Lung cancer incidence—the new-diagnosis rate—stands more than twice higher in US women than men with HIV infection, according to analysis of two longitudinal HIV cohorts [1]. The study also found that current US screening guidelines [2] perform poorly in people with HIV, and they suggested ways to improve those criteria.

Lung cancer poses a major threat to people with HIV infection. University of North Carolina researchers and collaborators from other centers noted that lung cancer gets diagnosed at an earlier age in people with HIV than in the general population. HIV-positive people run a higher risk of lung cancer at lower cumulative smoking pack-years and have worse survival.

Current United States Preventive Services Task Force (USPSTF) guidelines call for lung cancer screening at ages 55 to 80 in people with at least a 30 pack-year smoking history, including current smokers and former smokers who quit within 15 years [2]. US researchers conducted this study to assess lung cancer screening criteria in people with HIV and to examine alternative criteria.

The investigators explored data from two US HIV cohorts, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS), both of which include people with and at risk for HIV infection who make twice-yearly study visits. MACS recruits gay and bisexual men. The research team designed a case-control comparison in which cases were HIV-positive people with a confirmed lung cancer diagnosis who were current or former smokers and 40 or older. An equal number of controls without lung cancer before or during study follow-up were matched to cases by 5-year age group. Demographic and clinical data came from the visit before lung cancer diagnosis in cases and at a randomly selected study visit in controls.

Lung cancer incidence proved more than twice higher in WIHS women than MACS men with HIV: 270 versus 104 cases per 100,000 person-years. Women with lung cancer had a significantly lower CD4 count than those without lung cancer (median 348 versus 452, \( P < 0.05 \)), but the proportion of current smokers (61% and 59%) and women with at least a 30 pack-year smoking history (30% versus 20%) did not differ significantly between lung cancer cases and controls. Among men CD4 count was also lower in those with than without cancer (median 387 and 549), and men with lung cancer were more likely to be current smokers (71% versus 24%) and to have at least a 30 pack-year history (71% versus 24%).

USPSTF lung cancer screening criteria had strikingly low sensitivity for identifying lung cancer in WIHS women with HIV (16%) and MACS men with HIV (24%). Specificity, the ability of criteria to correctly classify people who do not have lung cancer, was high in both women (93%) and men (94%).

In women lowering pack-year history from at least 30 to at least 15 in increments of 1 while maintaining other criteria improved screening sensitivity to 30%. Raising the quit time from at least 15 to at least 30 years in increments of 1 year while maintaining other criteria modestly improved screening sensitivity in women (18%). For women cutting the lower screening age limit from 55 to 40 years in increments of 1 also improved sensitivity (25%). Those same three changes improved screening sensitivity in MACS men.
with HIV. Slicing the lower screening age limit from 55 to 40 had the greatest impact in men with HIV, improving sensitivity to 71%. All of these changes maintained relatively high screening specificity.

The researchers proposed that adding sex and HIV status to risk prediction modeling may improve the ability to spot people who run a higher risk of lung cancer. They suggested that younger screening age and a lower pack-year history could improve screening sensitivity in people with HIV.

References

Conclusions and Implications

• Lung cancer incidence is higher in women with HIV compared to men with HIV
• Current USPSTF criteria for lung cancer screening by LDCT perform poorly in PLWH
• Risk prediction modeling incorporating sex and HIV status may improve selection of patients at increased risk for lung cancer
• Alternative thresholds of younger age and decreased pack-year history may be more sensitive in PLWH

Optimal Lung Cancer Screening Criteria Among Persons Living With HIV

Subhashini A Sellers, D.; Andrew Edmonds Ph.D., Catalina Ramirez MPH CCRP; Sushma K. Cribbs MD MSc; Igbo Ofotokun MD MSc; Laurence Huang MD; Alison Morris MD MS; Meredith C. McCormack MD MHS; Ken M. Kunisaki MD MS; M. Patricia Rivera MD; M. Brad Drummond, MD MHS; Adaora Adimora, MD MPH
Lung cancer is a leading cause of mortality in PLWH

- Higher prevalence of smoking compared to general population
- HIV may be an independent risk factor for lung cancer development
- Compared to general population:
  - Diagnosed at an earlier age
  - Have a higher risk with a lower cumulative pack-year history
  - Worse survival

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- Image shows 5-year cumulative incidence estimates for all HIV-infected individuals after accounting for competing risk of death

Lung cancer screening

**Current USPSTF guidelines:**
- Ages 55-80
- ≥ 30 pack-year smoking history
- If former smoker, quit within 15 years

**NLST:**
- Randomized trial
- 55,000 participants
- 20% relative reduction in lung cancer mortality
- **PLWH were not specifically included**


-53,454 persons at high risk for lung cancer at 33 U.S. medical centers.

