Who Should Be Screened for Lung Cancer: Weighing Risks and Benefits

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Consultant, Medial Cancer Screening, Ltd

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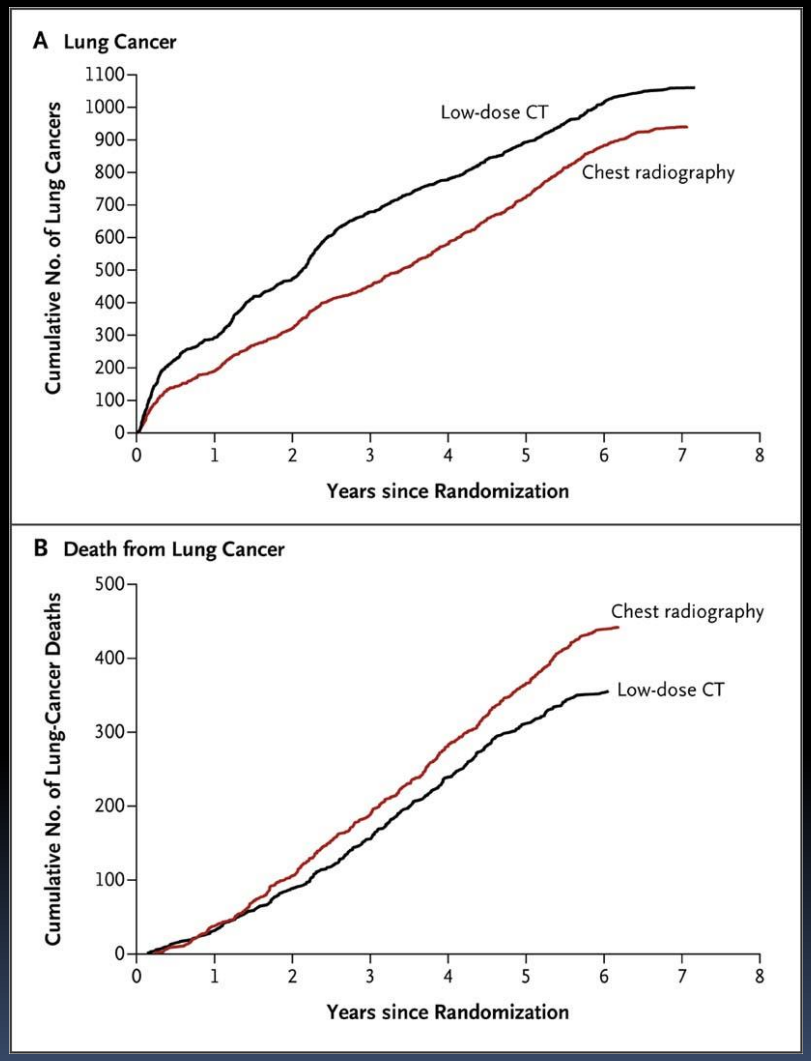
The FDA does not have jurisdiction over use of helical CT or CXR screening for lung cancer as it does for mammography. Takes act of Congress.

Lecture Objectives

- Information from NLST
  - Benefits
  - False-positives
  - Radiation risk
  - Smoking cessation
- Where next with lung cancer screening in the U.S.
  - Current guidelines
  - Risk-based screening to maximize benefit
  - More efficient approach to positive screens
- Next steps

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.



The National Lung Screening Trial Research Team. N Engl J Med 2011;365:395-409

The NEW ENGLAND JOURNAL of MEDICINE

True and false positive screens

Screening Result	Low-dose Helical CT		
	Screen 1 N (%)	Round 2 N (%)	Round 3 N (%)
Total Positives/Total Screens	**7,191/26,309 (27.3)**	**6,901/24,715 (27.9)**	**4,054/23,346(16.8)**
Lung cancer	**270 (4)**	**168 (2)**	**211 (5)**
No lung cancer	**6,911 (96)**	**6,728 (98)**	**3,838 (95)**

Data reflect the final interpretation, including benefit of historical comparison exams.

