette smoke contains more than 7,000 chemicals, including more than 60 established carcinogens and other toxicants associated with chronic diseases. 30 Although approximately 1 in 9 individuals who smoke develops lung cancer, the relative risk of lung cancer in those who are long-term smokers is estimated to be between 10- and 30-fold higher than that of a lifetime never-smoker. 19

The percentage of cigarette smoking among adults in the United States and most Western nations has been steadily declining during the past several decades — from 20.9% in 2005 to 16.8% in 2014 — and it continues to decline today due to successful tobacco-control efforts. 2,41 In the United States, smoking rates have steadily declined since the 1960s. 42 In 2014, the prevalence of smoking was higher among males (18.8%) than females (14.8%), and nearly 17% of adults still continue to smoke cigarettes. 31,43

By racial and ethnic groups, smoking prevalence rates were highest among American Indians/Alaska Natives (29.2%) and multiracial adults (27.9%) and lowest among Asians (9.5%). 31,43 For other racial and ethnic groups, smoking prevalence rates were 18.2% for whites, 17.5% for blacks, and 11.2% for Hispanics. 41,43 Although the annual incidence is highest among blacks compared with any other race, the prevalence of smoking among blacks is lower than American Indians/Alaska Natives, multiracial adults, and whites. 41,43 Moreover, significant differences have been reported in the association between cigarette smoking and the risk of lung cancer among 5 ethnic/racial groups. 44 Among those who smoked no more than 30 cigarettes per day, African Americans and Native Hawaiians had significantly greater risks of lung cancer than the other groups studied. 44 As such, these data provide further support for ethnic/racial differences, which could be attributed to innate genetic differences in the smoking-associated risk of lung cancer.

Other established and putative risk factors for lung cancer include exposure to secondhand smoke (ie, passive smoke), history of chronic obstructive pulmonary disease, family history of lung cancer, radon exposure, and occupational exposure (eg, asbestos, arsenic, diesel exhaust, chromium). 19,45-46 Evidence is conflicting regarding the impact of exogenous hormones on women, diet, and body mass index in association with risk of lung cancer. 46-53 Moreover, few studies have assessed the potential racial and ethnic differences for such risk factors. 50

**Prevention and Early Detection**

Until recently, no screening method was shown to decrease the mortality rates for NSCLC. The National Lung Screening Trial (NLST) randomized 53,452 individuals who were former or current cigarette smokers, between the ages of 55 and 74 years, and had a pack-year smoking history of at least 30 years into either low-dose helical computed tomography (LDCT) or standard chest radiography — both arms were administered 3 annual screenings (baseline screening and 2 follow-up screening sessions approximately 12 months apart). 54 After a median follow-up period of 6.4 years, a 20% relative reduction in rate of lung cancer mortality was observed for the LDCT group compared with those assigned to standard chest radiography. 54 The rate of lung cancer detected via screening (ie, diagnosed on follow-up screening intervals) accounted for 58% of all LDCT-detected cases of lung cancer, were 2.7-fold higher in the LDCT arm vs the chest radiography arm, were associated with a stage shift from late-stage to more early-stage lung cancer, and demonstrated improved rates of 5-year survival.
compared with cancers diagnosed at the baseline prevalence screening.54

An important benefit of early detection is the ability to detect more cases of early-stage lung cancer. A meta-analysis revealed that the rate of detection of stage I lung cancer was 70% with LDCT screening compared with 16% when detected during routine care.55 Thus, the incidence of lung cancer detected in screening and then diagnosed as a result of LDCT have better surgical outcomes and improved 5-year survival rates than prevalence and routine care–detected lung cancer diagnosed when patients develop symptoms of late-stage disease.19 Based on the findings from the NLST, the US Preventive Services Task Force issued a recommendation in December 2013 for annual screening for lung cancer using 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.54,56

