Lung Cancer Priorities

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Disclosures

• I consult and serve as education faculty:
  – Olympus
  – Biodesix
  – Cook
  – Boston Scientific
  – Intuitive
Overview

- Lung Cancer History and Statistics
- Risk Factors
- Lung Cancer Screening
- Diagnosis and Biomarker Testing
Once a rare disease...“Mountain Sickness”
The 20th Century

PRIMARY MALIGNANT GROWTHS OF THE LUNGS AND BRONCHI
A PATHOLOGICAL AND CLINICAL STUDY

BY
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'Oportet omnia sigma contemplari'

LONGMANS, GREEN, AND CO.
FOURTH AVENUE & 30TH STREET, NEW YORK
LONDON, BOMBAY, AND CALCUTTA
1912

CHAPTER I
INTRODUCTORY

Is it worth while to write a monograph on the subject of primary malignant tumors of the lung? In the course of the last two centuries an ever-increasing literature has accumulated around this subject. But this literature is without
Our Why

Every 2.2 minutes someone is diagnosed with lung cancer

2,100,000 new diagnoses globally annually

Annual Global Cancer Mortality

- Lung: 2,100,000
- Prostate: 307,000
- Esophageal: 400,000
- Breast: 522,000
- Colorectal: 694,000
- Stomach: 723,000
- Liver: 746,000
Non-Small Cell Lung Cancer (NSCLC) Background

From 2011 to 2020, overall lung cancer mortality rates declined by ~4% per year.

2023 estimates of lung cancer incidence, mortality:

5-year relative survival rate (NSCLC)

8% 5-year survival rate for distant disease (NSCLC)

From 2011 to 2020, overall lung cancer mortality rates declined by ~4% per year


Siegel, CA A Cancer J Clinicians, 2023:73:17-48
A Few Surprising Facts

~65% of all new lung cancer diagnoses are among people who have never smoked or are former smokers.

~10–20% of new lung cancer cases are among never-smokers.

~ 25% women diagnosed are never smokers

1 in 16 women (both who did and did not smoke) will be diagnosed with lung cancer in their lifetimes.

2X more black than white men will be diagnosed with lung cancer if all risk factors are equal.
Radon

- Decay product of uranium-238 and radium-226
  - Widely distributed in rock, soil, groundwater
  - Associated with an increased risk of lung cancer
  - Interactive effect with cigarette smoking
- 2nd most important cause of lung cancer in the USA
  - Implicated in 26% of lung cancer in never-smokers
  - Implicated in 13.4% of lung cancers overall (co-carcinogenic with cigarette exposure)

EPA Assessment of Risks from Radon in Homes. Office of Radiation and Indoor Air United States Environmental Protection Agency. Washington, DC 204602003
Prevention

State Rankings by Percent of Tests At or Above EPA Action Level

- In Delaware, **15.4%** of radon tests results were at or above the action level recommended by EPA.
- It ranks **17th** among all states, placing it in the **above average tier**.
Lung Screening

• Cancer screening is a test to check for disease in someone who does not have any symptoms

• Goal of screening is to find cancer early when it is more treatable and even curable
Lung Screening

• Not a new concept

Journal of Occ Med and Tox 2014.9:14
Lung Screening

- National Lung Screening Trial (NLST)
  - 53,454 persons at high risk for lung cancer
  - 33 U.S. medical centers
  - August 2002 – April 2004
- > 25% of the low dose CT group had a positive finding
  - 96.4% false positive
  - 20% relative risk reduction in mortality from lung cancer
  - 6.9% all-cause mortality reduction
  - Number needed to screen 320