-Results
- Lung cancer deaths: LDCT 247 deaths per 100,000 person-years versus 309 deaths per 100,000 person-years (relative reduction in mortality of 20%; 95% CI 6.8-26.7, p=0.004)
- All cause mortality reduction 6.7% (95% CI 1.2-13.6, p=0.02)
- USPSTF adopted recommendations to use annual LDCT in high risk individuals
  Expanded age criteria to include adults 55-80

-Exclusion criteria: Persons who had previously received a diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, or had an unexplained weight loss of more than 6.8 kg (15 lb) in the preceding year
-Other results:
-Lung cancer incidence: LCDT 645 cases per 100,000 person-years versus 572 cases per 100,000 person-years (IRR 1.13; 95% CI 1.03-1.23
-Positive screens: LDCT 24.2% versus CXR 6.9%

-False positives: LDCT 96.4% versus CXR 94.5%

PLWH may not be adequately captured by current recommendations

Objective:
• Examine performance characteristics of current lung cancer screening criteria and alternative criteria among participants of two longitudinal cohort studies of HIV infection

Hypothesis:
• The current USPSTF screening criteria perform poorly in PLWH.
• Adjusting risk factors (younger age, lower pack-year history and/or including markers of HIV infection) may improve the ability to capture participants at increased risk for lung cancer who may benefit from screening

Analytic Cohort

• Women’s Interagency HIV Study (WIHS)
  • Recruited women with and without HIV from 9 centers
  • Total of 4982 participants; 3677 participants with HIV

• Multicenter AIDS Cohort Study (MACS)
  • Recruited men who reported having sex with men from 4 centers
  • Total of 7357 participants; 3914 with HIV

• Semi-annual visits for standardized interview, clinical evaluations, laboratory tests and specimen storage
Study Design and Approach

- **Cases:**
  - PLWH with confirmed lung cancer, current/former smokers, and ≥ 40 years old at the time of diagnosis
  - Cancer diagnosis confirmation:
    - MACS: ICD-O3 and clinical confirmation
    - WIHS: previously adjudicated or National Death Index with ICD-10

- **Controls:**
  - Equal number of PLWH in each cohort matched to cases by 5-year age group
  - No incident or prevalent lung cancer during all follow-up visits

- **Demographic and clinical information (via self-report):**
  - Cases: at the visit just prior to lung cancer diagnosis
  - Controls: randomly selected follow-up visit

- Performance characteristics of current USPSTF recommendations and alternative thresholds of criteria were examined within each cohort

- In MACS, confirmation was based on the presence of an ICD code indicating pulmonary site, pulmonary morphology and presence of clinical evidence, biopsy, autopsy, death certificate, cytology, imaging, biochemical markers or state registry confirmation.

- In WIHS, confirmed cases were previously adjudicated in the WIHS database or located in the national death index with ICD-10 code confirming lung cancer.

- Participants reporting lung cancer at cohort entry were excluded from analysis.

- Demographic data, smoking status and intensity, ART adherence and substance use history were obtained via self-report at the visit just prior to the date of the lung cancer diagnosis and for a randomly selected follow-up visit for controls

### Lung cancer incidence was higher in women

#### Lung Cancer Cases:
- WIHS 44
- MACS 17

<table>
<thead>
<tr>
<th>Histology type</th>
<th>WIHS (n=30)</th>
<th>MACS (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>9 (30)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>6 (20)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Non-small cell carcinoma, NOS</td>
<td>7 (23)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>1 (3)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Carcinoma, NOS</td>
<td>4 (13)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (10)</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

Morphology based on data from state cancer registries. Data available on 30 of 44 lung cancers identified in WIHS and all cancers identified in MACS.
- Women with lung cancer also were more likely to have quit within 15 years compared to those without lung cancer; however, there was no difference in the proportion who were current smokers or who had a 30 or more pack-year history

- Men with lung cancer were more likely to be current smokers and have smoked ≥ 30 pack-years

**USPSTF criteria performed poorly in PLWH**

**Current criteria:**
- Ages 55-80
- Pack-year history ≥ 30
- Current smoker or quit ≤ 15 years ago

**WIHS women:**
- Sensitivity 16%
- Specificity 93%

**MACS men:**
- Sensitivity 24%
- Specificity 94%
Alternative criteria thresholds improved sensitivity in **women**

- Maintain quit time and age the same
- Decrease pack-year history from ≥ 30 to ≥ 15 in increments of 1
  - Sensitivity 30%
  - Specificity 84%

**Diagnostic Parameters**

- Sensitivity
- Specificity

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Alternative criteria thresholds improved sensitivity in **women**

- Maintain pack-years and age the same
- Increase quit time from ≤ 15 to ≤ 30 year in increments of 1
  - Sensitivity 18%
  - Specificity 91%

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Alternative criteria thresholds improved sensitivity in **women**

- Maintain pack-years and quit time the same
- Decrease lower limit of age from 55 to 40 years in increments of 1 year
  - Sensitivity 25%
  - Specificity 84%

