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Lung cancer histology, stage, treatment, and survival in American Indians and Alaska Natives and whites

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Abstract

Background—Studies of lung cancer disparities between American Indians and Alaska Natives (AIANs) and whites have yielded mixed results. No studies have investigated whether race-based differences in histology could explain survival disparities.

Methods—We obtained data on AIANs and whites with lung cancer from the 17 population-based cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) program from 1973–2006. We used logistic regression to determine whether race and other covariates were associated with histology, stage at diagnosis, and receipt of surgery. We used Cox regression to determine the risk of death associated with race, after adjusting for histology, stage, and other covariates.

Results—Histology, but not race, was associated with stage at diagnosis, and both race and stage were associated with histology. AIANs were less likely to receive surgery than whites, after adjusting for patient and tumor characteristics. Survival improved for both AIANs and whites after 2000, compared to the 1973–1999 period, but survival was consistently shorter for AIANs. The association between AIAN race and decreased survival was strongest in the later time period.

Conclusion—Lung cancer histology is associated with tumor characteristics, treatment, and survival. AIAN race is associated with tumor histology, receipt of surgery, and survival. Future studies with access to smoking data, patient comorbidity information, and health systems-level data will be able to identify factors responsible for the disparities observed in these analyses.

Keywords

lung cancer; survival; histology; health status disparities; operative therapy

American Indians and Alaska Natives (AIANs) experience disparities in incidence and survival compared to whites for several cancers,(1,2) However, studies aimed at identifying lung cancer disparities between AIANs and whites have had mixed results. A nationwide study of lung cancer incidence found that incidence and stage at diagnosis did not differ between AIANs and whites, although 42% of AIANs were diagnosed before age 65, compared to 30% of whites.(3) Another study of AIANs in the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) Registry from 1974 through 1989 observed that lung cancer stage distribution at diagnosis and survival were similar for

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AIANs and whites.(4) A later study using SEER data from 1988 through 1995 noted that AIANs with lung cancer had worse 5-year survival rates than any other racial/ethnic group.(5) In terms of differences in tumor characteristics, several studies have observed that the incidence of squamous cell lung cancer is higher in AIANs than whites.(3,5) Because survival differs by histology type,(6) race-based differences in histology distribution may be mirrored in survival differences. However, the relationship of histology to survival disparities among AIANs is unknown.

To our knowledge, the existence and magnitude of disparities in lung cancer survival and cancer-directed surgery between AIANs and whites has not been established in a population-based sample. No recent nationwide studies have examined whether lung cancer stage at diagnosis and survival differs between AIANs and whites, and whether any differences are related to histology types. Further, the most recent study using SEER data only included patients diagnosed through 1995. These prior studies warrant updating because the overall survival of lung cancer patients has increased as detection and treatment methods improved over time.(7)

To address these knowledge gaps, we analyzed SEER data from 1973–2006 to determine if race, histology, and survival in lung cancer were associated among patients in two time periods and to document changes in lung cancer disparities between AIANs and whites over time.

Methods

Case Selection

Lung cancer cases were drawn from the 17 population-based cancer registries participating in the SEER program anytime from 1973–2006. The populations under SEER registry surveillance encompass 26% of the U.S. population, including 42% of the AIAN population, and are estimated to include greater than 95% of all incident cancers in their catchment areas.(8) All AIAN and white cases diagnosed with lung cancer (ICD-O 33.9 – 34.9) at age 21 or older were potentially eligible for inclusion in these analyses. We limited our analyses to non-small cell carcinoma cases diagnosed with one of five histology subtypes, comprised of the following ICD-O histology codes: adenocarcinoma (8140, 8251, 8255, 8260, 8310, 8323, 8480, 8481, 8570), bronchioloalveolar carcinoma (8250, 8252, 8253), large cell carcinoma (8012, 8031), squamous cell carcinoma (8052, 8070, 8071, 8072, 8073, 8074), and other non-small cell carcinoma (ONSCLC) (8010, 8020, 8022, 8032, 8033, 8046, 8050, 8490, 8550, 8560). Cases with *in situ* stage, unknown stage and/or unknown surgery status were also excluded from all analyses.

