CT screening for lung cancer

Should it be done in the Indian context?

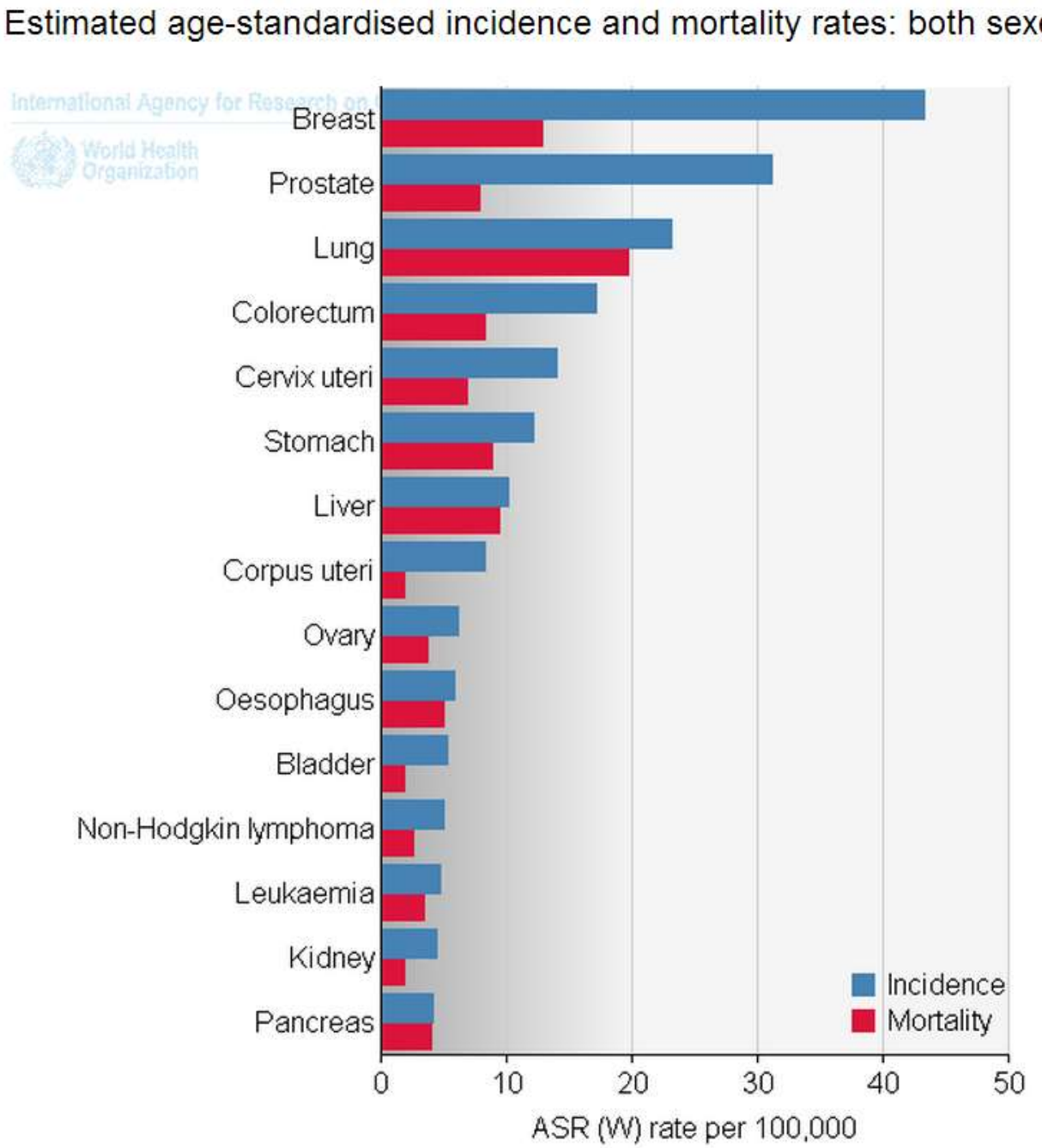
Wilson and Jungner screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including dx and tx of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

Principles and practice of screening for disease. Wilson JMG, Jungner G. WHO 1968

Is lung cancer suitable for screening?

- Is the burden of the disease significant?
- Does it cause significant mortality/morbidity?
- Is there a preclinical phase where early Dx and Rx produce better outcomes?



