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<b>14. ABSTRACT</b>  Lung cancer is the leading cause of cancer deaths in the U.S. among men and women. Only 16% of lung cancer patients survive more than five years. African Americans, poor, uninsured, and less educated individuals are more likely to die from lung cancer. These groups of patients are also less likely to have beneficial surgery that may cure lung cancer. Because few lung cancer research studies have specifically focused on low income or African American populations, the factors influencing their survival from lung cancer are not well understood. In our analysis of the impact of genetic ancestry on lung cancer survival, we found that African ancestry did not have a significant impact on survival when stage and treatment were included in the multivariable model. These findings support that early detection and early stage of presentation will have the greatest impact on survival. We also examined genetic variants from prior lung cancer survival studies conducted in European American populations to determine their association in African Americans. Genetic analyses also considered common variants in exonic gene regions associated with lung cancer survival. Our analyses identified gene regions that likely play a role in lung cancer survival among African Americans.					
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## **Introduction**

Lung cancer is the leading cause of cancer deaths in the U.S. among men and women. Only 16% of lung cancer patients survive more than five years.<sup>1-3</sup> African Americans, poor, uninsured, and less educated individuals are more likely to die from lung cancer. These groups of patients are also less likely to have beneficial surgery that may cure lung cancer. Because few lung cancer research studies have specifically focused on these populations, the factors influencing their survival from lung cancer are not well understood.<sup>1</sup> This study identified the reasons for poor survival after a lung cancer diagnosis, especially among people at greatest risk. Discovery of genes that affect lung cancer survival can identify new targets for drug treatments and lead to the development of important clinical tests to improve survival of lung cancer. Understanding the factors that impact survival after a lung cancer diagnosis will help patients and physicians develop personalized treatment options, guided by access to resources or therapies.

## **Key words**

Lung cancer survival, distant stage, quality of care, genetic

## Overall Project Summary

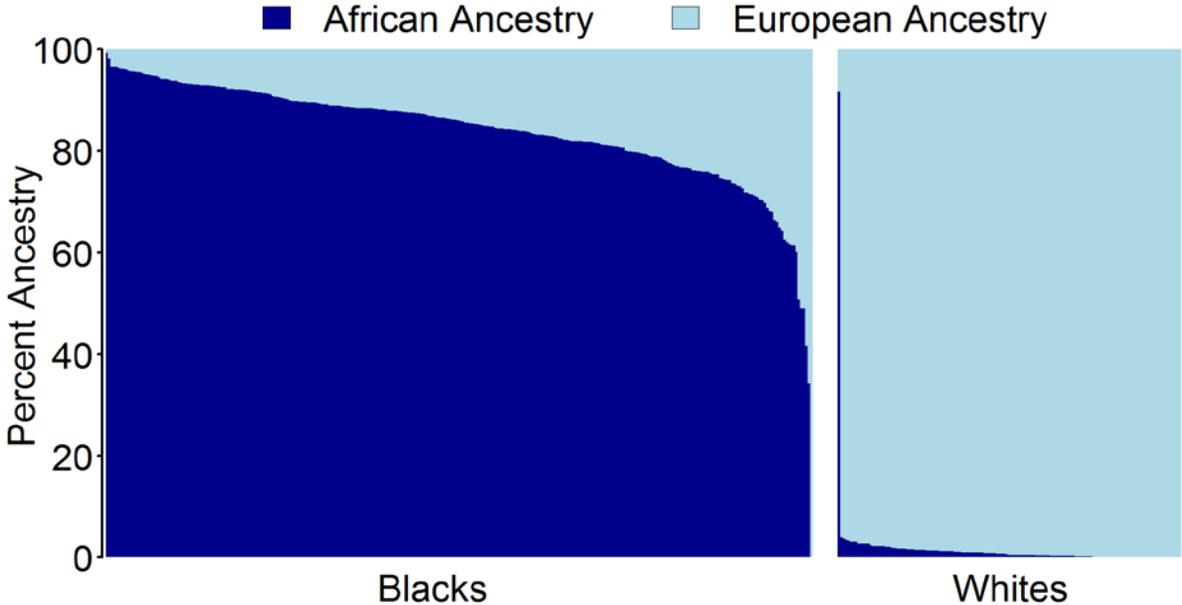
### **Aim 2. To genotype a panel of ancestry informative markers in lung cancer cases participating in the Southern Community Cohort Study. (Responsible PI – Aldrich)**

Prior to initiating this aim, Dr. Aldrich led efforts to examine racial differences in lung cancer survival in the Southern Community Cohort Study. We published a manuscript describing the epidemiology of lung cancer survival in this low-income mostly rural and underserved minority population (Aldrich MC, Grogan EL, et al. JTO 2013). In our initial description of the population, we found a greater proportion of underserved blacks are diagnosed with distant stage of disease compared to whites. Blacks also had greater crude mortality and shorter median survival time, yet when lung cancer stage, smoking and demographic factors were controlled for, mortality did not differ between blacks and whites. These data suggest future efforts should focus on identifying factors predictive of early stage of disease in both blacks and whites when clinical interventions are possible.

For Specific Aim 2, Dr. Aldrich leveraged readily available genotyping from another genetic project led by Dr. Aldrich in the same African American study population. With the use of a high quality biospecimen tracking system, lung cancer cases were identified in the SCCS biorepository, managed by the laboratory of Dr. Cai within the Molecular Epidemiology Core Laboratory at Vanderbilt University. The purified DNA from these lung cancer cases was hand delivered to the DNA Resources Core of the Vanderbilt Center for Human Genetics Research (CHGR) for genotyping. For cost effective reasons, Dr. Aldrich chose to use the Illumina HumanExome BeadChip for genotyping. This chip contains >240,000 genetic markers consisting of primarily rare variants, as well as a panel of approximately 3,200 ancestry informative markers (AIMs) to estimate European and African ancestry. Exome chip data were clustered and genotype calls were made by the DNA Resources Core. Genotyping data were converted to PLINK format, a preferred format for analysis of genetic data, and uploaded to a private Linux server. All genetic analyses were conducted by human genetics PhD student Ms. Carissa Iverson with guidance from Drs. Aldrich, Grogan, Blume, Bush and Crawford. Data were filtered based on standard quality control methods. The majority of genotyped lung cancer cases were self-reported whites or blacks.