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 1 race or ethnic group (n = 1,062), and 1.7% were Hispanic or Latino (n = 935).54 Although the NLST did not provide ethnic/racial-specific results,54 a posthoc analysis by Tanner et al57 assessed racial differences in outcomes between blacks and whites who participated in the NLST. Although demographics associated with improved survival in lung cancer, such as 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 mortality in all racial groups, but more so in blacks (hazard ratio [HR] 0.61 for blacks vs HR 0.86 for whites).57 Among all racial groups, Tanner et al57 also noted that study participants who currently smoked had worse rates of lung cancer–specific mortality; however, the risk was 2-fold higher in blacks who were current smokers compared with white current smokers. In addition, the rate of all-cause mortality was 1.35 times higher in blacks vs whites, but blacks screened with LDCT had a statistically significant reduction in all-cause mortality when compared with whites.57 As such, screening for lung cancer appears to be beneficial in blacks, but different strategies are needed to achieve a significant reduction in lung cancer–related mortality in this population.57 Ongoing disparities in access to screening and follow-up visits (in the case of abnormal results) underscore the importance of health care institutions to offer screening and then quickly resolve any abnormal findings.

In a separate posthoc analysis of the NLST, Kumar et al58 examined racial differences in smoking behaviors among white and black study participants in the NLST who were current smokers at screening. They analyzed data from a follow-up survey on 24-hour and 7-day cessation attempts, 6-month continuous abstinence from smoking, and the use of smoking cessation programs and cessation aids 12 months after screening. The authors reported that blacks were more likely than whites to have 24-hour and 7-day cessation attempts; however, these attempts did not translate to increased rates of 6-month continuous abstinence among blacks.58 Specifically, 1 year after screening, blacks were more likely to report a 24-hour (52.7% for blacks vs 41.2% for whites; P < .01) or 7-day (33.6% for blacks vs 27.2% for whites; P < .01) cessation attempt.58 Although no statistically significant racial differences were found in 6-month continuous abstinence (5.6% for blacks vs 7.2% for whites), black race was a statistically significant predictor in multivariable analyses of a higher likelihood of a 24-hour and 7-day cessation attempt.58 Race was not associated with 6-month, continuous abstinence; by contrast, a positive result on screening for lung cancer was the only significantly predictor of successful 6-month, continuous abstinence.58 At present, knowledge is lacking about the effectiveness of screening for lung cancer with LDCT in other racial and ethnic groups.

The data from the NLST demonstrated that screening with LDCT can mitigate lung cancer mortality via early detection.59 Screening with LDCT appears to be second only to primary prevention (ie, smoking prevention/cessation) for mitigating lung cancer–related mortality — and the single remaining option for those who have already quit smoking. The risk of lung cancer caused by smoking is reduced following smoking cessation, but this risk always remains elevated compared with those who are lifetime never-smokers.59

Genomics

The most frequently mutated genes in lung cancer are TP53 (53.6%), KRAS (16.1%), STK11 (9.8%), EGF R (7.2%), KEAP1 (6.6%), and NEF2L2 (4.5%).60 The frequency of mutations in oncogenes and tumor-suppressor genes differ across racial and ethnic populations and are selectively shown in the Table. Advances in tumor genomic profiling have resulted in a paradigm shift, whereby types of lung cancer are characterized and classified by genetic alternations in oncogenes and tumor-suppressor genes critical to tumor growth and survival and can be exploited with specific targeted agents.61

The focus of this paper is 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, current data are limited and suggest that no differences exist in these genes.62

Because most types of lung cancer harbor somatic mutations, alterations, or both, the use of targeted therapy is important to improve outcomes.63 Research
has been limited on the impact of race and ethnicity in targeted therapies. The impact and frequency of tumor mutations are not as well characterized in blacks and Hispanics/Latinos to the same extent as they are in Asians and whites.\textsuperscript{62,64} Although evidence suggests that racial and ethnicity differences exist in markers of susceptibility, we have chosen to focus on somatic mutations because of their clinical implications and observed racial and ethnic differences, as well as because germline variations in lung cancer have yet to be deemed clinically actionable.\textsuperscript{62,65}