Statistical Analysis

All analyses were performed using SAS. We compared the distribution of age at diagnosis, year of diagnosis, sex, SEER historic stage, surgery status, and histology between AIANs and whites using a Chi-squared test. We used multinomial regression to test our hypothesis that race is associated with lung cancer histology type, using adenocarcinoma as the comparison category of the dependent variable. We used multinomial regression to test our hypothesis that race and histology type are predictors of stage at diagnosis, using localized/regional stage as the comparison category of the dependent variable. We used logistic regression models test our hypothesis that race and histology type are associated with receipt of cancer-directed surgery. Finally, we used Cox regression to test our hypothesis that race and histology type are associated with risk of death. All regression analyses were adjusted for sex, SEER site, and age at diagnosis. The multinomial regression on histology was additionally adjusted for stage, and the Cox regression analyses were additionally adjusted

for stage and receipt of surgery. To account for advances in treatment for lung cancer, all regression analyses were adjusted for categorical year of diagnosis (1973–1999 and 2000–2006). We also constructed models including a race*time period interaction term to determine whether any association between race and histology differed by time period. This study involved de-identified, non-human subjects data only, and was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Results

Demographic characteristics for AIANs and whites with lung cancer are detailed in Table 1. AIANs were more likely than whites to be diagnosed before age 60 (30% vs. 23%, respectively, $p < 0.0001$), and more likely to be diagnosed with localized or regional stage disease (54% vs. 51%, respectively, $p = 0.02$). Among patients with regional stage disease, 42% of AIANs and 52% of whites received surgery ($p < 0.0001$). This disparity extended to patients diagnosed with distant stage disease, with 6% of AIANs and 10% of whites receiving surgery ($p = 0.004$). Finally, the distribution of histology types differed by race ($p < 0.0001$): the most common histology type among AIANs was squamous cell carcinoma, comprising 32% of cases, while adenocarcinoma was the most frequent histology in whites, comprising 39% of cases.

Table 2 displays the association between race and histology group. AIANs were significantly more likely than whites to be diagnosed with ONSCLC (OR = 1.22, 95% CI: 1.01 – 1.48) or squamous cell carcinoma (OR = 1.25, 95% CI: 1.02 – 1.52) versus adenocarcinoma, and the overall association between race and histology was significant ($p = 0.02$). Sex and stage were also significantly associated with histology type among all patients (both $p<0.0001$). Women were more likely to be diagnosed with bronchioloalveolar carcinoma, and less likely to be diagnosed with squamous cell carcinoma than men. Patients diagnosed with distant stage disease were less likely to have bronchioloalveolar, large cell, or squamous cell histologies than patients with localized/regional stage disease.

As shown in Table 3, race was not significantly associated with stage at diagnosis, after adjusting for histology, SEER site, time period, and age at diagnosis. However, histology was significantly associated with stage at diagnosis. Patients with bronchioloalveolar carcinoma had a greatly reduced risk of distant-stage diagnosis compared to patients with adenocarcinoma (OR = 0.25, 95% CI: 0.23 – 0.26), and less substantial reductions in risk were observed for patients with large cell carcinoma (OR = 0.91, 95% CI: 0.87 – 0.94) and squamous cell carcinoma (OR = 0.49, 95% CI: 0.47 – 0.50). Patients with ONSCLC were more likely to be diagnosed at distant stage (OR = 1.28, 95% CI: 1.25 – 1.31) than patients with adenocarcinoma. We repeated these analyses including a race*histology interaction term, which was not statistically significant (data not shown) and was therefore removed from the model.

Table 3 also displays the association between race and histology with receipt of surgery. AIANs were less likely to receive surgery than whites (OR = 0.68, 95% CI: 0.55 – 0.83). Histology type was also associated with surgery; patients with bronchioloalveolar carcinoma were more likely to receive surgery (OR = 3.15, 95% CI: 2.97 – 3.35) and patients with ONSCLC were less likely to receive surgery (OR = 0.30, 95% CI: 0.29 – 0.31) than those with adenocarcinoma. Women were less likely than men to be diagnosed with distant disease (OR = 0.88 (95% CI: 0.86 – 0.90), and more likely to receive surgery (OR = 1.05, 95% CI: 1.03 – 1.07).