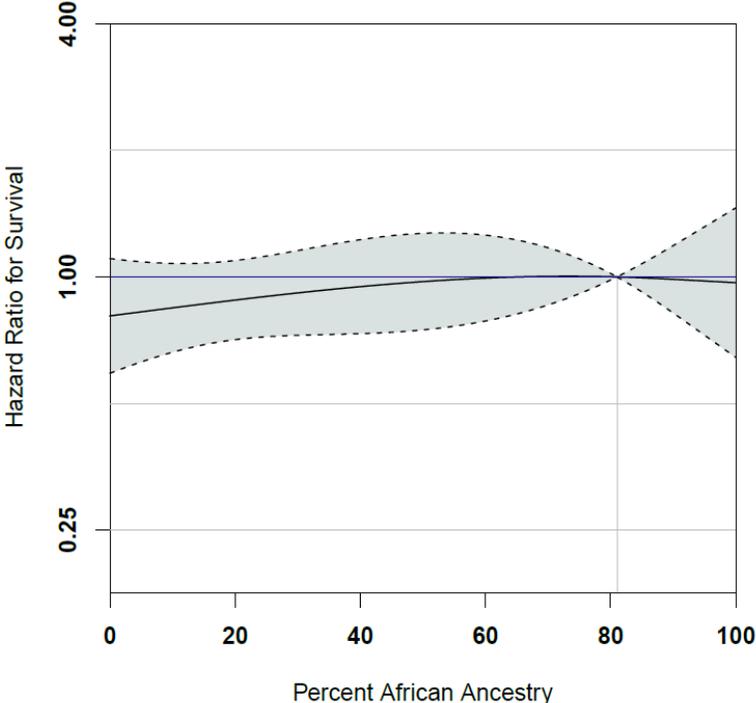
After QC filters were applied, approximately 1,198 AIMs remained in whites and 1,424 remained in the blacks. With the software program ADMIXTURE<sup>4</sup>, these genetic markers were used to estimate global ancestry for African American lung cancer cases in the Southern Community Cohort Study (SCCS). The median proportion of European ancestry in self-reported whites was 99%, indicating these individuals have very little African ancestry, as expected. African Americans in the SCCS had 86% median African ancestry (**Figure 1**). These estimates are higher than published findings in other African American study populations. Using the genotyping data described above, we conducted two distinct analyses.

**Figure 1.** Genetic ancestry estimates for self-reported blacks and whites in the Southern Community Cohort Study.



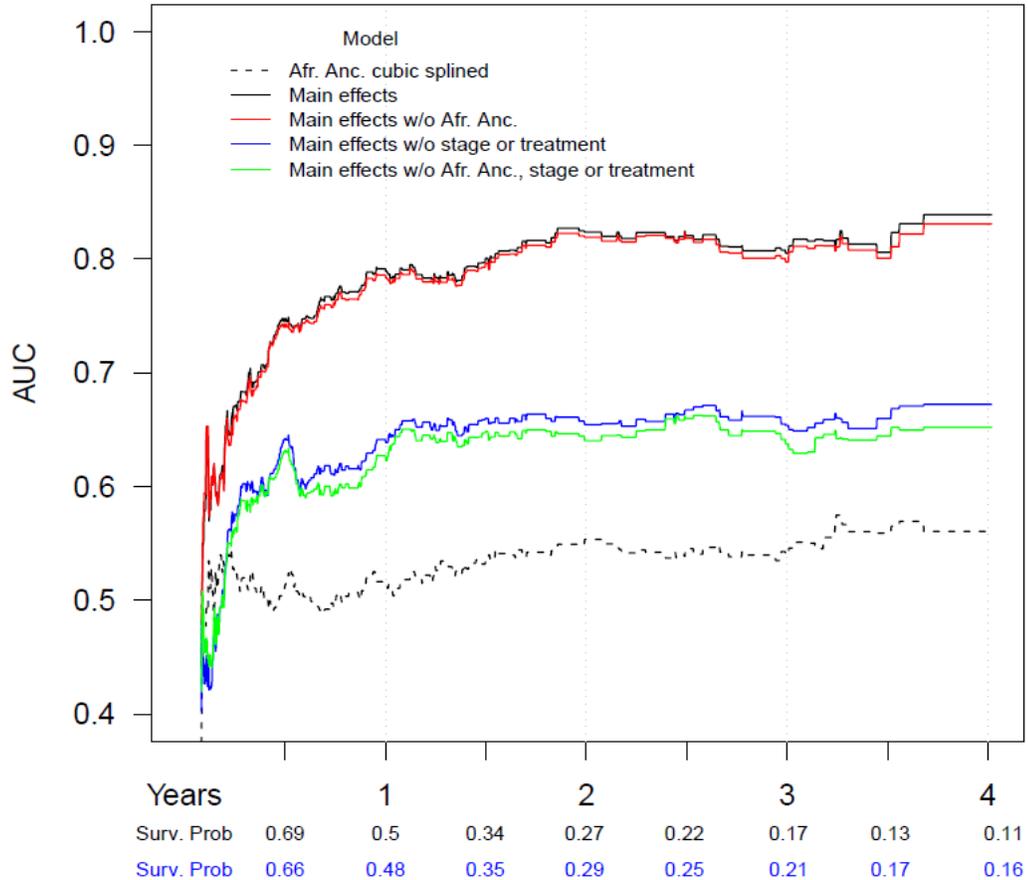
**Specific Aim 2, Analysis 1: Examination of association between African ancestry and lung cancer survival.** We examined the association between African ancestry and lung cancer survival as outlined in the grant. Using Cox proportional hazard models, we estimated hazard ratios for the association between African ancestry and lung cancer survival, adjusted for age, sex, body mass index (BMI), cigarettes per day, disease stage, treatment, education, and family history of lung cancer (we refer to this as the ‘main effects’ model). Variables BMI, age, cigarettes per day and global African ancestry were modeled using restricted cubic splines. We found African ancestry was not associated with lung cancer survival (**Figure 2**). We estimated time dependent area under the curve (AUC) to assess the impact of African ancestry on lung cancer survival, controlling for potential confounders such as stage and lung cancer treatment. We found that the main effects model had an average AUC of 0.79 (**Figure 3 and Table 1**). When global African ancestry was excluded, the AUC remained the

**Figure 2.** Impact of African ancestry on lung cancer survival



same, indicating no influence of African ancestry (**Table 1**). When interactions were added to the main effects model, the AUC increased to 0.83. Removal of global African ancestry from the interactions model reduced the AUC to 0.82 (**Table 1**), again indicating no influence of African ancestry on lung cancer survival. We were able to include a replication population from our collaborators at Wayne State University and observed similar changes in the AUC with each model. We conclude that African ancestry has little effect on overall survival. These findings were presented at the 2014 American Association for Cancer Research (AACR) meeting (abstract attached) and are in preparation for publication.

**Figure 3.** Time dependent AUCs for Cox proportional models for the Southern Community Cohort Study.



**Table 1.** Average time dependent AUCs for Cox proportional hazard models among all individuals in the SCCS and African Americans from Wayne State University (WSU).

Model	Average AUC	
	SCCS (N=425)	WSU (N=316)
Afr. ancestry only	0.53	0.53
Main Effects	0.79	0.74
Main Effects without Afr. ancestry	0.79	0.73
Interactions	0.83	0.78
Interactions without Afr. ancestry	0.82	0.77

**Specific Aim 2, Analysis 2: Association of exonic genetic variants and lung cancer survival.**

We identified variants previously associated with lung cancer survival from the NHGRI GWAS catalog on the Illumina ExomeChip genotyping array as described above. For each of these common variants, we ran a Cox proportional hazards model in African Americans adjusted for age, sex, global African ancestry, stage at diagnosis, and lung cancer treatment. We found a variant in the chemokine receptor-like 1 (*CMKLR1*) gene was associated with reduced mortality (hazard ratio (HR) = 0.71, 95% confidence interval (CI): 0.54-0.92, p=0.01, **Table 2**). We have since replicated this protective association in two independent cohorts of African Americans, although associations were not statistically significant (**Figure 4**). The protective effect was most pronounced amongst individuals with stage IV disease. The improved survival is in contrast to a prior lung cancer survival GWAS of similar sample size conducted among whites<sup>5</sup> suggesting ethnic-specific associations potentially due to differing linkage disequilibrium and causal variants.