**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.\textsuperscript{66} EGFR is expressed on the cell surface. Tyrosine kinase inhibitors can be effective therapy for patients whose tumors harbor activating mutations in the tyrosine kinase domain of EGFR.\textsuperscript{66} Therefore, mutation testing is routinely performed to identify patients harboring targetable EGFR mutations, given that selection based on clinical and pathological characteristics alone is inadequate. Overall, approximately 10% of patients with NSCLC in Western countries and 35% of patients in East Asia have a tumor that exhibits an EGFR mutation.\textsuperscript{67,68} The most frequent EGFR mutations occur in exons 18 to 21, encoding a portion of the EGFR kinase domain; in addition, EGFR mutations are often heterozygous, with the mutant allele also showing gene amplification.\textsuperscript{69} Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations.\textsuperscript{70} Irrespective of ethnicity, EGFR mutations are more often found in females who are never-smokers and have adenocarcinoma histology.\textsuperscript{67,68} However, EGFR mutations can also be found in other histological subtypes of NSCLC, and they can be found in former and current smokers.\textsuperscript{71-73}

In-frame deletions and insertions in exon 19 and the point mutation L858R in exon 21 are the most common activating EGFR mutations, and their prevalence is significantly higher in individuals of Japanese, Korean, and Chinese descent than American or European whites.\textsuperscript{74} Based on data from the Iressa Pan-Asia Study, the frequency of activating EGFR mutations in Asian never-smokers or light smokers with advanced-stage adenocarcinoma was nearly 60%.\textsuperscript{75} By contrast, the rate of frequency was 15% in non-Asian patients based on data from phase 3 trials of retrospective EGFR mutation testing of archival samples.\textsuperscript{76,77} One study compared EGFR mutations in individuals of Asian and Russian descent with advanced NSCLC and reported that the frequency of EGFR mutations in adenocarcinoma was 49% in East Asians and 18% in Russians, and the frequencies of EGFR mutations in nonadenocarcinoma lung cancers were 14% and 4%, respectively.\textsuperscript{78} Several studies have explored whether the frequencies of EGFR mutations differ by race and ethnicity, and others have compared the frequencies of EGFR mutations between blacks and whites with NSCLC, however, the results are conflicting.\textsuperscript{79-82} Specifically, Yang et al\textsuperscript{79} and Leidner et al\textsuperscript{80} found a lower frequency of EGFR mutations among blacks, whereas Riely et al,\textsuperscript{81} Cote et al,\textsuperscript{82} and Reinersman et al\textsuperscript{83} did not find a statistically significant difference between the 2 groups.

Few studies have addressed the frequency of mutations in lung cancer among Hispanics/Latinos. Arrieta et al\textsuperscript{84} analyzed 1,150 biopsy specimens from patients with NSCLC who were from Argentina, Colombia, Peru, and Mexico and found that the combined frequency of EGFR mutations among all 4 countries was 32.5%. The frequencies of mutations by country were 19.3% in Argentina, 24.8% in Colombia, 31.2% in Mexico, and 67.0% in Peru.\textsuperscript{81} The high frequency of

| Table. — Estimated Frequencies of Select Mutated Genes in Lung Cancer |
|-------------------------|---------------------------|
| **Gene**                | **Frequency, %**          |
| **By region**           |                           |
| Asian populations       | 30.0–40.0                 |
| Western populations     | 10.0–20.0                 |
| **By country**          |                           |
| Argentina               | 19.3                      |
| Colombia                | 24.8                      |
| Costa Rica              | 26.0–35.3                 |
| Mexico                  | 31.2                      |
| Panama                  | 24.8                      |
| Peru                    | 67.0                      |
| **KRAS**                |                           |
| By region               |                           |
| Asian populations       | 3.8–8.0                   |
| Western populations     | 18.0–26.0                 |
| **STK11**               |                           |
| By region               |                           |
| Asian populations       | 3.0–7.0                   |
| Western populations     | 9.0–17.0                  |
| **BRAF**\textsuperscript{a} |                         |
| Overall                 | 1.0–3.5                   |
| **PIK3CA**\textsuperscript{a} |                       |
| Overall                 | 1.0–3.0                   |
| **ALK Fusion**          |                           |
| By region               |                           |
| Asian populations       | 2.3–6.7                   |
| Western populations     | 1.0–3.0                   |

