Racial Disparities in Lung Cancer Risk and Outcomes

Ann G. Schwartz, PhD, MPH
January 18, 2023
A Short and Winding Road

**Education**

BS, Zoology, University of Michigan

MS, Biophysics, WSU

MPH, Environmental Health, University of Michigan

PhD, Epidemiology, University of Michigan (while working at the Michigan Cancer Foundation)
A Longer Road Back to the Beginning

Academic Appointments
Michigan Cancer Foundation
University of Pittsburgh
Allegheny Health Sciences
WSU/Karmanos Cancer Institute
Deputy Center Director
Assoc. Chair, Oncology
Professor
Cancer Continuum

Prevention & Risk Reduction
- Tobacco Use
- Diet
- Physical Activity
- Environmental Exposures
- Alcohol Use
- Immunization

Risk Profiles/Screening
- Risk/Screening
  - Age
  - Race
  - Gender
  - Smoking
  - Family Hx
  - COPD
  - Genetic Testing

Diagnosis
- Biopsy
- Pathology
- Staging
- Biomarkers
- Molecular Profiling

Treatment
- Systemic Therapy
- Radiation
- Surgery
- Personalized Treatments

Survivorship
- CIPN
- COVID-19
- Surveillance
- Screening for second primary cancers
- Tobacco Use
- Physical Activity
- Mental Health

End of Life
- Advanced care
- Hospice care
- Bereavement care

Crosscutting Areas
- Care Planning
- Psychosocial Support
- Palliative Care
- Family and Caregiver Support
- Prevention and Management of Long Term and Late Effects

Health Communication, Epidemiology, HEALTH DISPARITIES, Surveillance, Implementation Science, Healthcare Delivery
Lung Cancer in the US

Lung Cancer Statistics

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of new cases annually</td>
<td>228,000</td>
</tr>
<tr>
<td>Estimated deaths annually</td>
<td>136,000</td>
</tr>
<tr>
<td>% surviving 5 years</td>
<td>19%</td>
</tr>
<tr>
<td>% of lung cancer cases who are ever smokers</td>
<td>~80%</td>
</tr>
</tbody>
</table>

Stage at Diagnosis

- Local: 57
- Regional: 16
- Distant: 5
- Unstaged: 5

5-Yr Survival %

- Local: ~60%
- Regional: ~40%
- Distant: ~10%
- Unstaged: ~0%
African Americans, as compared to whites, tend to have:

- Fewer pack-years of cigarette exposure
- Higher risk associated with family history \((Cote \ et \ al, \ JAMA \ 2005)\)
- Lower risk associated with COPD
Self-reported history of COPD as a risk factor for lung cancer

<table>
<thead>
<tr>
<th></th>
<th>White OR* (95% CI)</th>
<th>African American OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>1.9 (1.2-2.8)</td>
<td>1.1 (0.5-2.5)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>3.8 (1.7-8.3)</td>
<td>1.9 (0.4-8.2)</td>
</tr>
<tr>
<td>Chronic Bronchitis</td>
<td>1.8 (1.1-2.9)</td>
<td>1.4 (0.6-3.4)</td>
</tr>
</tbody>
</table>

* Adjusted for pack-years, age, race, sex, family history of lung cancer, education, BMI and regular aspirin use

Schwartz et al, J Thoracic Oncol, 2009

78% of African Americans with lung cancer self-reported NO history of COPD, but had spirometry or CT evidence of COPD suggesting severe under-reporting or under-diagnosing of COPD in African Americans.

Mina et al, Clin Lung Cancer, 2012
Pathogenesis in lung cancer and COPD

Adcock et al, Respiration, 2011
Define the role of specific COPD phenotypes and inflammatory/immune pathway genes in the development of lung cancer by race.

- 1,560 Hospital-based lung cancer cases: 30% African American, 9.5% never smokers
- 1,760 Volunteer controls without lung cancer: 41% African American, 13% never smokers

- **Interview** to collect smoking history, family cancer history and other risk factor data
- **Blood draw/saliva** collection for germline DNA
- **Spirometry** to measure lung function, COPD diagnosis
- **Low Dose Chest CT** for quantitative imaging studies
- **Tumor and adjacent normal tissue** collection to measure tumor characteristics and gene expression

Schwartz, R01CA141769
Quantitative Imaging Markers of Lung Function on Risk of Lung Cancer

- Quantitative image analysis measured:
  - % emphysema as % total lung voxels < -950 HU in inspiration across both lungs
  - % air trapping quantified as % voxels < -856 HU on expiratory scans
- Spirometry measured FEV$_1$/FVC
- Models adjusted for age, race, gender, pack years, scanner and total lung volume (inspiratory and expiratory)