**Table 2.** Multivariable Cox proportional hazard models for five NHGRI GWAS catalog SNPs previously associated with lung cancer survival and included on the Illumina HumanExome BeadChip v1.1

SNP	Chr.	bp Position <sup>a</sup>	Allele <sup>b</sup>	MAF <sup>b</sup>	Gene <sup>c</sup>	HR	95% CI	p value
rs1878022	12q23.3	108699032	C/T	0.14	<i>CMKLR1</i>	0.71	(0.54-0.92)	0.01
rs1209950	21q22.2	40173528	T/C	0.15	<i>ETS2</i>	1.17	(0.91-1.50)	0.23
rs9981861	21q22.2	41415044	C/T	0.30	<i>DSCAM</i>	1.08	(0.88-1.33)	0.45
rs1656402	2q37.1	233426526	A/G	0.42	<i>EIF4E2</i>	0.93	(0.76-1.13)	0.46
rs716274	11q22.3	103418158	G/A	0.42	<i>DYNC2H1</i>	1.02	(0.84-1.23)	0.87

<sup>a</sup>dbSNP build 137/GRCH37.p5

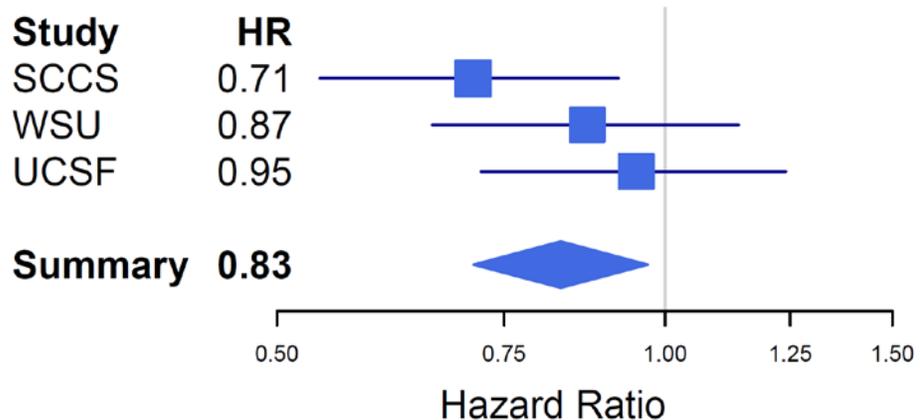
<sup>b</sup>Minor/major allele; MAF = minor allele frequency

<sup>c</sup>For variants outside of gene boundaries, || denotes the location of the variant in relation to the closest gene.

We then sought to identify novel variants associated with lung cancer survival by examining the remaining common variants genotyped on the ExomeChip. Out of 28,041 variants, 12 were nominally significant with lung cancer survival ( $p < 1 \times 10^{-4}$ , **Figure 5**). Nine of

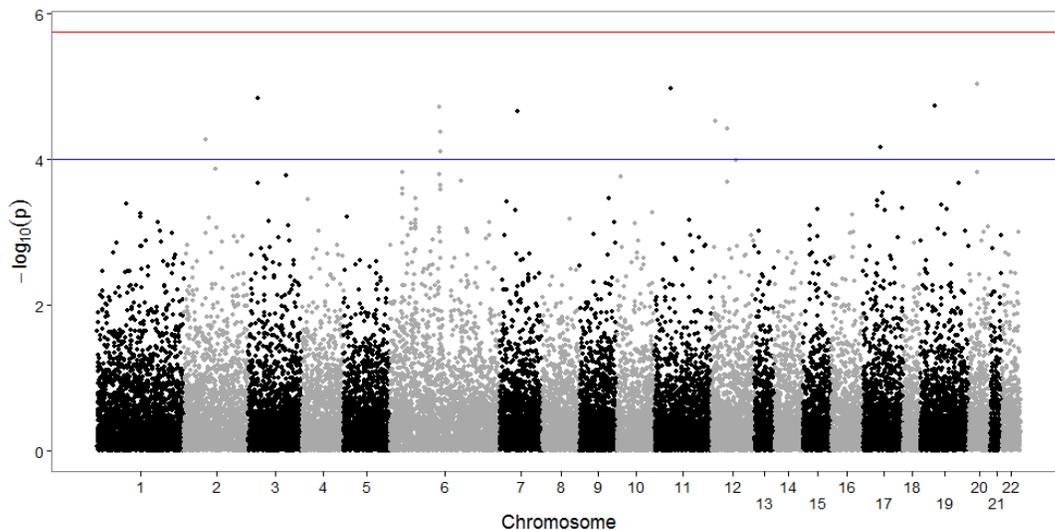
the most statistically significant variants were located within gene boundaries, five of which were exonic (**Table 3**). We observed a peak on chromosome 6p21.33 containing three non-coding

**Figure 4.** Meta-analysis of Cox proportional hazards results for rs1878022 in the SCCS and two replication cohorts, Wayne State University (WSU), and University of California San Francisco (UCSF).



variants (rs605203, rs2072633, and rs537160) associated with reduced mortality. This 6p21 region has been previously associated with lung cancer risk.<sup>6,7</sup> Additionally, we identified an African specific variant, rs7626962, located within the sodium channel, voltage gated, type V alpha subunit gene (*SCN5A*). Voltage-gated sodium channels have been shown to play a role in lung cancer invasiveness.<sup>8,9</sup> Finally, we identified the variant rs1639122, located within the chromodomain helicase DNA binding protein 4 (*CHD4*) associated with increased mortality among lung cancer cases. *CHD4* has been shown to play a role in nucleosome remodeling, as well as DNA damage response and cell cycle progression.<sup>10-12</sup> Replication of these findings remains necessary. This genome-wide study is the first to examine genetic variation associated with lung cancer survival in African Americans. These findings were presented at the American Society of Human Genetics (ASHG) 2014 meeting (abstract attached) and are currently in preparation for publication.

**Figure 5.** Multivariable Cox proportional hazards results for common SNPs associated with lung cancer survival in African Americans. Blue line represents suggestive significance threshold ( $p < 1.0 \times 10^{-4}$ ). Red line represents a Bonferroni corrected significance threshold



**Table 3.** Multivariable Cox proportional hazards results for common variants with a p value  $< 1.0 \times 10^{-4}$ .

SNP	Chr.	Allele <sup>b</sup>	MAF <sup>b</sup>	Gene <sup>c</sup>	HR	95% CI	p value
rs1133358	20q11.21	A/T	0.27	<i>SUN5</i>	0.62	(0.50-0.76)	$9.24 \times 10^{-06}$
rs8176785	11p15.1	A/G	0.28	<i>NELL1</i>	1.66	(1.20-1.84)	$1.05 \times 10^{-05}$
rs7626962	3p22.2	T/G	0.09	<i>SCN5A</i>	1.95	(1.35-2.42)	$1.43 \times 10^{-05}$
rs35761244	19p13.2	C/G	0.16	<i>CCDC130</i>	1.66	(1.28-2.01)	$1.81 \times 10^{-05}$
rs605203	6p21.33	G/T	0.09	<i>SLC44A4</i>    <i>EHMT2</i>	0.47	(0.37-0.70)	$1.88 \times 10^{-05}$
rs6959964	7q11.22	T/C	0.41	<i>AUTS2</i>	1.56	(1.18-1.74)	$2.14 \times 10^{-05}$
rs1639122	12p13.31	C/A	0.15	<i>CHD4</i>	1.81	(1.28-2.18)	$2.98 \times 10^{-05}$
rs7138803	12q13.12	A/G	0.16	<i>BCDIN3D</i>    <i>FAIM2</i>	1.70	(1.14-1.86)	$3.78 \times 10^{-05}$
rs2072633	6p21.33	T/C	0.35	<i>CFB</i>	0.66	(0.55-0.80)	$4.13 \times 10^{-05}$
rs1505229	2p12	T/C	0.46	<i>LRRTM4</i>	0.67	(0.61-0.87)	$5.36 \times 10^{-05}$
rs7502216	17q12	C/A	0.33	<i>ARHGAP23</i>	0.67	(0.56-0.80)	$6.72 \times 10^{-05}$
rs537160	6p21.33	T/C	0.17	<i>CFB</i>	0.61	(0.54-0.84)	$7.67 \times 10^{-05}$