International Agency for Research on Cancer

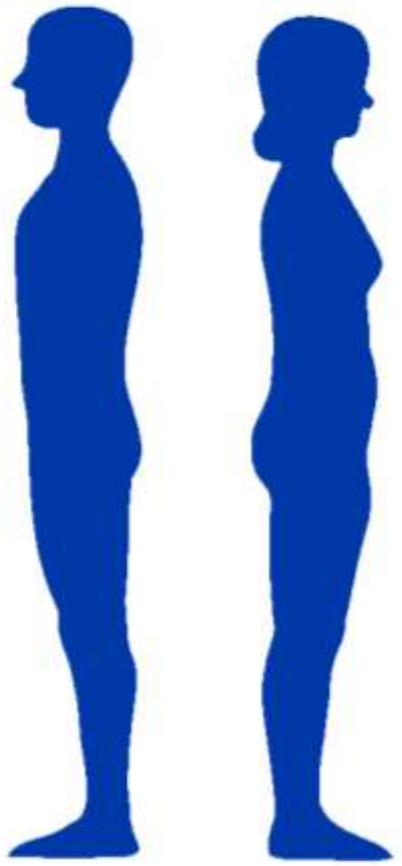
World Health Organization

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

- Lung cancer is the most common cause of death from cancer worldwide (1.59 million deaths, 19.4% of the total)
- Lung cancer is the 3rd most common cancer worldwide
- Lung cancer is the most common cancer in men worldwide (Incidence in 2012: 1.2 million, 16.7% of the total)

USA 2013: Estimated Cancer Deaths

Men 306,920	
Lung & bronchus	28%
Prostate	10%
Colon & rectum	9%
Pancreas	6%
Liver & intrahepatic bile duct	5%
Leukemia	4%
Esophagus	4%
Urinary bladder	4%
Non-Hodgkin lymphoma	3%
Kidney & renal pelvis	3%
All other sites	24%



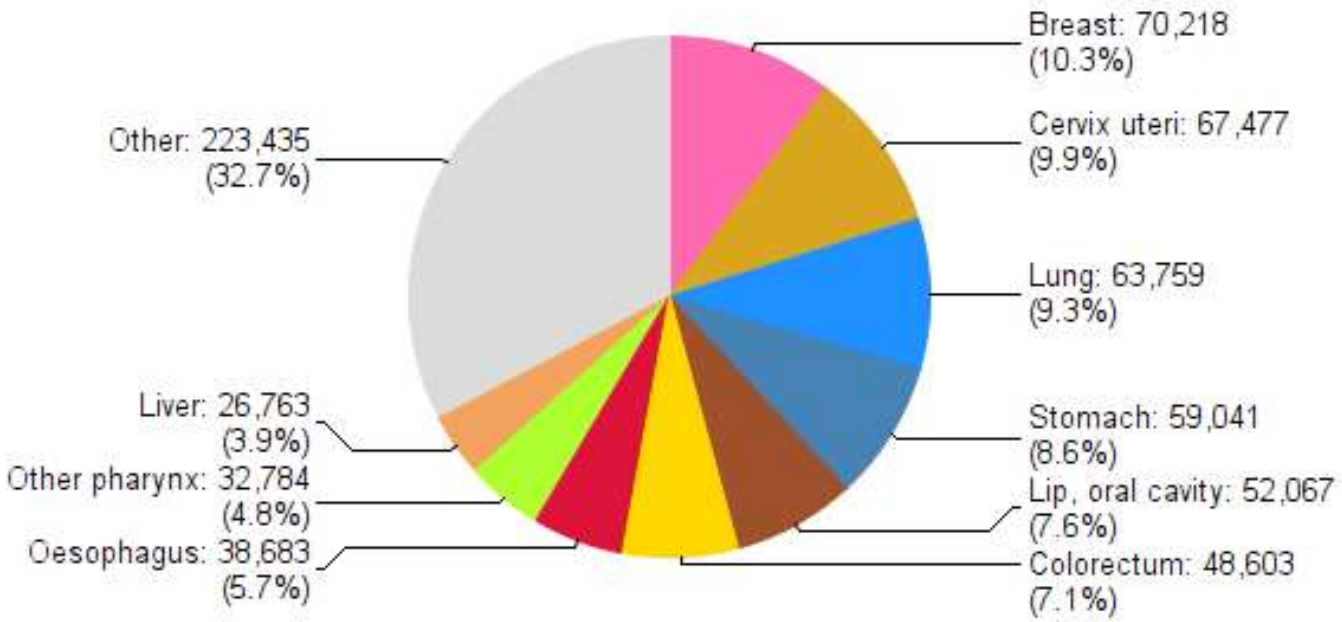
Women 273,430	
26%	Lung & bronchus
14%	Breast
9%	Colon & rectum
7%	Pancreas
5%	Ovary
4%	Leukemia
3%	Non-Hodgkin lymphoma
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/other nervous system
25%	All other sites