### Table 3. Lung-Cancer Stage and Histologic Type of All First-Detected Lung Cancers in Male Participants at 10 Years of Follow-up or on December 31, 2015.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screening-Detected Lung Cancer (N=203)</th>
<th>Non-Screening-Detected Lung Cancer (N=141)</th>
<th>Any Lung Cancer (N=344)</th>
<th>Any Lung Cancer (N=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of participants (percent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>95 (46.8)</td>
<td>10 (7.1)</td>
<td>105 (30.5)</td>
<td>21 (6.9)</td>
</tr>
<tr>
<td>IB</td>
<td>24 (11.8)</td>
<td>10 (7.1)</td>
<td>34 (9.9)</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>IIA</td>
<td>8 (3.9)</td>
<td>4 (2.8)</td>
<td>12 (3.5)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>IIB</td>
<td>11 (5.4)</td>
<td>6 (4.3)</td>
<td>17 (4.9)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>IIIA</td>
<td>20 (9.9)</td>
<td>14 (9.9)</td>
<td>34 (9.9)</td>
<td>43 (14.1)</td>
</tr>
<tr>
<td>IIIB</td>
<td>13 (6.4)</td>
<td>14 (9.9)</td>
<td>27 (7.8)</td>
<td>34 (11.2)</td>
</tr>
<tr>
<td>IV</td>
<td>19 (9.4)</td>
<td>73 (51.8)</td>
<td>92 (26.7)</td>
<td>139 (45.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (6.4)</td>
<td>10 (7.1)</td>
<td>23 (6.7)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td><strong>Histologic type‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>123 (60.6)</td>
<td>56 (39.7)</td>
<td>179 (52.0)</td>
<td>133 (43.8)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>39 (19.2)</td>
<td>38 (27.0)</td>
<td>77 (22.4)</td>
<td>94 (30.9)</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>13 (6.4)</td>
<td>27 (19.1)</td>
<td>40 (11.6)</td>
<td>46 (15.1)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>8 (3.9)</td>
<td>8 (5.7)</td>
<td>16 (4.7)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (9.9)</td>
<td>12 (8.5)</td>
<td>32 (9.3)</td>
<td>18 (5.9)</td>
</tr>
</tbody>
</table>
Number Needed to Screen (NNS) to Prevent 1 Death and Compliance with Screening

<table>
<thead>
<tr>
<th>Compliance (%)</th>
<th>Colon cancer</th>
<th>Cervical cancer</th>
<th>Breast cancer</th>
<th>Lung cancer (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance (%)</td>
<td>68.8%</td>
<td>80.0%</td>
<td>70.0%</td>
<td>5.9%</td>
</tr>
<tr>
<td>NNS</td>
<td>1,250</td>
<td>1,140</td>
<td>781</td>
<td>320</td>
</tr>
</tbody>
</table>

- ASCO daily news ([Lung Cancer Screening Remains Poor, Here’s How to Increase Rates and Save Lives](ascopubs.org)
Following NLST

- In 2012 and 2013 our guidelines recommended lung cancer screening
  - 55-74 years old
  - 30 pack year smoking history
  - Currently smoking or if they have quit smoking, it has been within 15 years

- 8 million people in the US qualify for Lung Cancer Screening
Updated Screening Criteria 2021

- Age 50-80 years
- 20 pack year smoking history
- Currently smoking or having quit within the last 15 years

15 million eligible compared to the 8 million previously

Women are under-represented
- 41% NLST and 16% NELSON

Results suggest LDCT screening for lung cancer in women → larger reduction in lung cancer mortality

**BMJ** 2017;356:j347
**NEJM** 2011 Aug; 365(5): 395-409
How many more people will be eligible for lung cancer screening with the new ACS guideline?

• Presently about **14.3 million** people are eligible for screening under the 2021 USPSTF recommendation (**32%** of those who ever smoked)

• The 2023 ACS guideline increases the number to **19.2 million** (**43%** of those who ever smoked)
Lung cancer diagnosis and mortality beyond 15 years since quit in individuals with a 20+ pack-year history: A systematic review

Karli K. Kondo PhD\textsuperscript{1,2} | Basmah Rahman MPH\textsuperscript{1} | Chelsea K. Ayers MPH\textsuperscript{3} | Rose Relevo MLIS, MSMI\textsuperscript{1} | Jessica C. Griffin MS\textsuperscript{1} | Michael T. Halpern MD, PhD, MPH\textsuperscript{4}

- Rates of lung cancer diagnosis (incidence) and mortality remain elevated in people who formerly smoked at ALL TIME POINTS compared to those who never smoked
- Will need to examine impact of smoking of different duration and different intensities

CA Cancer J Clin 2024 Jan-Feb;74(1):84-114.
Observational Studies are Identifying a Substantial Number of Lung Cancer Cases Who Do Not Meet Screening Eligibility Because of YSQ

Lifetime Smoking History and Risk of Lung Cancer: Results From the Framingham Heart Study
Hilary A. Tindle, Meredith Stevenson Duncan, Robert A. Greevy, Ramachandran S. Vasan, Suman Kundu, Pierre P. Massion, Matthew S. Freiberg

• “Notably, only about half of lung cancer cases among former and current smoking persons did not meet the current screening eligibility criteria at the time of diagnosis, including 41% who formerly smoked but had more than 15 YSQ.