Positive Screens were > 3-fold higher in the LDCT arm

Cancer Yield by Nodule Size

	T0		T1		T2	
	Lung Cancer Yes/No	Yield	Lung Cancer Yes/No	Yield	Lung Cancer Yes/No	Yield
Nodule Size						
4 – 6 mm	18/3642	0.5%	12/3822	0.3%	15/2023	0.7%
7 – 10 mm	35/2079	1.7%	46/1959	2.4%	58/2023	5.1%
11 – 20 mm	111/821	11.9%	74/815	9.1%	86/588	14.6%
21 – 30 mm	58/137	29.7%	20/114	17.5%	23/100	23.0%
> 30 mm	45/64	41.3%	8/55	14.5%	20/62	32.8%

Radiation risks versus benefits: Radiation dose

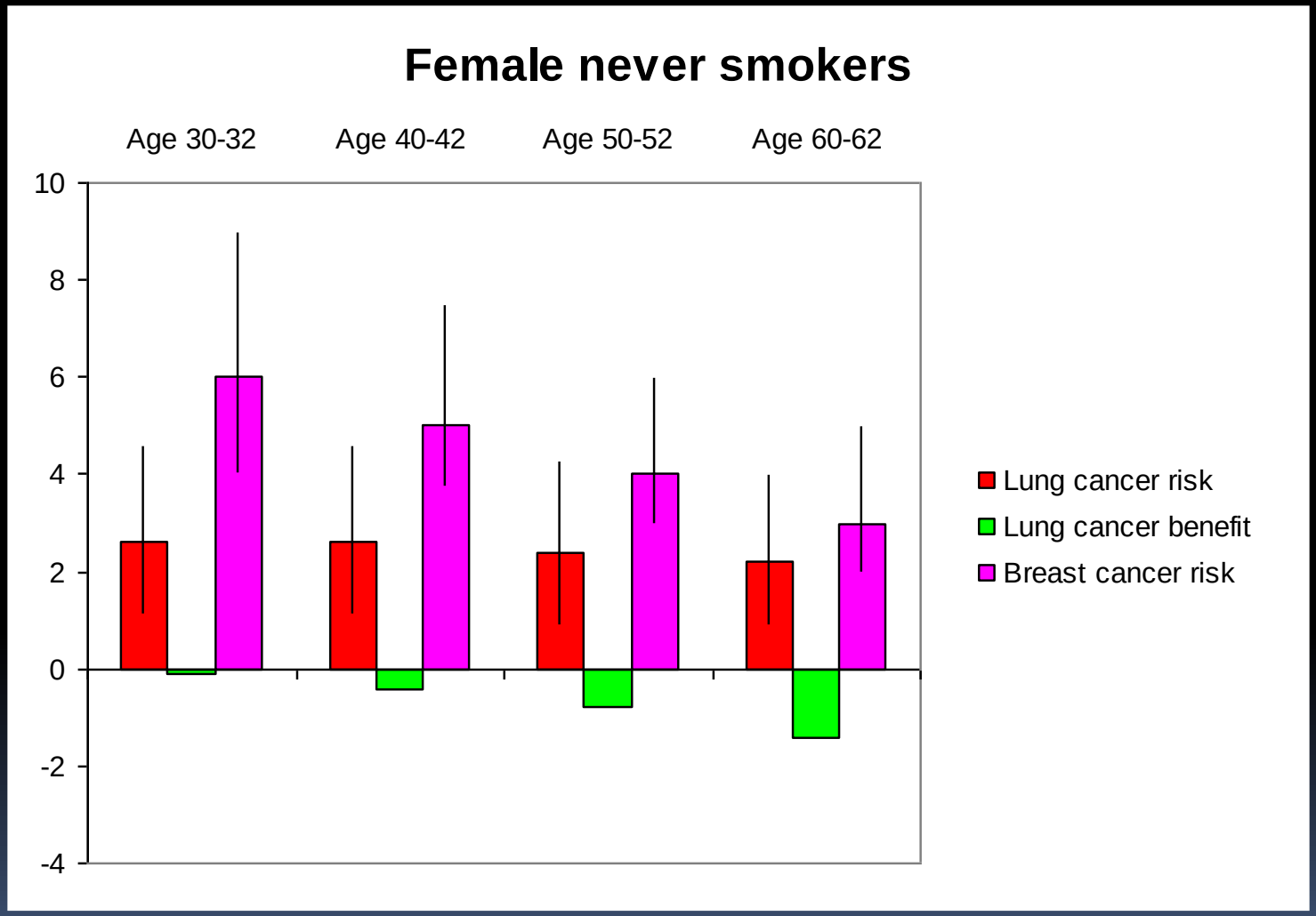
- Low dose helical CT: estimates of organ specific dose
  - Lung: 4 mGy
  - Breast: 4 mGy
  - Red bone marrow, stomach, liver and pancreas: each ~1 mGy
- Organ specific dose:
  - Mammography : 4mGy (two view)
- Whole body effective dose (weighted average dose to each organ)
  - Low dose helical CT: 1.5 mSv (diagnostic CT 7.0 mSv)
  - Mammogram: 0.7mSv
  - CXR-PA: 0.02 mSv