<table>
<thead>
<tr>
<th>Measure</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% gas trapping</td>
<td>1.04 (1.03, 1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spirometry (FEV$_1$/FVC &lt; 0.70)</td>
<td>1.64 (1.13, 2.37)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Schwartz et al., CEBP 2016
Lusk et al, CEBP, 2019
### Defining a “Lung Health” Profile

Hierarchical clustering of INHALE current/former smoking controls with qCT and spirometry (N=1179)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>64</td>
<td>232</td>
<td>73</td>
<td>609</td>
<td>201</td>
</tr>
<tr>
<td>Pack years</td>
<td>47.5 (24.1)</td>
<td>38.4 (31.4)</td>
<td>26.0 (18.7)</td>
<td>34.2 (20.9)</td>
<td>22.5 (19.6)</td>
</tr>
<tr>
<td>Quit years</td>
<td>2.6 (4.9)</td>
<td>1.1 (3.1)</td>
<td>6.2 (10.1)</td>
<td>1.8 (3.6)</td>
<td>25.9 (9.9)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>0.53 (0.11)</td>
<td>0.69 (0.10)</td>
<td>0.47 (0.11)</td>
<td>0.77 (0.07)</td>
<td>0.77 (0.07)</td>
</tr>
<tr>
<td>% predicted FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>53.9 (18.6)</td>
<td>67.0 (16.6)</td>
<td>49.1 (16.2)</td>
<td>83.5 (16.9)</td>
<td>86.5 (17.6)</td>
</tr>
<tr>
<td>qCT % emphysema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16.3 (7.3)</td>
<td>2.6 (2.4)</td>
<td>1.5 (1.6)</td>
<td>1.2 (1.4)</td>
<td>2.4 (2.5)</td>
</tr>
<tr>
<td>qCT % air trapping&lt;sup&gt;b&lt;/sup&gt;</td>
<td>51.3 (13.6)</td>
<td>30.6 (16.9)</td>
<td>11.2 (9.6)</td>
<td>7.1 (6.7)</td>
<td>14.9 (13.5)</td>
</tr>
<tr>
<td>qCT MLD ratio&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.94 (0.04)</td>
<td>0.95 (0.05)</td>
<td>0.86 (0.06)</td>
<td>0.84 (0.05)</td>
<td>0.86 (0.06)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percent lung voxels < -950 HU on inspiration across both lungs.
<sup>b</sup>Percent lung voxels < -856 HU on expiration across both lungs.
<sup>c</sup>Mean lung density (MLD) ratio = expiratory MLD / inspiratory MLD

*Lusk et al., CEBP, 2019*
**Lung Health**

**Figure 1.** Mean trends are shown for variables used in clustering. Arrows indicate standardized group means for particular variables, relative to the overall mean ($\mu = 1$), as follows: $\uparrow/\downarrow = 0.2$-1 SD above/below overall mean, $\uparrow\uparrow/\downarrow\downarrow = 1$-1.9 SDs above/below overall mean, $\uparrow\uparrow\uparrow/\downarrow\downarrow\downarrow > 2$ SDs above/below overall mean, $-- = $ within 0.1 SDs above/below mean. Red indicates negative mean trend; blue indicates beneficial mean trend.

<table>
<thead>
<tr>
<th>Clustering Variables</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack years</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
<td>$--$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Quit years</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$--$</td>
<td>$\downarrow$</td>
<td>$\uparrow\uparrow$</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>$\downarrow\downarrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow\downarrow$</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>% predicted FEV1</td>
<td>$\downarrow\downarrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow\downarrow$</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td><strong>qCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% emphysema</td>
<td>$\uparrow\uparrow\uparrow$</td>
<td>$--$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$--$</td>
</tr>
<tr>
<td>% air trapping</td>
<td>$\uparrow\uparrow\uparrow$</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>$--$</td>
</tr>
<tr>
<td>MLD ratio</td>
<td>$\uparrow$</td>
<td>$\uparrow\uparrow$</td>
<td>$--$</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
</tr>
</tbody>
</table>
Lung health clusters and lung cancer risk

- ORs comparing odds of lung cancer in each cluster to odds of lung cancer in cluster 5, adjusted for age, race, sex, and BMI
- Odds of lung cancer are significantly (p<0.05) elevated in each cluster except in cluster 4 in total sample and for Whites, but only cluster 2 is significantly associated with the odds of lung cancer in African Americans
African Americans were significantly more likely to fall into a risk “cluster” characterized by younger age, lower smoking exposure, poorer FEV$_1$/FVC, but lower quantitative CT measures of emphysema and air trapping.