Conclusion
Persons who formerly smoked retain significant life-long risk of lung cancer. The logic for including YSQ smoking as a criterion for lung cancer screening eligibility must be reexamined.

Tindle, et al. JNCI 2018; DOI: 10.1093/jnci/djy041
People who formerly smoked, lung cancer risk remains elevated even after they quit
Who Supports Lung Cancer Screening?

- US Preventive Services Task Force (2021)
- National Comprehensive Cancer Network (2022)
- American Academy of Family Physicians (2021)
- Centers for Medicare/Medicaid (2022)
- American Cancer Society (2023)
- American Society of Clinical Oncology (2019)
- American College of Chest Physicians (2018)
- American Association of Thoracic Surgery
- Canadian Task for on Periodic Heath Examination (2016)
What Does Lung Screening Entail?
Key Lung Screening Program Elements

- Physician champions
- Multidisciplinary steering committee
- Access/volume assessment
- Primary care/physician/public education and outreach
- Database
- Standardized reporting system
- Program navigator
Shared Decision Making

Harms of the screening test
Risks of invasive procedures for benign disease
Overtreatment for indolent disease

VS.

Benefits of early detection


Example lung cancer risk calculator

Given your age and smoking history, you are **eligible** for screening according to the US Preventive Services Task Force criteria.

The chance of you developing lung cancer in the next 6 years is 8.4%. Talk to your doctor about the option to screen or not to screen as s/he will understand your situation best.

How Well Do We Do with Cancer Screening?

• 2021 National Health Interview Survey screening for eligible patients:
  – Breast: 75.7%
  – Cervical: 75.2%
  – Colorectal: 72.2%

• American Lung Association 2022 report:
  – Lung cancer: 5.8% of eligible patients are screened

Sabatino, et al. Prev Chronic Dis 2023
Screening

**State Ranking by High-Risk Screening Rate**

- **Top Tier**
- **Above Average Tier**
- **Average Tier**
- **Below Average Tier**
- **Bottom Tier**

**Screening for High Risk:**
- In Delaware, 6.3% of those at high risk were screened, which was **significantly higher** than the national rate of 4.5%.
- It ranks **18th** among all states, placing it in the **above average tier**.
- Actual screening rates may be higher in states with large, regional managed care providers that did not share screening data.
Coverage of Lung Cancer Screening in State Medicaid Fee-for-Service Programs

Medicaid Coverage:

- Delaware was one of the 49 states whose Medicaid fee-for-service programs covered lung cancer screening as of October 2023.

- In addition, their program used recommended guidelines for determining eligibility and did not require prior authorization or copays.
Stage and 5 Year Survival Rate

National Stage at Diagnosis and 5-Year Survival Rate

Stage at Diagnosis
- Early (Localized - confined to primary site): 27%
- Regional (spread to regional lymph nodes): 22%
- Distant (cancer has metastasized): 44%
- Unstaged tumors: 8%

5-Year Survival
- Early (Localized - confined to primary site): 63%
- Regional (spread to regional lymph nodes): 35%
- Distant (cancer has metastasized): 8%
- Unstaged tumors: 15%

Early Diagnosis:
- 28.4% of cases are caught at an early stage, which is significantly higher than the national rate of 26.6%.
- It ranks 10th among the 47 states with data on diagnosis at an early stage, placing it in the above average tier.
- Over the last five years, the early diagnosis rate in Delaware did not change significantly.
Lung Cancer Survival

5-Year Survival Rate:

- The percent of people alive five years after being diagnosed with lung cancer (the survival rate) in Delaware is 28.3%, which is not significantly different than the national rate of 26.6%.
- It ranks 12th among the 42 states with survival data, placing it in the average tier.
- Over the last five years, the survival rate in Delaware improved by 31%.
Challenges to Screening in Early-Stage Lung Cancer