---
Alternative criteria thresholds improved sensitivity in **men**

![Graph showing sensitivity and specificity changes with lower limit pack-year history.](image)

- Maintain age and quit time the same
- Decrease pack-year history from \( \geq 30 \) to \( \geq 15 \) in increments of 1
  - Sensitivity 24%
  - Specificity 94%

---

Alternative criteria thresholds improved sensitivity in **men**

![Graph showing sensitivity and specificity changes with lower limit quit time.](image)

- Maintain age and pack-year history the same
- Increase quit time from \( \leq 15 \) years to \( \leq 30 \) year in increments of 1
  - Sensitivity 24%
  - Specificity 94%

---

Alternative criteria thresholds improved sensitivity in **men**

![Graph showing sensitivity and specificity changes with lower limit age.](image)

- Maintain quit time and pack-year history the same
- Decrease lower limit of age from 55 years to 40 years in increments of 1
  - Sensitivity 71%
  - Specificity 82%
Replacing age criteria with HIV disease characteristics, while keeping cumulative pack-years and quit time at current recommendations did not improve test characteristics beyond already optimized criteria. When having a nadir CD4 count ≤ 200 cells/uL replaced age criteria, sensitivity and specificity were 11% and 88% respectively in WIHS women. When prior history of AIDS replaced age criteria, sensitivity and specificity in women were 16% and 91%.

### Optimal screening criteria

| Performance characteristics of variable screening thresholds for WIHS |
|---|---|---|---|---|---|
| USPSTF | Age | Pack-years | Quit time | Sensitivity | Specificity |
| 55      | 30   | 15          | 16%       | 93%         |
| Optimal | 49   | 16          | 15        | 52%         | 75%         |

### Optimal screening criteria for MACS

| Performance characteristics of variable screening thresholds for MACS |
|---|---|---|---|---|---|
| USPSTF | Age | Pack-years | Quit time | Sensitivity | Specificity |
| 55      | 30   | 15          | 24%       | 94%         |
| Optimal | 43   | 19          | 15        | 82%         | 76%         |

- Replacing age criteria with HIV markers did not improve test characteristics beyond already optimized criteria.

### Optimal screening criteria in WIHS women

| Performance characteristics of variable screening thresholds for WIHS |
|---|---|---|---|---|---|
| Age | Pack-years | Quit time | Sensitivity | Specificity |
| 55 | 30 | 15 | 16% | 93% |
| 51 | 20 | 15 | 36% | 87% |
| 49 | 19 | 4  | 82% | 76% |
| 49 | 16 | 15 | 52% | 75% |

- Replacing age criteria with HIV disease characteristics, while keeping cumulative pack-years and quit time at current recommendations did not improve test characteristics beyond already optimized criteria. When having a nadir CD4 count ≤ 200 cells/uL replaced age criteria, sensitivity and specificity were 11% and 88% respectively in WIHS women. When prior history of AIDS replaced age criteria, sensitivity and specificity in women were 16% and 91%.
Optimal screening criteria in MACS men

| Performance characteristics of variable screening thresholds for MACS |
|-------------------------|----------------|----------------|----------------|
| Age | Pack-years | Quit time | Sensitivity | Specificity |
| 55L  | 30 | 15 | 24% | 94% |
| 50  | 30 | 2 | 53% | 100% |
| 50  | 30 | 15 | 59% | 94% |
| 44  | 30 | 15 | 71% | 82% |
| 43  | 19 | 15 | 82% | 76% |

• Replacing age criteria with HIV markers did not improve test characteristics

- When having a nadir CD4 count ≤ 200 cells/μL replaced age criteria sensitivity improved to 35% and specificity remained 94% respectively in MACS men. In men, replacing age with prior history of AIDS changed sensitivity to 29% and specificity to 94%.

Replacing age criteria with HIV markers did not improve test characteristics

| Performance characteristics of variable screening thresholds for WIHS |
|-------------------------|----------------|----------------|----------------|
| Nadir CD4+ ≤ 200 cells/μL | Pack-years | Quit time | Sensitivity | Specificity |
| 30 | 15 | 11% | 88% |
| History of AIDS | 20 | 15 | 16% | 91% |

| Performance characteristics of variable screening thresholds for |
|-------------------------|----------------|----------------|----------------|
| Nadir CD4+ ≤ 200 cells/μL | Pack-years | Quit time | Sensitivity | Specificity |
| 30 | 15 | 11% | 88% |
| History of AIDS | 20 | 15 | 16% | 91% |

Acknowledgements

• MACS and WIHS Participants
• MACS and WIHS Staff
• National Institutes of Health
• Adaora Adimora, MD MPH
• Catalina Ramirez
• Andrew Edmonds, PhD
• M. Brad Drummond, MD MHS
• M. Patricia Rivera, MD
• All co-authors