<sup>a</sup>dbSNP build 137/GRCH37.p5

<sup>b</sup>Minor/major allele; MAF = minor allele frequency

<sup>c</sup>For variants outside of gene boundaries, || denotes the location of the variant relative to the closest gene.

We used the remaining genotyping and sample processing funds to follow-up on preliminary findings in the same African American cohort that COPD is associated with greater lung cancer mortality. We genotyped SCCS participants to examine genetic variation associated with COPD and lung cancer. To our knowledge no studies have examined common genetic variation in African Americans with both concomitant COPD and lung cancer. We received the genotyping data in March 2015 and are examining genetic factors influencing the development of COPD and lung cancer vs lung cancer alone in the Southern Community Cohort Study.

### **Key Research Accomplishments**

1. Described the epidemiology of lung cancer survival in a low-income mostly rural and underserved minority population.
2. Identified greater African ancestry among blacks participating in the Southern Community Cohort Study, compared to published estimates in other African American populations.
3. African ancestry is not associated with lung cancer survival, adjusting for sex, age, BMI, smoking, education, insurance, family history of lung cancer, recruitment source, stage and treatment.
4. Stage and treatment are significantly associated with lung cancer survival.
5. Variants in the *CMKLR1* gene are associated with improved lung cancer survival in African Americans. This is in the opposite direction of what has been previously published, likely due to differing linkage disequilibrium and causal variants between whites and African Americans.
6. Common variants on chromosome 6p21.33 and within the *SCN5A* and *CHD4* genes are associated with lung cancer survival in African Americans.

### **Conclusion**

We found a greater proportion of underserved blacks are diagnosed with distant stage of disease compared to whites. Blacks also had greater crude mortality and shorter median survival time. In our analysis of the impact of genetic ancestry on survival, we found that African ancestry did not have a significant influence on survival when stage and treatment were included in the multivariable model. These findings support the finding that early detection of lung cancer resulting in early stage of presentation will have the greatest impact on survival. Furthermore, there may be germline genetic regions to target for therapeutic interventions for improved survival. Finally, to explain the stage of presentation and treatment differences observed between the SCCS and Wayne State cohorts, additional research into access of care, utilization of care and social norms may provide insight into how lung cancer survival in underrepresented populations can be improved.

### **Publications, Abstracts, and Presentations**

1. Aldrich MC, Grogan EL, Munro HM, Signorello LB, Blot WJ. (2013) Stage-adjusted Lung Cancer Survival Does Not Differ Between Low-Income Blacks and Whites. *Journal of Thoracic Oncology*. 8:1248-1254. PMID: 24457235 PMCID: PMC3901948 (Appendix 1)

2. Iverson CC, Fletcher S, Blume J, Dilks H, Chen H, Deppen SA, Bush WS, Crawford DC, Blot WJ, Grogan EL, Aldrich MC. Global African ancestry is not associated with lung cancer survival. (2014) *American Association for Cancer Research*, San Diego, CA. (Appendix 2)
3. Iverson CC, Bush WS, Crawford DC, Dilks HH, Long J, Blot WJ, Grogan EL, Aldrich MC. Rare and common variants contribute to lung cancer survival in African Americans. (2014) *American Society of Human Genetics*, San Diego, CA. (Appendix 3)

## **Inventions, Patents, and Licenses**

Nothing to report.

## **Reportable Outcomes**

### Manuscript Published:

- Aldrich MC, Grogan EL, Munro HM, Signorello LB, Blot WJ. (2013) Stage-adjusted Lung Cancer Survival Does Not Differ Between Low-Income Blacks and Whites. *Journal of Thoracic Oncology*. 8:1248-1254. PMID: 24457235 PMCID: PMC3901948 (Appendix 1)

### Abstracts Presented

- Iverson CC, Fletcher S, Blume J, Dilks H, Chen H, Deppen SA, Bush WS, Crawford DC, Blot WJ, Grogan EL, Aldrich MC. Global African ancestry is not associated with lung cancer survival. (2014) *American Association for Cancer Research*, San Diego, CA. (Appendix 2)
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## Appendices

1. Aldrich MC, Grogan EL, Munro HM, Signorello LB, Blot WJ. (2013) Stage-adjusted Lung Cancer Survival Does Not Differ Between Low-Income Blacks and Whites. *Journal of Thoracic Oncology.* 8:1248-1254. PMID: 24457235 PMCID: PMC3901948 (Appendix 1)
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## Appendix 1

### Stage-Adjusted Lung Cancer Survival Does Not Differ between Low-Income Blacks and Whites

Aldrich MC, Grogan EL, Munro HM, Signorello LB, Blot WJ. *Journal of Thoracic Oncology*. (2013) 8:1248-1254. PMID: 24457235 PMCID: PMC3901948

# Stage-Adjusted Lung Cancer Survival Does Not Differ between Low-Income Blacks and Whites

Melinda C. Aldrich, PhD,\*† Eric L. Grogan, MD,\*‡§ Heather M. Munro, MS,||  
Lisa B. Signorello, ScD,¶ and William J. Blot, PhD†||

**Introduction:** Few lung cancer studies have focused on lung cancer survival in underserved populations. We conducted a prospective cohort study among 81,697 racially diverse and medically underserved adults enrolled in the Southern Community Cohort Study throughout an 11-state area of the Southeast from March 2002 to September 2009.

**Methods:** Using linkages with state cancer registries, we identified 501 incident non-small-cell lung cancer cases. We applied Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for subsequent mortality among black and white participants.

**Results:** The mean observed follow-up time (the time from diagnosis to death or end of follow-up) was 1.25 years (range, 0–8.3 years) and 75% ( $n = 376$ ) of cases died during follow-up. More blacks were diagnosed at distant stage than whites (57 versus 45%;  $p = 0.03$ ). In multivariable analyses adjusted for pack-years of smoking, age, body mass index, health insurance, socioeconomic status and disease stage, the lung cancer mortality HR was higher for men versus women (HR = 1.41; 95% CI, 1.09–1.81) but similar for blacks versus whites (HR = 0.99; 95% CI, 0.74–1.32).

**Conclusion:** These findings suggest that although proportionally more blacks present with distant-stage disease there is no difference in stage-adjusted lung cancer mortality between blacks and whites of similar low socioeconomic status.