Table 4 summarizes results of the survival analysis. Compared to whites, AIANs had an increased risk of death (Hazard Ratio (HR) = 1.09, 95% CI: 1.01 – 1.19). Histology was

significantly associated with risk of death, with the most substantial difference observed in cases with bronchioloalveolar carcinoma, who had a HR of 0.68 (95% CI: 0.66 – 0.70) compared to cases with adenocarcinoma. Statistically significant, but clinically minor survival differences were observed for large cell carcinoma, ONSCLC, and squamous cell carcinoma. We repeated these analyses including a race*histology interaction term, and then a race*time period interaction term. Neither interaction term was statistically significant (data not shown) and were therefore removed from the models. Figure 1 displays Kaplan-Meier survival curves for AIANs and whites, stratified by year of diagnosis category. Although both AIANs and whites diagnosed in later years had longer survival times than patients diagnosed in earlier years, whites consistently have longer survival than AIANs in both year of diagnosis categories, and across all timepoints.

Discussion

The goal of these analyses was to determine whether race is associated with lung cancer histology, and whether race and histology are associated with death among lung cancer patients in a population-based sample. We found that AIAN race was associated with lung cancer histology type and survival, and that survival time differed according to histology type. Further, the association between AIAN race and lung cancer histology, as well as survival disparities between AIANs and whites, appeared to persist even after adjustment for time period, age, treatment, and stage at diagnosis. Our observation that histology was associated with stage at diagnosis is in line with current understanding of lung cancer development and progression. For example, bronchioloalveolar carcinoma was more likely than adenocarcinoma to be diagnosed at an early stage, consistent with the slow growth typical of bronchioloalveolar tumors.(9) Likewise, we noted that squamous cell tumors were most likely diagnosed at an early stage, congruent with the fact that these tumors often arise near the central airway,(10) and thus may be symptomatic earlier than tumors in peripheral airways.

Smoking behavior could explain the higher incidence of squamous cell carcinomas among AIANs compared to whites. The majority of lung cancers diagnosed among non-smokers or infrequent smokers are adenocarcinomas or bronchioloalveolar carcinomas.(11) The prevalence of smoking is in AIANs varies widely by age and tribe,(12) but the Nationwide Tobacco Use Supplement to the Current Population Survey (TUS-CPS) found that a higher proportion of AIANs smoke than whites. The 2003 TUS-CPS data show that among AIANs, 34% of men and 30% of were current smokers, compared to 21% of white men and 18% of white women.(13) Thus, it is not surprising that the incidence of smoking-related lung cancer histology is also higher in AIANs. Our analyses were unable to account for smoking behavior because SEER does not collect smoking data, but future studies should address the role of smoking in the race-histology association.

As illustrated in Figure 1, survival time increased from the earlier to later time periods in both AIAN and whites, although survival among AIANs was still shorter. A case-control study on AIANs diagnosed with cancer in Montana from 1984–1993 found that AIANs were less likely to receive surgery than whites, but that survival among lung cancer cases did not vary by race.(14) In partial contrast, we observed disparities between whites and AIANs from 1973 – 2006 in *both* receipt of surgery *and* risk of death. This survival disparity trend may partially be due to racial disparities in access that changed over time. In the 1970s and 1980s, modern treatments such as advanced radiation techniques, adjuvant chemotherapy, and chemoradiation for regional stage disease and palliative chemotherapy for distant stages did not exist. In recent years, lung cancer survival has increased due to advances in surgical techniques,(15–17) the adoption of adjuvant chemotherapy,(18–21) the increased frequency of chemotherapy treatment in advanced stages,(22) and stage migration due to novel staging

methods.(23) As medical practice advanced, the existing racial gap in access to treatments may have widened and resulted in the survival disparities observed in recent time periods. More research is required to determine whether AIANs have reduced access to emerging lung cancer treatments compared to whites, and whether any access gap is reflected in survival disparities.