ACS 2013 Cancer Statistics

India: Both sexes

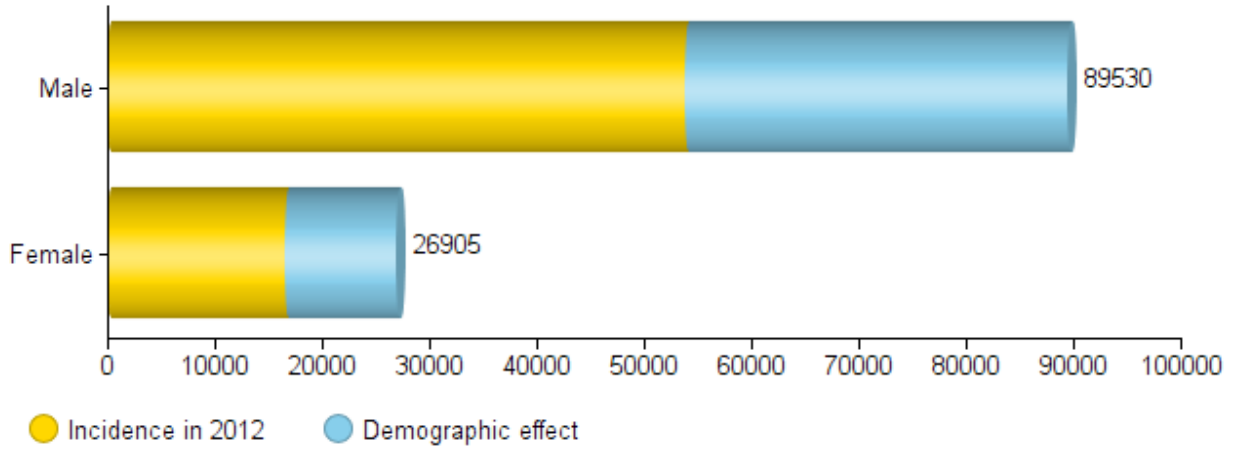
Estimated number of cancer deaths, all ages (total: 682,830)

India 2012: Estimated cancer deaths



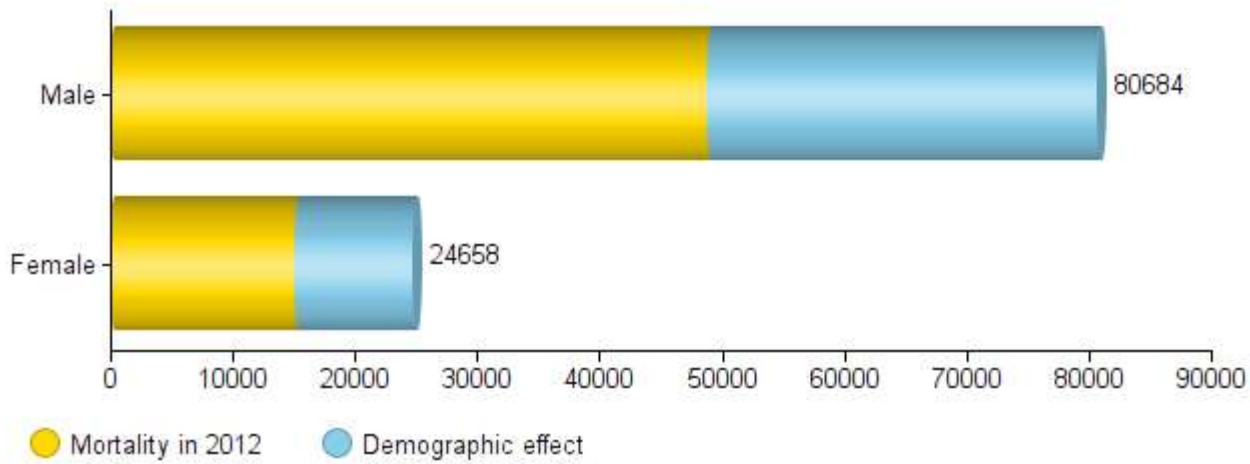
GLOBOCAN 2012 (IARC)

India
Lung
Number of new cancers in 2030 (all ages)



GLOBOCAN 2012 (IARC) (26.1.2014)

India
Lung
Number of cancer deaths in 2030 (all ages)



GLOBOCAN 2012 (IARC) (26.1.2014)