**Key Words:** Lung cancer, Race, Disparities, Survival, Socioeconomic status.

(*J Thorac Oncol.* 2013;8: 1248–1254)

Lung cancer is the leading cause of cancer-related mortality in the United States among men and women, with an overall 5-year relative survival of only 16%.<sup>1–3</sup> According to the American Cancer Society, an estimated 160,340 lung cancer deaths occurred in the United States in 2012, accounting for 28% of all cancer deaths.<sup>4</sup> Although survival from lung cancer has improved since the early 1990s, racial differences in lung cancer survival persist such that blacks experience poorer 5-year survival for lung cancer compared with whites.<sup>1,3,5–8</sup> Specifically, recent 5-year relative survival estimates from the Surveillance Epidemiology and End Results 18 areas indicates blacks have a 13.0% 5-year relative survival whereas whites have a 16.3% 5-year relative survival.<sup>3,9</sup> Moreover, blacks are less likely to present with localized disease<sup>2,10</sup> and also have a poorer prognosis even when diagnosed with localized disease, which is more successfully treated.<sup>2,11</sup> Advanced stage of disease at diagnosis is the primary factor contributing to the poor prognosis of lung cancer, although other risk factors identified to date include low socioeconomic status (SES), male sex, and incomplete lung resection.<sup>12,13</sup> Populations living in Southern United States experience the highest mortality for lung cancer, especially among men.<sup>2,6</sup>

Because of the high burden of lung cancer in underserved populations,<sup>14</sup> understanding lung cancer prognosis in these populations is necessary for targeted public health interventions for reducing lung cancer deaths. Moreover, the paucity of lung cancer studies conducted among minority and low-income populations emphasizes the need to understand lung cancer survival in these understudied populations. Using data from the Southern Community Cohort Study (SCCS),<sup>15,16</sup> which includes a large proportion of blacks and underserved low-income individuals, we examined whether lung cancer survival differs between socioeconomically similar white and black populations living in Southern United States.

## PATIENTS AND METHODS

### Study Population

The SCCS is an ongoing prospective cohort study established to examine cancer disparities among a predominantly

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low-income population. From March 2002 to September 2009, 70,748 racially diverse adults were enrolled into the SCCS at community health centers, institutions providing basic health care and preventative services in medically underserved geographic areas, throughout an 11-state area of the Southeast (Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia). Additional participants ( $n = 10,949$ ) were enrolled from the same 11-state area into the SCCS by selecting a random sample of adults identified from voter registration, driver's license records, and commercial records. Participants were aged 40 to 79 years at enrollment and approximately two thirds self-reported as black/African American. Extensive details of the SCCS study design and participant recruitment are summarized elsewhere.<sup>15,16</sup> Briefly, participants were eligible if they spoke English, were between the ages of 40 to 79 years, and were not under treatment for cancer (except for nonmelanoma skin cancer) within the prior 12 months. For this analysis, participants were excluded if they had a prior diagnosis of lung cancer at cohort entry. The SCCS was approved by institutional review boards at Vanderbilt University and Meharry Medical College. Written informed consent was obtained from all participants.

### Baseline Characteristics

Epidemiologic data were collected by trained interviewers during in-person computer-assisted personal interviews conducted at the community health centers or by mailed questionnaire from the random sample of the general population. Information was ascertained on demographic characteristics and exposure histories, including race/ethnicity, tobacco-smoking history, medical history, and health insurance status. From March 2002 to September 2007, self-reported weight and height were ascertained from the baseline questionnaire administered by trained study interviewers. Participants were provided with the 2000 U.S. Census categories for race/ethnicity and asked to mark all that applied to their race and ethnic background.

### Lung Cancer Case Identification and Mortality Assessment

Incident lung cancer cases (International Classification of Diseases for Oncology, 3rd edition, codes C340-C349) were identified via linkage with state cancer registries operating in the 11-state study area. Lung cancer stage and cell type were obtained from the state cancer registries. The cohort was followed up for all-cause mortality, with the number of survival days defined as the time from date of diagnosis until date of death, loss to follow-up or censoring, by linkage with the National Death Index through December 31, 2010 and the Social Security Administration through February 4, 2011. Cause of death was available only for deaths occurring through 2010.

### Statistical Analysis

Lung cancer patients reporting races other than non-Hispanic white or non-Hispanic black ( $n = 25$ ) were excluded from analyses. Differences in baseline characteristics

between black and white lung cancer cases were evaluated using the  $\chi^2$  test and two-sample  $t$  test for categorical or continuous variables, respectively. Kaplan–Meier curves were plotted to visualize survival probabilities, and differences in survival between whites and blacks were assessed using the log-rank test. We estimated hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) for lung cancer mortality using Cox proportional hazard (PH) models, adjusted for demographic and clinical characteristics, to evaluate whether lung cancer survival differed between blacks and whites. Age of the participant at diagnosis was included as a covariate in Cox PH models. The PHs assumption was assessed by including an interaction term between race and time and we found that hazards remained constant over time. We estimated odds ratios (ORs) for the association between education and health insurance and stage of diagnosis (coded as local versus distant/regional), using multivariable logistic regression models. All analyses were conducted using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). Statistical tests were two-sided and an  $\alpha$  of 0.05 was used to assess statistical significance.

### RESULTS

We identified 501 incident non–small-cell lung cancer cases (149 non-Hispanic white, 352 non-Hispanic black) occurring among the 81,697 participants during the follow-up period from March 2002 to February 2011. During an average of 1.3 (maximum 8.3) years of follow-up, 376 deaths occurred and 309 (82%) had lung cancer as the primary cause of death. Most cases (88%) were recruited from community health centers. Among the lung cancer cases 66% had an annual household income less than \$15,000, 42% had less than a high-school education, 58% were overweight or obese, 71% were current smokers, and 34% reported having no medical insurance at cohort entry, reflecting the overall demographics of the SCCS cohort.<sup>15</sup> Approximately half (49%) of the lung cancer cases were diagnosed with distant-stage lung cancer, whereas only 16% of cases were diagnosed at local stage. The most frequent histologic tumor type was adenocarcinoma (39%), followed by squamous cell carcinoma (27%), and non–small-cell not otherwise specified (27%), and other non–small-cell lung cancer tumors (e.g., large cell; 8%).

No differences were observed between black and white lung cancer cases for household income or smoking status (current/former/never smoker), the primary lung cancer risk factor (Table 1). More blacks smoked menthol cigarettes compared with whites. More whites self-reported a physician diagnosis of emphysema or chronic bronchitis and a first-degree relative with lung cancer. Health insurance status differed between blacks and whites ( $p = 0.007$ ), with more blacks uninsured (36 versus 30%, respectively) and receiving Medicaid (25 versus 18%, respectively) than whites (Table 1). A greater percentage of blacks were diagnosed with distant-stage lung cancer than whites (57 versus 45%, respectively;  $p = 0.03$ ; Fig. 1). Histologic subtypes of disease did not differ between blacks and whites. The overall mean age at diagnosis for lung cancer cases was 60.0 years (SD, 8.9).