We observed significant associations between sex and lung cancer tumor characteristics and survival. Interestingly, female sex and AIAN race appeared to have opposite associations with lung cancer histology and survival. This is consistent with the hypothesis that smoking behavior, and/or smoking-related comorbidities could be associated with histology type and survival, because women tend to smoke less than men, and as noted above, AIANs smoke more than whites.(13)

This study has several important limitations. Although the SEER database provided a large number of population-based AIAN lung cancer patients, SEER does not collect information on smoking behavior, clinical performance status at diagnosis, or treating surgeon experience with regards to lung cancer, all of which are strongly linked to lung cancer survival.(24–27) Survival outcomes also depend on the volume of lung cancer surgeries performed at medical centers and the quality of supportive care for patients recovering from surgery and receiving chemotherapy,(27,28) However, this systems-level information is also not available in SEER. Therefore, while we can document differences in lung cancer histology and survival between AIANs and whites, we cannot determine whether these disparities are caused by race-specific differences in access to quality care, or by race-based differences in the prevalence of comorbid conditions (such as diabetes, smoking behavior, and smoking-related disorders) that may complicate treatment, recovery, and survival.

Although SEER is a good source for cancer data on a large number of AIANs, future studies of the clinical attributes and prognosis of lung cancer in AIANs could supplement SEER data with detailed smoking information, including type of cigarette smoked and pack-years. This enrichment of SEER data could be achieved by administering a survey to rapidly-identified lung cancer cases reported to SEER. These studies could also collect data on comorbidities, in order to control for the effect of overall health on survival outcomes. In addition, SEER does not capture information on tribal membership, which may be associated with health-related behaviors and access to care. Our adjustment for SEER site partially accounts for geographic differences, but is unable to completely account for differences between AIAN tribes. Future studies should include factors related to access to quality care, such as hospital volume and provider experience. These studies could differentiate between biological, access, and behavior-based causes for the observed disparities in survival.

In conclusion, our analyses describe differences in lung cancer histology, treatment, and survival between AIANs and whites. Although both racial groups have experienced improvements in survival over time, survival disparities persist and may be increasing, even after adjusting for stage, histology, and treatment. Future studies should consider patient comorbidities and access to quality care as potential confounders of the association between AIAN race and shortened lung cancer survival.

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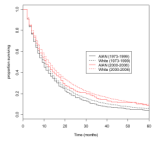

Figure 1.
Kaplan-Meier survival curves comparing all-cause survival between AIANs and whites among lung cancer cases diagnosed from 1973–1999, and from 2000–2006.

Table 1

Demographic characteristics of lung cancer cases by race

	AIAN		white		total		
	N	%	N	%	N	%	
Total	1050	0.53	197896	99.47	198946	100.00	**p-value** *
Age at diagnosis							
<50	89	0.08	12805	0.06	12894	0.06	<0.0001
50–59	229	0.22	33242	0.17	33471	0.17	
60–69	355	0.34	60877	0.31	61232	0.31	
70–79	278	0.26	65238	0.33	65516	0.33	
80+	99	0.09	25734	0.13	25833	0.13	
Mean age (SD)	65.11	(10.94)	67.43	(10.94)			
Year of diagnosis							
1973–1999	449	0.43	82359	0.42	82808	0.42	0.45
2000–2006	601	0.57	115537	0.58	116138	0.58	
Sex							
Male	607	0.58	110293	0.56	110900	0.56	0.18
Female	443	0.42	87603	0.44	88046	0.44	
SEER Historic Stage							
Localized/Regional	571	0.54	101109	0.51	101680	0.51	0.02
Distant	479	0.46	96787	0.49	97266	0.49	
Surgery, localized/regional cases							
None	334	0.58	48425	0.48	48759	0.48	<0.0001
Cancer-directed	237	0.42	52684	0.52	52921	0.52	
Surgery, distant cases							
None	450	0.94	87028	0.90	87478	0.90	0.004
Cancer-directed	29	0.06	9759	0.10	9788	0.10	
Histologic type							
Adenocarcinoma	324	0.31	76223	0.39	76547	0.38	<0.0001
Bronchioloalveolar carcinoma	32	0.03	7482	0.04	7514	0.04	