Measures of lung function, and subsequent lung cancer risk, vary considerably among smokers and are not fully explained by smoking intensity.

Combining spirometry and radiologic measures of COPD aid in defining a spectrum of lung disease that predicts lung cancer risk differentially among patient clusters.
Lung cancer screening
National Lung Cancer Screening Trial (NLST)

• Prospective randomized trial comparing low dose helical computed tomography (CT) to chest radiograph (X-ray), annual scan, 3 years

• Eligibility: ages 55-74, current or former smoker (quit within 15 years), ≥30 pack years of smoking, 41% female

• Results: a relative reduction in the rate of death from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004)

<table>
<thead>
<tr>
<th>NLST/NCCN group 1</th>
<th>USPSTF 2013</th>
<th>NCCN group 2</th>
<th>USPSTF 2021</th>
<th>PLCOm2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 55 - 74 years</td>
<td>Age 55 - 80 years</td>
<td>Age ≥ 50 years</td>
<td>Age ≥ 50 years</td>
<td>Age ≥ 50 years</td>
</tr>
<tr>
<td>≥ 30 pack-year smoking history</td>
<td>≥ 30 pack-year smoking history</td>
<td>≥ 20 pack-year smoking history</td>
<td>≥ 20 pack-year smoking history</td>
<td></td>
</tr>
<tr>
<td>Smoking cessation &lt; 15 years.</td>
<td>Smoking cessation &lt; 15 years.</td>
<td>1 additional risk factor (other than secondhand smoke).</td>
<td>Smoking cessation &lt; 15 years.</td>
<td></td>
</tr>
<tr>
<td><strong>Risk ≥ 1.51% is used as cut off for screening eligibility</strong></td>
<td></td>
<td>--cancer history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Age**
- **Race**
- **Education**
- **BMI**
- **COPD**
- **Personal history of cancer**
- **Family history of lung cancer**
- **Radon exposure**
- **Occupational exposure to silica, cadmium, asbestos, arsenic, beryllium, chromium (VI), diesel fumes, and nickel.**
- **Chronic obstructive pulmonary disease (COPD)**
- **Pulmonary fibrosis**
- **Smoking status**
- **Smoking intensity**
- **Duration of smoking**
- **Smoking quit time**
Sensitivity of lung cancer screening eligibility criteria in INHALE

Pu et al., JAMA Oncol, 2022
## Sensitivity of screening eligibility in INHALE lung cancer cases

<table>
<thead>
<tr>
<th>Screening Eligibility Guidelines</th>
<th>White $n=625$</th>
<th>African American $n=287$</th>
<th>White vs African American</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>NLST</td>
<td>47.7%</td>
<td>39.7%</td>
<td>1.2 (1.0,1.4)</td>
</tr>
<tr>
<td>USPSTF 2013</td>
<td>51.8%</td>
<td>42.2%</td>
<td>1.2 (1.1,1.4)</td>
</tr>
<tr>
<td>NCCN group 2</td>
<td>66.7%</td>
<td>50.9%</td>
<td>1.3 (1.2,1.4)</td>
</tr>
<tr>
<td>USPSTF 2021</td>
<td>65.3%</td>
<td>63.4%</td>
<td>1.0 (0.9,1.1)</td>
</tr>
<tr>
<td>PLCOm2012 ≥ 1.51%</td>
<td>68.4%</td>
<td>66.9%</td>
<td>1.0 (0.9,1.1)</td>
</tr>
</tbody>
</table>
• African American lung cancer patients are significantly under-represented under USPSTF 2013 and NCCN grp 2 criteria

• USPSTF 2021 and PLCOm2012 guidelines improve on earlier, fixed screening criteria for lung cancer, broadening eligibility and reducing the racial disparity in access to screening

• There are still barriers to screening uptake, with heightened need to increase awareness among primary care physicians and the community
Is overall survival related to differential gene expression of immune pathways genes? Are there differences by race?