**TABLE 1.** Demographic Characteristics by Race of Incident NSCLC Cases Occurring in the Southern Community Cohort Study, 2002–2011

Characteristic	NSCLC Cases N = 501	
	Black (n = 352) n (%)	White (n = 149) n (%)
Sex		
Male	209 (59.4)	67 (45.0)
Female	143 (40.6)	82 (55.0)
Vital status <sup>a</sup>		
Died	270 (76.7)	106 (71.1)
Alive	82 (23.3)	43 (28.9)
Person-years of follow-up	410.4	218.0
Lung cancer stage at diagnosis		
Distant	181 (56.9)	60 (45.5)
Local	48 (15.1)	30 (22.7)
Regional	89 (28.0)	42 (31.8)
Unknown	51	
Histology		
Adenocarcinoma	139 (39.5)	55 (36.9)
Non–small-cell lung cancer-NOS	97 (27.6)	38 (25.5)
Squamous	89 (25.3)	44 (29.5)
Other NSCLC	27 (7.7)	12 (8.1)
Mean age at enrollment, yr (SD)	55.7 (8.8)	59.7 (8.8)
Mean age at diagnosis, yr (SD)	59.0 (8.7)	62.3 (9.0)
Mean observed duration of disease among those who died, <sup>b</sup> yr (SD)	0.74 (0.85)	0.82 (0.93)
Mean observed duration of disease among those alive at last follow-up, <sup>b</sup> year (SD)	2.57 (1.9)	3.05 (1.7)
Highest education level, yr		
<12	161 (45.9)	51 (34.5)
≥12	190 (54.1)	97 (65.5)
Unknown	2	
Household income in last year		
<\$15,000	232 (66.5)	94 (63.9)
≥\$15,000	117 (33.5)	53 (36.1)
Unknown	5	
Smoking status at cohort entry		
Current	253 (72.5)	102 (68.9)
Former	75 (21.5)	40 (27.0)
Never	21 (6.0)	6 (4.1)
Smokes (or smoked) menthol cigarettes <sup>c</sup>		
Yes	231 (70.6)	24 (17.1)
No	96 (29.4)	116 (82.9)
Unknown	7	
Self-reported doctor diagnosis of emphysema or chronic bronchitis		
Yes	39 (11.1)	45 (30.2)
No	312 (88.9)	104 (69.8)
Unknown	1	
First-degree relative with lung cancer		
Yes	26 (9.4)	28 (23.5)
No	251 (90.6)	91 (76.5)
Unknown	105	

(Continued)

TABLE 1. (Continued)

Characteristic	NSCLC Cases N = 501	
	Black (n = 352)	White (n = 149)
	n (%)	n (%)
<25	160 (45.7)	50 (33.8)
25–29	107 (30.6)	55 (37.2)
≥30	83 (23.7)	43 (29.1)
Unknown	3	
Health insurance status		
Uninsured	126 (36.1)	44 (29.7)
Medicare, aged <65 yr	51 (14.6)	25 (16.9)
Medicare, aged ≥65 yr	25 (7.2)	28 (18.9)
Medicaid	88 (25.2)	27 (18.2)
Private	42 (12.0)	22 (14.9)
Military/other	17 (4.9)	2 (1.4)
Unknown	4	

Numbers may not add to 100% because of rounding.  
<sup>a</sup>Date of last follow-up February 4, 2011.  
<sup>b</sup>Date of diagnosis to date of last follow-up (or death).  
<sup>c</sup>Among current and former smokers only.  
 NSCLC, non-small-cell lung cancer; NOS, not otherwise specified.

By the end of study follow-up, 75% of identified lung cancer cases were deceased with a median overall survival of 0.73 years. Kaplan–Meier product-limit survival estimates demonstrated blacks had shorter median survival times (0.67 versus 1.02 years) and poorer overall survival compared with whites ( $p = 0.06$ , log-rank test; Fig. 2). Figure 3 illustrates the poor survival of black men compared with women and white men ( $p < 0.0001$ , log-rank test; Fig. 3). Age at diagnosis did not

significantly impact survival (data not shown). After adjusting for disease stage, pack-years of smoking, age at diagnosis, sex, education, baseline body mass index, health insurance status, and study site, blacks and whites had no difference in mortality (HR = 0.99; 95% CI, 0.74–1.32; Table 2). Including an indicator for rural versus urban county of residence did not

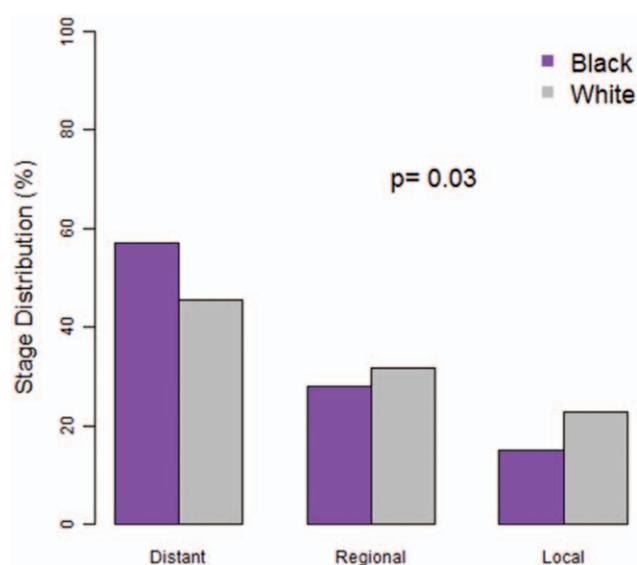


FIGURE 1. Stage distribution for black and white incident non-small-cell lung cancer cases occurring from 2002 to 2011 in Southern Community Cohort Study participants.

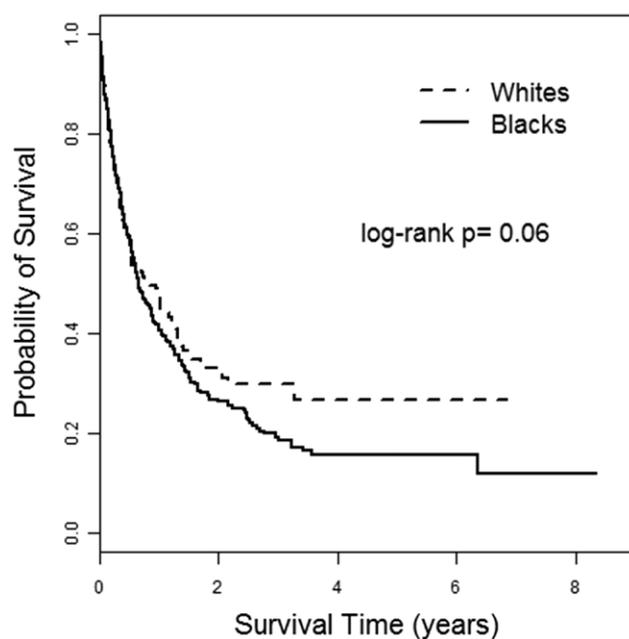
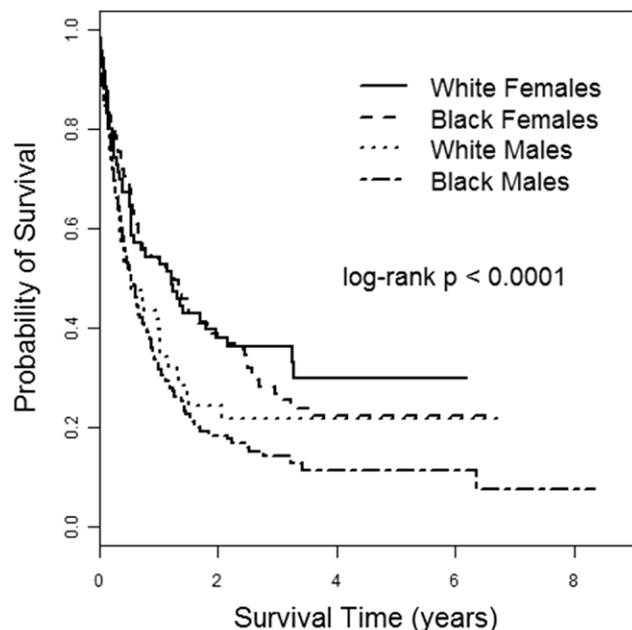


FIGURE 2. Kaplan–Meier curves for black and white incident non-small-cell lung cancer cases occurring from 2002 to 2011 in Southern Community Cohort Study participants.