Screening Barriers

**Barriers for Providers**
- Interpretation of guidelines
- Lack of notification from EMR (electronic medical records)
- Concern for false positives
- Time constraints
- Lack of knowledge about insurance coverage

**Barriers for Patients**
- Racial disparities in healthcare
- Distance from screening center
- Lack of knowledge about screening guidelines
- Insurance challenges
- Lack of insurance coverage

**Screening and Treatment Concerns**
- Radiation exposure concerns
- Cost concerns
- Overtreatment concerns

**Healthcare Disruptions**
- COVID-19 pandemic

**Screening Limitations**
- Lack of screening for never smokers

Research Letter | Surgery

Eligibility for Lung Cancer Screening Among Women Receiving Screening for Breast Cancer

Ashley L. Titan, MD; Ioana Baiu, MD, MPH; Doug Liou, MD; Natalie S. Lui, MD; Mark Berry, MD; Joseph Shrager, MD; Leah Backhus, MD, MPH

### Table 2. Clinicians Ordering Lung Cancer Screening for Eligible Participants

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Clinicians, No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ordered mammogram</td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>30 (85.7)</td>
<td></td>
</tr>
<tr>
<td>Pulmonology</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>3 (8.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other*</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ordered LCS</td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>21 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Pulmonology</td>
<td>10 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>4 (11.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Other specialty not specified in the table.
Lung Cancer Screening is Different Due to Stigma Associated with Smoking

- Many of those eligible don’t get screened
- Healthcare professionals and patients unaware of option for LCS
- Former smokers especially unaware of their risk
- Time constraints
- Low use shared decision making in clinical practice
- Stigma associated with smoking
- Reimbursement
- Who orders the screening test?
- Misinformation
- Terminology
Physician Recommendation Primary Reason for Getting Screened

**Baseline: Lung Screening and Lung Cancer Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual Care (N=46)</th>
<th>Telephone Counseling (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Screening history (% yes)</td>
<td>47.8%</td>
<td>39.1%</td>
</tr>
<tr>
<td>Primary reasons for screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor recommendation</td>
<td>82.6%</td>
<td>82.2%</td>
</tr>
<tr>
<td>Peace of mind about lung cancer</td>
<td>80.4%</td>
<td>84.4%</td>
</tr>
<tr>
<td>Personal History of Cancer (e.g., skin, prostate, breast)</td>
<td>26.7%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Family History of Lung Cancer</td>
<td>34.8%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Perceived worry about developing LC (% very much/extremely)</td>
<td>45.6%</td>
<td>44.5%</td>
</tr>
<tr>
<td>Perceived risk about developing LC (% higher/much higher risk than others)</td>
<td>50%</td>
<td>48.9%</td>
</tr>
</tbody>
</table>

No significant group differences

**Journal Article**

A qualitative study exploring patient motivations for screening for lung cancer

Joshua A Roth, Lisa Carter-Harris, Susan Brandzel, Diana S M Bulist, Karen J Wernli

*PloS One 2018, 13 (7): e0198758*

**BACKGROUND:** Low-dose computed tomography (LDCT) of the chest for lung cancer screening of heavy smokers was given a ‘B’ rating by the U.S. Preventive Services Task Force (USPSTF) in 2013, and gained widespread insurance coverage in the U.S. in 2015. Lung cancer screening has since had low uptake. However, for those that do choose to screen, little is known about patient motivations for completing screening in real-world practice.

**OBJECTIVE:** To explore the motivations for screening-eligible patients to screen for lung cancer.

**METHODS:** Semi-structured qualitative interviews were conducted with 20 LDCT screen-completed men and women who were members of an integrated mixed-model healthcare system in Washington State. From June to September 2015, participants were recruited and individual interviews performed about motivations to screen for lung cancer. Audio-recorded interviews were transcribed and analyzed using inductive content analysis by three investigators.

**RESULTS:** Four primary themes emerged as motivations for completing LDCT lung cancer screening: 1) trust in the referring clinician; 2) early-detection benefit; 3) low or limited harm perception; and 4) friends or family with advanced cancer.