http://www.radiologyinfo.org/en/safety/index.cfm?pg=sfty_xray

Radiation Risks vs Benefits

- 3 screens Smokers Age 55 – 57
- Whole body effective dose (weighted average dose to each organ)
  - Low dose helical CT: 1.5mSv
- Radiation risk from screens
  - 1-3 lung cancer deaths per 10,000 screened
  - 0.3 breast cancers per 10,000 females screened
- Radiation risk from follow-up CT scans
  - Low-dose or thin-section chest CT + 25%
  - Diagnostic chest CT + 100%
- Cumulative mortality reduction NLST
  - 30 lung cancer deaths per 10,000 screened

Change in cancer risk per 10,000 screened (assuming 20% mortality reduction)



Berrington de Gonzalez A, Kim KP, Berg CD. J Med Screen 2008;15:153-158.

NLST LSS Study of Factors Associated with Smoking Behavior

Odds ratios from multivariable* longitudinal logistic analysis for ***being a current smoker*** given the ***previous screening result***.

Screening Result	**Odds Ratios** (95% CI; p-values)
Normal – no abnormalities (Referent group)	1.00
Negative for lung cancer, minor other abnormalities	**0.85** (0.72-0.99; p = 0.037)
Negative for lung cancer, significant other abnormalities	**0.68** (0.52-0.89; p = 0.004)
Positive for lung cancer	**0.46** (0.37-0.57; p < 0.001)
Positive for lung cancer, stable, no significant change from previous screen	**0.67** (0.52-0.87; p = 0.003)

***Conclusion*:** The probability of subsequent smoking is inversely associated with the abnormality of screening result in a dose-response fashion. Tammemagi, M and Taylor K

What next and for whom?

Challenges for Successful Lung Cancer Screening Programs

- Effective smoking cessation
- Selection of high-risked individuals most likely to benefit from lung cancer screening
- Effective and efficient evaluation of abnormal low-dose helical CT examinations
- Monitoring of quality standards in ongoing program

US Preventive Services Guideline
Final Recommendations for Lung Cancer Screening
December 31, 2013

- Grade B Recommendation
- The USPSTF has found moderate level evidence for moderate level benefit for lung cancer screening with CT
- The population recommended to be screened annually is:
  - Ages 55 – 79; 30 pack years; if former smoker quit within 15 years
- Medicare will review; the PPACA is supposed to require insurance companies to cover screening for eligible patients without a deductible

Organization	Type of Statement	NLST Like Subjects?	Others?
ACCP/ ASCO/ ATS endorsed	Evidence based guideline	Suggest it be offered	No
ACS	Guideline	May be considered	No
ALA	Guidance	Recommended	No
NCCN	Consensus guidelines	Recommended	Yes, for some individuals
AATS	Guideline	Recommended	Age 50-79; 20 pack years and five year cumulative risk of 5% or more; lung cancer survivors
USPSTF	Guideline	Recommended	Ages 50 to 79 with annual screening until age 79 or more than 15 years post smoking cessation

American Academy of Family Practitioners
Clinical Recommendation
Lung Cancer Screening
January 13, 2104

- I Recommendation: Insufficient evidence

- Comments:
  - Paucity of high-quality evidence; only one study at major medical centers and with strict follow-up of nodules
  - Favorable results of NLST not replicated in a community setting