**FIGURE 3.** Kaplan–Meier curves for black and white incident non–small-cell lung cancer cases, stratified by sex, occurring from 2002 to 2011 in Southern Community Cohort Study participants.

alter this finding (data not shown). Male lung cancer cases had a statistically significant 41% greater mortality compared with females (HR = 1.41; 95% CI, 1.10–1.80; Table 2). As expected, distant stage of disease at diagnosis was strongly associated with mortality, with almost a fivefold increased mortality compared with those diagnosed at localized stage (Table 2). No significant differences in mortality were found according to health insurance classification. Blacks (OR = 0.72; 95% CI, 0.40–1.31), males (OR = 0.61; 95% CI, 0.35–1.06), and those enrolled at a community health center (OR = 0.55; 95% CI, 0.23–1.32) were less likely (although not statistically significant) to have localized stage of disease, after adjusting for pack-years of smoking, education, body mass index, and age of diagnosis.

## DISCUSSION

This survival analysis of incident lung cancers nested within a large prospective cohort study of blacks and whites revealed greater crude mortality and shorter median survival for blacks compared with whites but no racial difference in overall mortality between low-income blacks and whites after controlling for stage of diagnosis. We were uniquely positioned to examine lung cancer mortality for both blacks and whites in the Southeastern United States after good control for SES, because both blacks and whites in the cohort had generally similar low household income, low education, health insurance and access to basic health services, with minor differences adjusted for in our statistical analyses. Our findings in this population of blacks and whites with similar individual-level SES are analogous to results of lung cancer investigations in other populations with similar access to health care or surgical

**TABLE 2.** All-Cause Mortality among Incident NSCLC Cases Participating in the Southern Community Cohort Study, 2002–2011

Variable	NSCLC Cases		
	HR	95% CI	<i>p</i>
	N = 424		
Race			
White	1.0	Referent	
Black	0.99	0.74–1.32	0.94
Smoking pack-years	1.005	1.00–1.009	0.04
Age at diagnosis	1.00	0.98–1.02	0.99
Sex			
Female	1.0	Referent	
Male	1.41	1.09–1.81	<0.01
Education, yr			
<12	1.0	Referent	
≥12	1.04	0.81–1.33	0.79
BMI, kg/m <sup>2</sup>			
<25	1.0	Referent	
25–29	1.00	0.76–1.30	0.98
≥30	0.92	0.69–1.24	0.60
Health insurance status			
No	1.0	Referent	
Medicare, aged <65 yr	0.92	0.65–1.32	0.66
Medicare, aged ≥65 yr	0.72	0.44–1.20	0.21
Medicaid	1.21	0.89–1.65	0.22
Private	0.74	0.49–1.12	0.15
Military/other	1.33	0.75–2.35	0.33
Disease stage			
Localized	1.0	Referent	
Regional	2.23	1.45–3.43	<0.01
Distant	4.99	3.33–7.48	<0.01
Study site			
General population	1.0	Referent	
CHC	1.13	0.72–1.76	0.60

Cox proportional hazards analysis of lung cancer mortality among SCCS participants.

HR, hazard ratio; CI, confidence interval; NSCLC, non–small-cell lung cancer; CHC, community health center; SCCS, Southern Community Cohort Study; BMI, body mass index.

treatment between blacks and whites<sup>12,17,18</sup> or investigations stratified by cancer stage.<sup>19</sup> Our findings provide evidence to support that when demographic factors, smoking, and lung cancer stage are controlled, lung cancer survival between black and white lung cancer patients is similar, even among primarily low-income and medically underserved populations. However, similar to national data,<sup>3</sup> our study found an increased mortality for males compared with females. This finding deserves further investigation to clarify predictors of local stage when clinical interventions are possible.

Prior research on racial disparities in lung cancer has found that blacks are more likely to be diagnosed at advanced

stage of lung cancer compared with whites.<sup>10</sup> Similarly, within the SCCS, we found that a greater percentage of blacks were diagnosed at advanced stage of disease compared with whites, despite having similar smoking status and access to basic health care. Research suggests blacks may tend to hold different beliefs regarding lung cancer treatments compared with whites, including inaccurate beliefs regarding tumor spread when surgically exposed to air,<sup>7</sup> which may lead to a later stage of presentation. Diagnosis at an early stage of disease is crucial because lung cancers diagnosed at a localized stage have a 52% 5-year relative survival rate; however, only 15% of lung cancers are diagnosed at this early stage,<sup>3,11</sup> consistent with the 16% of localized stage lung cancers identified in our study population.

Contrary to prior investigations by others,<sup>13,20,21</sup> we did not find that the SES, measured using highest education level attained, was associated with localized stage of lung cancer. Lung cancer incidence is higher among poor and low-education populations,<sup>14</sup> yet few lung cancer studies have been devoted to underserved populations. It is well documented that educational attainment is associated with improved cancer survival such that poorly educated<sup>20,22</sup> and low-income populations experience worse outcomes compared with higher-income populations.<sup>1,23</sup> Several studies using census-level data have found inverse associations between SES and lung cancer mortality.<sup>13,21,24</sup> Using census block group data to construct an SES metric, Schwartz et al.<sup>13</sup> found that SES predicted lung cancer stage at diagnosis, with individuals living in professional occupation block groups having a reduced mortality compared with individuals living in working poor block groups. Similarly, Erhunmwunsee et al.<sup>21</sup> found individuals living in census tracts with lower incomes and less education had shorter survival compared with individuals living in regions with higher incomes or greater education level. However, these ecologic studies are constrained by the lack of data on important individual-level factors influencing survival, and ascribing attributes of a group to an individual can result in inaccurate inferences.<sup>25</sup> Using U.S. mortality data and education data from the U.S. Current Population Survey, Albano et al.<sup>20</sup> identified an increased mortality among blacks and whites diagnosed with lung cancer and having less than 12 years of education compared with those with 12 or more years, especially among men. However, where health care access has been universal and treatment has been similar, such as among military populations or clinical populations, no racial differences in lung cancer survival between blacks and whites have been observed.<sup>12,17,18,26</sup> Thus racial differences in lung cancer survival seem to manifest differently across populations, yet few have examined low-income populations. Our study sheds light on low-income populations and indicates that blacks tend to be diagnosed with lung cancer at later stage and have poorer survival than whites, but when stage and other factors are controlled, racial differences disappear.