**CONCLUSION:** Participants in our study were primarily motivated to screen for lung cancer based on perceived benefit of early-detection, absence of safety concerns, and personal relationships. Our findings provide new insights about patient motivations to screen, and can potentially be used to improve lung cancer screening uptake and shared decision-making processes.
Screening for Non-Smokers

- Taiwan Lung Cancer Screening for Never-Smoker Trial (TALENT)
  - Positive family history of lung cancer is a significant contributor to lung cancer risk in never-smokers
  - In Taiwan, 53% of lung cancer deaths occur in never-smokers
  - 12,011 never-smoking individuals aged 55 to 75 years with a high-risk feature (family history of lung cancer, history of chronic lung disease, cooking without ventilation, and cooking with high intensity of frying)
  - 73.8% of the study population were women
- Prevalence of lung cancer (6 year follow-up): 2.6%
- Patients with family history of lung cancer: 3.2%

Yang, P. JTO March 2021; 16 (3): S58
Volume Measurements

3/05

4.3 mm

787 mm³

4.3 mm

9/05

4.5 mm

1.334 mm³

4.5 mm
AI might change everything
Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography

- Benign appearing (Lung-RADS 1 or 2) nodules that were given high AI risk scores and ultimately found to be cancer

There are several known driver oncogenes and mutations in cancer, including:

- **EGFR mutations**
- **ALK rearrangements**
- **ROS1 rearrangements**
- **BRAF V600E mutation**
- **NTRK rearrangements**
- **MET exon 14 skipping**
- **RET rearrangements**
- **KRAS G12C mutation**
- **HER2 (ERBB2) mutations**
- **MET amplification**
- Other possible targetable driver oncogenes

These mutations and oncogenes can be targeted by various therapeutic approaches:

- **FDA-Approved Therapeutics**
- **Emerging Therapeutics**
- **Evolving Therapeutics**
Biomarkers Are Common in NSCLC

**Metastatic NSCLC (mNSCLC) Nonsquamous**

More than 60% of patients have oncogenic drivers—and of these patients, about 2 in 3 have an actionable biomarker

*Regardless of PD-L1 expression.

**Stages I-III NSCLC**

- ~13% of patients have EGFR mutations
- 2%-5% of patients are ALK
- 1%-3% of patients have RET fusions
- ~45% of patients are PD-L1

Evolving biomarkers include:
- BRAF
- MET
- NTRK
- ROS1

*FDA-approved therapeutics

*Emerging therapeutics

*Johns Hopkins Medicine*
Advances in the treatment of resectable NSCLC

Adjuvant cisplatin doublet chemotherapy

Neoadjuvant meta-analysis

Neoadjuvant working group meta-analysis

ADAURA shows DFS advantage to adjuvant osimertinib

Osimertinib
So what’s the problem?

- Guidelines now advocate for mutation screening as standard of care
- Lung cancer diagnosis was historically obtained from solid tissue biopsy alone
- There are limitations with solid tissue sampling:
  - Invasiveness
  - May be difficult to obtain
  - Patients may require repeated invasive procedures following disease progression
  - May have insufficient tissue for detailed sequencing analysis
## Delaware

<table>
<thead>
<tr>
<th>Rate of New Cases</th>
<th>Survival Rate</th>
<th>Early Diagnosis</th>
<th>Surgical Treatment</th>
<th>Lack of Treatment</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>Average</td>
<td>Above Average</td>
<td>Average</td>
<td>Average</td>
<td>Above Average</td>
</tr>
</tbody>
</table>

**Fee-For-Service Medicaid Coverage of Screening**
Covered and Using Updated Guidelines

**Highlighted Disparity**
Black individuals in Delaware are least likely to be diagnosed early.

One Breath Bubble Challenge

UNITED STATES POST OFFICE
NORTH POLE, AK. 99705

Challenge.com
Conclusions

– Creative programs can help with smoking cessation
– Early detection for lung cancer is possible with low dose CT screening AND WILL SAVE LIVES
– Many reasons why lung screening has not been well-adopted
– Risk factors such as family history, radon exposure, second hand smoke exposure may help to create a stratification score that will better identify who to screen
– Although lung cancer treatments are improving survival, biomarker testing is critical and under-utilized
– Blood assays to look for biomarkers
– Education, awareness and research efforts
Thank You
aargent1@jh.edu