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	AIAN		white		total		
	N	%	N	%	N	%	
Large cell carcinoma	59	0.06	13205	0.07	13264	0.07	
Other non-small cell	298	0.28	50030	0.25	50328	0.25	
Squamous cell carcinoma	337	0.32	50956	0.26	51293	0.26	

* p-value for Chi-square test

AIAN: American Indians and Alaska Natives; SD: standard deviation

Table 2

Association between race and histology

	Odds Ratios and 95% confidence intervals for Histology type					
	Adenocarcinoma	**Bronchioloalveolar carcinoma**	**Large cell carcinoma**	**Other non-small cell**	**Squamous cell carcinoma**	**p-value**
AIAN vs. white race	1 (reference)	0.64 (0.37 – 1.09)	1.29 (0.94 – 1.79)	1.22 (1.01 – 1.48)	1.25 (1.02 – 1.52)	0.02
Age at diagnosis						
1-year increments	1 (reference)	1.01 (1.01 – 1.01)	0.78 (0.75 – 0.81)	0.83 (0.81 – 0.85)	0.52 (0.51 – 0.54)	<0.0001
Sex						
Female vs. male	1 (reference)	1.46 (1.39 – 1.53)	0.78 (0.75 – 0.81)	0.83 (0.81 – 0.85)	0.52 (0.51 – 0.54)	<0.0001
SEER Historic Stage						
Distant vs. Localized/Regional	1 (reference)	0.25 (0.23 – 0.26)	0.91 (0.87 – 0.94)	1.28 (1.25 – 1.31)	0.49 (0.47 – 0.50)	<0.0001

* adjusted for SEER site, and year of diagnosis

AIAN: American Indians and Alaska Natives

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Table 3

Association between race, histology, and stage at diagnosis; and association with surgery

	Odds Ratio* (95% CI)	Odds Ratio† (95% CI)
	distant vs. localized/regional	**surgery vs. no surgery**
Race		
AIAN vs. white	0.92 (0.79 – 1.07)	0.68 (0.55 – 0.83)
Sex		
Female vs. male	0.88 (0.86 – 0.90)	1.05 (1.03 – 1.07)
Histology		
Adenocarcinoma	1 (reference)	1 (reference)
Bronchioloalveolar carcinoma	0.25 (0.23 – 0.26)	3.15 (2.97 – 3.35)
Large cell carcinoma	0.91 (0.87 – 0.94)	0.57 (0.54 – 0.59)
Other non-small cell	1.28 (1.25 – 1.31)	0.30 (0.29 – 0.31)
Squamous cell carcinoma	0.49 (0.47 – 0.50)	0.63 (0.61 – 0.65)

* adjusted for year of diagnosis, SEER site, and age at diagnosis

† adjusted for year of diagnosis, SEER site, age at diagnosis, and SEER historic stage

AIAN: American Indians and Alaska Natives, CI: confidence interval

Table 4

Survival analysis of race, histology and risk of death; stratified by and adjusted for year of diagnosis

Race	**Hazard Ratio* (95% CI)**
AIAN vs. white	1.09 (1.01 – 1.19)
Sex	
Female vs. male	0.85 (0.85 – 0.86)
Histology	
Adenocarcinoma	1 (reference)
Bronchioloalveolar carcinoma	0.68 (0.66 – 0.70)
Large cell carcinoma	1.15 (1.12 – 1.17)
Other non-small cell	1.10 (1.09 – 1.12)
Squamous cell carcinoma	1.05 (1.03 – 1.06)

*adjusted for SEER site, year of diagnosis, SEER historic stage, andsurgery

AIAN: American Indians and Alaska Natives, CI: confidence interval