\textsuperscript{a}No published reports have assessed racial and ethnic differences.
EGFR mutations in Peru could be attributed to Asian migration.\textsuperscript{62} The frequency of EGFR mutations ranges from 26.0\% to 35.3\% in Costa Ricans and is 24.8\% in Panamanians.\textsuperscript{85-87} By contrast, a lower frequency of EGFR mutations has also been reported among Hispanics/Latinos, and other conflicting reports have found no statistically significant difference between Hispanics/Latinos and whites.\textsuperscript{62}

**KRAS**

The RAS family, which includes HRAS, NRAS, and KRAS, encodes for membrane-bound guanosine triphosphate–binding proteins that regulate cell growth, differentiation, and apoptosis by interacting with mitogen-activated protein kinase, phosphoinositide 3-kinase, and signal transducer and activator of transcription cascades.\textsuperscript{88,89} When aberrantly activated, KRAS is a potent oncogenic driver when a point mutation occurs at codon 12 or 13 in exon 2 or codon 61 in exon 3.\textsuperscript{90} These mutations result in impaired guanosine-triphosphatase activity and a constitutive activation of RAS signaling.\textsuperscript{91} Mutations in KRAS occur frequently in NSCLC — particularly adenocarcinoma (20\%–30\%) — and less commonly in squamous cell carcinoma (~7\%).\textsuperscript{92,93}

Although mutationally activated KRAS tumors were originally identified in 1982,\textsuperscript{78} no successful treatment strategies target these tumors,\textsuperscript{93} and their impact on survival and prognosis in lung cancer is unclear and controversial.\textsuperscript{94,95} To date, more than 50 studies have evaluated KRAS mutations on clinical outcomes in lung cancer, the results of which are varied and inconsistent.\textsuperscript{94,95} A meta-analysis of 41 studies concluded that KRAS mutations are associated with a poor prognosis in patients with NSCLC, and this was particularly true for those with adenocarcinoma and early-stage NSCLC.\textsuperscript{95}

Data have also suggested that the rates of frequency of KRAS mutations differ by race and ethnicity. Specifically, KRAS mutations in the setting of lung cancer are less common in Asians compared with whites.\textsuperscript{96,97} The frequency of KRAS mutations ranged from 3.8\% to 8.0\% in studies of Chinese study participants with NSCLC — a rate lower than that seen in whites (range, 18\%–26\%).\textsuperscript{65,80,98} Few studies have assessed KRAS mutational status among blacks, and the published data are inconsistent: 3 studies reported no statistically significant difference in frequency of KRAS mutations between whites and blacks,\textsuperscript{90,93,99} and some noted that the frequency in Hispanics may actually be lower.\textsuperscript{94,100}

**STK11**

STK11 encodes a tumor suppressor located on chromosome 19p13.3 that encodes the serine/threonine kinase 11 (STK11) protein. The gene is made up of coding exons 1 to 9 and a final, noncoding exon 10. STK11 regulates cellular energy metabolism and cell polarity by initiating adenosine monophosphate–activated protein kinase (AMPK) and other members of the AMPK family.\textsuperscript{101,102} As a multifunctional kinase, STK11 is involved in a broad spectrum of cellular activity that includes metabolism, polarity, and epithelial-mesenchymal transition, as well as cell-cycle regulation, apoptosis, and autophagy.\textsuperscript{103} Germline mutations in STK11 were first identified in patients with Peutz-Jeghers syndrome,\textsuperscript{104} a rare autosomal dominant disorder associated with an increased risk of gastrointestinal and other malignancies.\textsuperscript{105} Studies have also reported that STK11 somatic mutations are common in NSCLCs: The prevalence of inactivating mutations can occur in more than 50\% of cases (range, 0.6\%–44.4\%), thus revealing an important role of STK11 in lung tumorigenesis.\textsuperscript{103,106-112} Previously published data have reported that STK11 inactivating mutations occur in other histology subtypes of lung cancer and include 19\% of squamous cell carcinomas, 14\% of large cell carcinomas, and 25\% of adenosquamous carcinomas.\textsuperscript{103,105,113,115}