Our study is limited by a lack of assessment of treatment received, treatment quality of care, and medically confirmed comorbidities. Although we do not have systematic treatment information available from clinical records, we

were able to adjust for stage and health insurance status as a proxy for treatment. Our findings suggest that if lung cancer treatment differences do exist between blacks and whites in this low-income population, the influence on survival may be minimal. Comorbidities are important predictors of lung cancer stage, treatment, and survival.<sup>27,28</sup> Our limited sample size, especially for whites, limits our statistical power, which may have resulted in less precision around our estimated HRs (i.e., wide CIs) and therefore our conclusions regarding statistically significant findings. Future studies are warranted to replicate our findings in larger populations of low-income blacks and whites, stratifying by histology and incorporating lung cancer treatment and comorbidities into analyses.

The strengths of our study are the inclusion of blacks and whites of similar low SES and incident lung cancer cases nested within a large prospective study. Notably, we obtained individual-level data on smoking and health insurance status, which prior studies using Surveillance Epidemiology and End Results cancer registry or census-level data have been unable to measure.<sup>10</sup> Furthermore, data were obtained before lung cancer diagnosis, thus minimizing the possibility of recall bias. Few studies have focused on medically underserved populations having such low SES. Importantly, our findings may be generally applicable to low-income, underserved populations thus filling an important research gap regarding lung cancer outcomes in groups frequently excluded from lung cancer investigations.

In summary, we observed that within an underserved population of blacks and whites of similar SES, blacks tend to be diagnosed with lung cancer at later stages of disease and have poorer overall survival, but after control for stage racial differences in mortality are no longer apparent. Regardless of race, the survival was low with 75% of the cases deceased over a mean 1.3 year follow-up period. The poor lung cancer prognosis remains true despite the steady decline in lung cancer incidence, declining smoking rates, increased awareness of the disease in the general population, and the advent of new technologies to detect lung cancers in early stages of the disease. This has prompted the National Cancer Institute to prioritize research aimed at improving early diagnosis of disease<sup>29</sup> and underscores the timeliness of the National Lung Screening Trial findings of improved survival associated with computed tomographic screening.<sup>30</sup> It remains to be determined whether the observed difference in histologic subtype and stage of presentation of lung cancer between blacks and whites is because of differences in comorbidities, cultural choices between blacks and whites, potential underlying biologic or genetic variations, or combinations of these factors. Importantly, these findings indicate that race per se may not be a predictor of poor survival, even among a primarily low-income and medically underserved population. Future efforts should identify opportunities for early diagnosis and treatment, especially for black males who experience a greater mortality from lung cancer.

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## Appendix 2

# Global African Ancestry is Not Associated with Lung Cancer Survival

Iverson CC, Fletcher S, Blume J, Dilks H, Chen H, Deppen SA, Bush WS, Crawford DC, Blot WJ, Grogan EL, Aldrich MC. (2014). Presented at the *American Association for Cancer Research Annual Meeting 2014*, San Diego, CA.

## **Global African Ancestry is Not Associated with Lung Cancer Survival**

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Lung cancer is the leading cause of cancer-related mortality among men and women in the United States, accounting for 27% of all cancer-related deaths. Blacks experience poorer 5-year survival compared to whites. We hypothesized that individuals with higher global African ancestry have poorer survival compared to individuals with lower global African ancestry. We identified incident non-small cell lung cancer cases in the Southern Community Cohort Study (SCCS), a prospective study of low-income adults recruited from across the Southeast region of the United States. Individuals who donated a biospecimen were genotyped using the Illumina Human Exome BeadChip, which contains a panel of ancestry informative markers (AIMs). After standard quality control, 398 individuals (262 self-reported black and 134 self-reported white) remained for analysis. Global ancestry was estimated from 2,604 AIMs using the software program ADMIXTURE. Self-reported blacks had a median global African ancestry of 88.12%, while the median global African ancestry in self-reported whites was less than 0.01%. We estimated hazard ratios and 95% confidence intervals using Cox proportional hazard models adjusted for age, sex, body mass index (BMI), cigarettes per day, disease stage, treatment, insurance coverage, family history of lung cancer and recruitment site. BMI, age, cigarettes per day and global African ancestry were modeled using restricted cubic splines. We estimated time dependent area under the curve (AUC) for our main effects model and a main effects model with interactions, both with and without genetic ancestry. We found that the main effects model had an average AUC of 0.81. When global African ancestry was excluded, the AUC was minimally reduced to 0.80. When interactions were added to the main effects model, the AUC increased to 0.88. Removal of global ancestry from the interactions model reduced the AUC to 0.84. In the main effects model, the two most predictive variables were stage and treatment with  $X^2$  values of 36.13 (degrees of freedom,  $df=2$ ) and 15.47 ( $df=4$ ), respectively. While we conclude that global African ancestry has little effect on overall survival, a relationship between global African ancestry and stage or treatment remains to be investigated.

Character Count: 2,032 (Maximum: 2,600 - not including spaces)

## Appendix 3

### Rare and Common Variants Contribute to Lung Cancer Survival in African Americans

Iverson CC, Bush WS, Crawford DC, Dilks HH, Long J, Blot WJ, Grogan EL, Aldrich MC. (2014). Presented at the *American Society of Human Genetics 2014 Annual Meeting*, San Diego, CA.

## Rare and Common Variants Contribute to Lung Cancer Survival in African Americans

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Lung cancer is the leading cause of cancer-related mortality in the U.S. Survival rates differ by race, with blacks experiencing poorer survival than whites, yet few studies have focused on blacks. Germline genetic variation may influence overall lung cancer survival. A total of 305 incident non-small cell lung cancer African American cases were identified from the prospective Southern Community Cohort Study through linkage with 12 state cancer registries. Vital status was determined by linking with the National Death Index or Social Security Administration. After 8.6 years of follow-up, 87% of lung cancer cases were deceased. We performed genotyping using the Illumina HumanExome BeadChip. After standard quality control, 301 individuals (60% male) and 274,438 variants remained for analysis. We identified variants previously associated with lung cancer survival from the NHGRI GWAS catalog on the ExomeChip array. For each of these SNPs, we ran a Cox proportional hazards model adjusted for age, sex, percent African ancestry (estimated from ancestry informative markers), stage at diagnosis, and treatment. We found the C allele at rs1878022, in the chemokine receptor-like 1 (*CMKLR1*) gene, was associated with reduced mortality [hazard ratio (HR): 0.72, 95% confidence interval (CI): 0.54-0.97,  $p=0.03$ ]. The improved survival is in contrast to a prior lung cancer survival GWAS of similar sample size conducted in whites, suggesting ethnic-specific associations. We then sought to identify rare variants in protein coding regions associated with lung cancer survival. We identified variants with a MAF < 5% ( $n=114,646$ ) and mapped them to 9,725 genes. We used the sequence kernel association test (SKAT) and burden test, adjusting for age, sex, and African ancestry, to examine associations between rare variants and lung cancer survival. The strongest association was with the *MICAL-L2* gene (HR =1.84, 95% CI: 1.42-2.37,  $p=1.04 \times 10^{-6}$ ) that interacts with actinin-4, which in turn harbors variants associated with poor lung cancer survival. A significant association was also found for the vascular epidermal growth factor B (*VEGFB*) gene ( $p=4.0 \times 10^{-6}$ ), which may play a role in tumor survival. We identified 3 genes associated with overall survival, which if validated could suggest potential new targets for lung cancer treatments. Fine-mapping in larger populations and functional studies are required to understand the role of these variants in lung cancer survival.

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