48 Immune-centric Pathways including 8 Major Pathways:
- Adaptive Immunity
- Innate Immunity
- Cytokine Signaling
- Adhesion-Extravasation-Migration
- Programmed Cell Death
- Reactive Oxygen/Nitrogen Generation
- Immune Signaling

~2,253 immune related genes

Affymetrix Whole-Transcriptome 2.1 Human Gene Array with 1.3 million probes on 280 lung cancer cases

Gene Expression in Lung Tumors Associated with Survival

- Gene Set Enrichment Analysis (GSEA) used to measure aggregate gene effects within each immune pathway
- Cox proportional hazards model, adjusted for stage and histology
- Interleukin Signaling pathway genes were significantly associated with survival

Watza et al., Carcinogenesis, 2018
23 Gene Signature and Survival

- “Interleukin signaling” pathway shows prognostic value
- Leading edge 23-gene signature is a predictor of survival
The most differentially-expressed (by race) immune-related genes make antibodies suggesting that B cell function might be distinct by race.
Tertiary Lymphoid Structures

Are TLS related to response to immunotherapy differentially by race?

What other biomarkers are related to immunotherapy differentially by race?

Figure 6. Putative TLS structure (red circle) identified in a CD8-stained (brown) lung cancer tissue section. Hematoxylin (blue) counterstain identifies rich aggregation of CD8+ and CD8- leukocytes.
Immunotherapy in the form of immune checkpoint inhibitors (ICIs) has been a breakthrough for the treatment of lung cancer.

ICI’s, either as single agents or in combination with platinum-based chemotherapy, are now front line therapy for metastatic non-small cell lung cancer (NSCLC).

Treatment response varies from 25% to 60%.

Immunotherapeutic benefit is dictated in part by imperfect biomarkers including PD-L1 expression and tumor mutational burden (TMB).

Little data exist on racial disparities in biomarkers and response to ICIs; only 4% of clinical trials participants were African American.
Immune Phenotypes and Outcomes

- Gene expression clustering
- Tumor mutation burden
- PD-L1, CTLA4, TILs, TLS
- Host genetics

Mediators of immune phenotypes

- Ancestry
- Age, sex, pack-years

Immune phenotypes as predictors of survival and response to immunotherapy

P20 SPORE Planning Grant in Health Disparities
While INHALE participants were treated pre-immunotherapy, we evaluated the tumor microenvironment for biomarkers of ICI response:

- Tumor mutation burden
- PD-L1, CTLA4, immune pathway gene expression
- Immune cell infiltration
- Tertiary lymphoid structures (TLS)
Summary of immune pathway markers

- Immune signatures in lung cancer differ by race
  - IFN-related signaling
  - B cell function

- Comprehensive analyses needed to tease out race-specific biomarkers in relation to ICI response

- Immune functional analyses may shed light on pathways regulating ICI response
  - Potential biomarkers
  - Potential new drug targets
The Detroit Research on Cancer Survivors (ROCS) Study

- The largest prospective cohort of African American cancer survivors: breast, prostate, lung, colorectal, and endometrial cancer dxed age 20-79, and any cancer dxed age 20-49; metro Detroit residents at diagnosis

- 5,073 Survivors and 1074 Caregivers enrolled

- Overarching goal to understand the multiplex causes of poorer outcomes in this high-risk population

U01 CA199240
Mean FACT-G scores in cancer patients has been reported to be 82.2 in a population that is 80% white.

We see lower scores at baseline, i.e., poorer overall health scores in African Americans with lung cancer.
The Detroit Research on Cancer Survivors (ROCS) Cohort

COVID-19 Supplement
U01CA199240-S3

Beebe-Dimmer et al, Cancer 2022

The IMPACT of the COVID-19 Pandemic on AA Cancer Survivors

Sleep Supplement
U01CA199240-S4

CIDR funding
X01 HG12908

Germline Whole Exome Sequencing of ~2,400 African American Cancer Survivors

- Use bioinformatics, family structure, gene expression and somatic alterations to characterize VUS.
- Characterize germline genetic variants associated with multiple primary cancers.
- Develop an online educational intervention to increase risk-appropriate genetic testing in African Americans.

Sleep Health & HRQoL

<table>
<thead>
<tr>
<th>Health Behaviors</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Behaviors</td>
<td>0.064</td>
</tr>
<tr>
<td>Cancer Related</td>
<td>0.127</td>
</tr>
<tr>
<td>Demographics</td>
<td>0.174</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>0.230</td>
</tr>
<tr>
<td>Sleep Health</td>
<td>0.295</td>
</tr>
</tbody>
</table>

Health Behaviors: exercise, fruit/vegetables, alcohol, smoking
Cancer Related: age at diagnosis, months since diagnosis, cancer site, stage, treatment, treatment status
Demographics: sex, education, marital status, income, poverty, insurance
Comorbidities: arthritis, COPD/emphysema, depression, diabetes, heart condition, hepatitis, high cholesterol, hypertension, stroke, thyroid, obesity
Sleep Health: IIS, ESS, PSQI
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Dave Pandolfi  Michele Cote, PhD

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