Similar to KRAS and EGFR, ethnic and racial differences appear in STK11 mutations. Studies in Asian populations (those of Japanese, Korean, and Chinese descent) have reported lower rates of STK11 mutations than whites (range, 3\%–7\%).\textsuperscript{115-118} This observation is similar to that seen in KRAS mutations in the setting of lung cancer, because they frequently co-occur with STK11. Lung tumors in Western populations harbor a higher frequency of KRAS mutations compared with Asian populations.\textsuperscript{98,119} Asian populations have also been found to express an STK11 germline F354L polymorphism at a frequency of approximately 10\%.\textsuperscript{117} This allele has been called a nonfunctional polymorphism in lung cancer, but it also affects cell polarity maintenance in an AMPK-dependent manner.\textsuperscript{120} At present, no data have been published on the frequency of STK11 mutations among blacks and Hispanics/Latinos.

**BRAF**

BRAF is a proto-oncogene that belongs to a family of serine-threonine protein kinases that also includes ARAF and RAFI. Mutant BRAF has been implicated in the pathogenesis of several cancers.\textsuperscript{98} The most commonly identified BRAF mutation is V600E, which accounts for 90\% of BRAF mutations in melanoma.\textsuperscript{121} By contrast, the frequency of BRAF mutations in NSCLC ranges from 1.0\% to 3.5\%.\textsuperscript{122-125} No reports have assessed racial and ethnic differences of BRAF mutations in patients with lung cancer, likely because this mutation is rare in this population.

**PIK3CA**

PIK3CA belongs to a gene family of lipid kinases involved in many cellular processes, including cell growth, proliferation, differentiation, motility, and survival. PIK3CA is mutated in more than 30\% of
coli.

References


23. Spiegelman D, Maurer LH, Ware JH, et al. Prognostic factors in colorectal cancer cases. By contrast, mutations in PIK3CA have been found in 1% to 3% of all types of NSCLC. Similar to BRAF, no reports have been published that have assessed racial and ethnic differences of PIK3CA mutations in the setting of lung cancer, likely because this mutation is rare in this patient population.

**ALK**

Anaplastic lymphoma kinase is a tyrosine kinase receptor 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 as a potentially novel oncogenic-driver mutant kinase. Approximately 3% to 7% of all lung tumors harbor ALK fusions, and EML4-ALK fusions are usually found in light- or never-smokers and are typically diagnosed at a young age.

EML4-ALK rearrangements may differ across different racial groups. The frequency of translocation ranges from between 2.3% and 6.7% among Asians. By contrast, EML4-ALK rearrangement is lower in whites and ranges from 1.0% to 3.0%. One study analyzed a cohort of NSCLC samples collected from Italy and Spain and found that 7.5% of the samples expressed EML4-ALK transcripts — a finding more similar to the data seen in Asians than whites.

**Conclusions**

Lung cancer is the most common cancer in the world and the second most common cancer in both men and women in the United States. Although lung carcinogenesis is a multifactorial process driven by exogenous exposure (e.g., cigarette smoking), inherited genetic variations, and an accumulation of somatic genetic events, it also appears to have racial and ethnic differences. However, many observed racial and ethnic disparities in lung cancer are not fully understood.

The genomic diversity of oncogenes and tumor-suppressor genes across racial and ethnic groups poses unique but important challenges for therapeutic opportunities to provide personalized medicine. Molecular genomic profiling for specific alterations is necessary to identify patients likely to benefit from targeted therapy. As such, identifying novel but actionable targetable mutations exclusive to specific racial and ethnic groups is critical to ensure these populations benefit from such therapies.

Even after smoking cessation is successfully accomplished, former smokers remain at significant risk of developing lung cancer. Although effective smoking cessation programs and early cancer detection will reduce the overall lung cancer burden, improvements to the access of these modalities and the affordability of health care are important topics to address.