Estimates of Screening Avertable Deaths with three rounds of screening

- Screen NLST population (55 – 74; current or former smokers of 30 pack years, smoked within 15 years); approximately 8.8 million people
  - % of cancers: 26.7%
  - With 80% compliance 5% of lung cancer deaths averted (8,150)
    - Pinsky and Berg, JMS 2012:19(154-156)
- Separate estimate by ACS researchers
  - Screen 8.6 million; Full compliance 12,250 deaths averted; 70% compliance 8575 deaths averted
    - Ma J et al Cancer on-line February 25, 2013

Optimizing screening avertable deaths

- Within the NLST, some subgroups may have little benefit from LDCT screening
- Use of risk might allow us to extend LDCT screening to smokers at high risk but who did not qualify under NLST criteria
- Organizations may wish to consider review of risk stratification options and consider revision of guidelines; what data needs to be collected for this to occur?

Several Risk Prediction Models

- Bach, Spitz, LLP, COSMOS
- NCCN: Back of the envelope risk but does consider occupational exposure
- Two models from NLST data in NEJM 2013
  - Tammemagi et al Incidence based: includes age, race or ethnic group, education, BMI, COPD, personal history of cancer and family history of lung cancer, smoking status, smoking intensity
  - Kovalchik et al Lung cancer mortality based

Table 4. Accuracy of Lung-Cancer Classification According to Alternative Criteria in the PLCO Intervention-Group Smokers.*

Criteria†	Participants with Lung Cancer (N=678)	Participants without Lung Cancer (N=36,654)	Total Participants (N=37,332)	Predictive Value
NLST				
Criteria positive	482 TP (3.4%)	13,662 FP (96.6%)	14,144	PPV, 3.4%
Criteria negative	196 FN (0.8%)	22,992 TN (99.2%)	23,188	NPV, 99.2%
Sensitivity	71.1%			
Specificity		62.7%		
$PLCO_{M2012}$ ‡				
Criteria positive	563 TP (4.0%)	13,581 FP (96%)	14,144	PPV, 4.0%
Criteria negative	115 FN (0.5%)	23,073 TN (99.5%)	23,188	NPV, 99.5%
Sensitivity	83.0%			
Specificity		62.9%		

Effective and efficient evaluation of abnormal low-dose helical CT examinations

- NLST had positivity rate of 24.2% overall ; average false-positive rate of 97%; Sens/Spec : 93.7%/76.6%; PPV 3.8%
  - High cost; higher radiation exposure for follow-up testing
- One approach to consider is prediction model for probability of lung cancer in a nodule
  - PanCan approach NEJM 369(10):910-919
- Model variables include patient characteristics and image characteristics
  - Age, gender, family history of lung cancer, emphysema
  - Nodule size, nodule type (nonsolid or with ground-glass opacity; part-solid; solid); nodule location, (upper vs. middle or lower lobe); nodule count per scan,, spiculation

Classification accuracy for predicting nodule malignancy

Parsimonious model with spiculation

Risk Score Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Proportion Nodules Positive (%)
≥2%	84.7	89.6	10.5	99.8	89.5	11.5
≥5%	71.4	95.5	18.5	99.6	95.1	5.5
≥10%	60.2	97.5	25.4	99.4	96.9	3.4

Abbreviations: PPV, positive predictive value; N, number; NPV, negative predictive value.

Summary

- Opportunity to significantly improve outcome of patients with lung cancer
- Selection of high-risk group to screen critical
- Current recommendations from all major groups may benefit from revision with new information from risk models
- Continued research to minimize burden of false-positives also critical
- International collaboration to better define the screening process and most cost-effective diagnostic and treatment pathways
- Screening is NOT a substitute for effective tobacco control policies

NLST Data, Image and Specimen Access

- Website https://biometry.nci.nih.gov/cdas/studies/nlst/
- Access to entire research community
- Data transfer agreement required
- Name, email, summary of research proposal on website
- Return of research papers requested for tracking and posting
- Biospecimens http://www.acrin.org/RESEARCHERS/POLICIES/NLSTACRINBIOREPOSITORY.aspx

Acknowledgements

Full list of all collaborators
http://www.nejm.org/action/showSupplements?doi=10.1056%2FNEJMoa1102873&viewType=Popup&viewClass=Suppl

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With appreciation

53,454 trial participants

without whom these studies would not have been possible