Five-year Relative Survival Rates* (%) by Stage at Diagnosis, 2002-2008

	All Stages	Local	Regional	Distant
Breast (female)	89	98	84	24
Colon & rectum	64	90	70	12
Esophagus	17	38	20	3
Kidney†	71	91	64	12
Larynx	61	76	42	35
Liver‡	15	28	10	3
Lung & bronchus	16	52	25	4
Melanoma of the skin	91	98	62	15
Oral cavity & pharynx	62	82	57	35
Ovary	44	92	72	27
Pancreas	6	23	9	2
Prostate	99	100	100	28
Stomach	27	62	28	4
Testis	95	99	96	73
Thyroid	98	100	97	54
Urinary bladder§	78	70	33	6
Uterine cervix	68	91	57	16
Uterine corpus	82	95	67	16

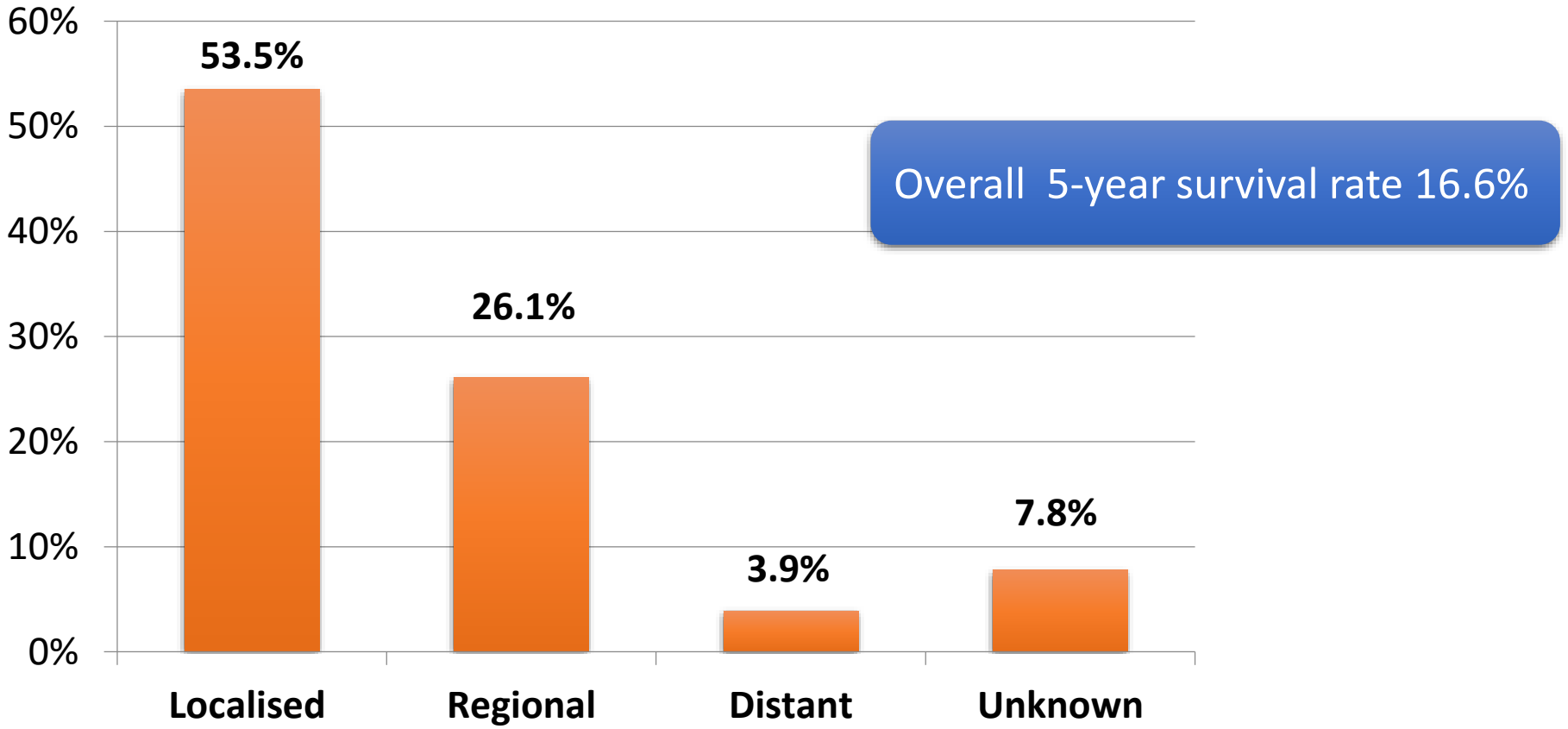
*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2002-2008, followed through 2009.
†Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes by way of lymphatic system; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). *SEER Cancer Statistics Review, 1975-2009*, National Cancer Institute, Bethesda, MD, www.seer.cancer.gov/csr/1975_2009/, 2012.

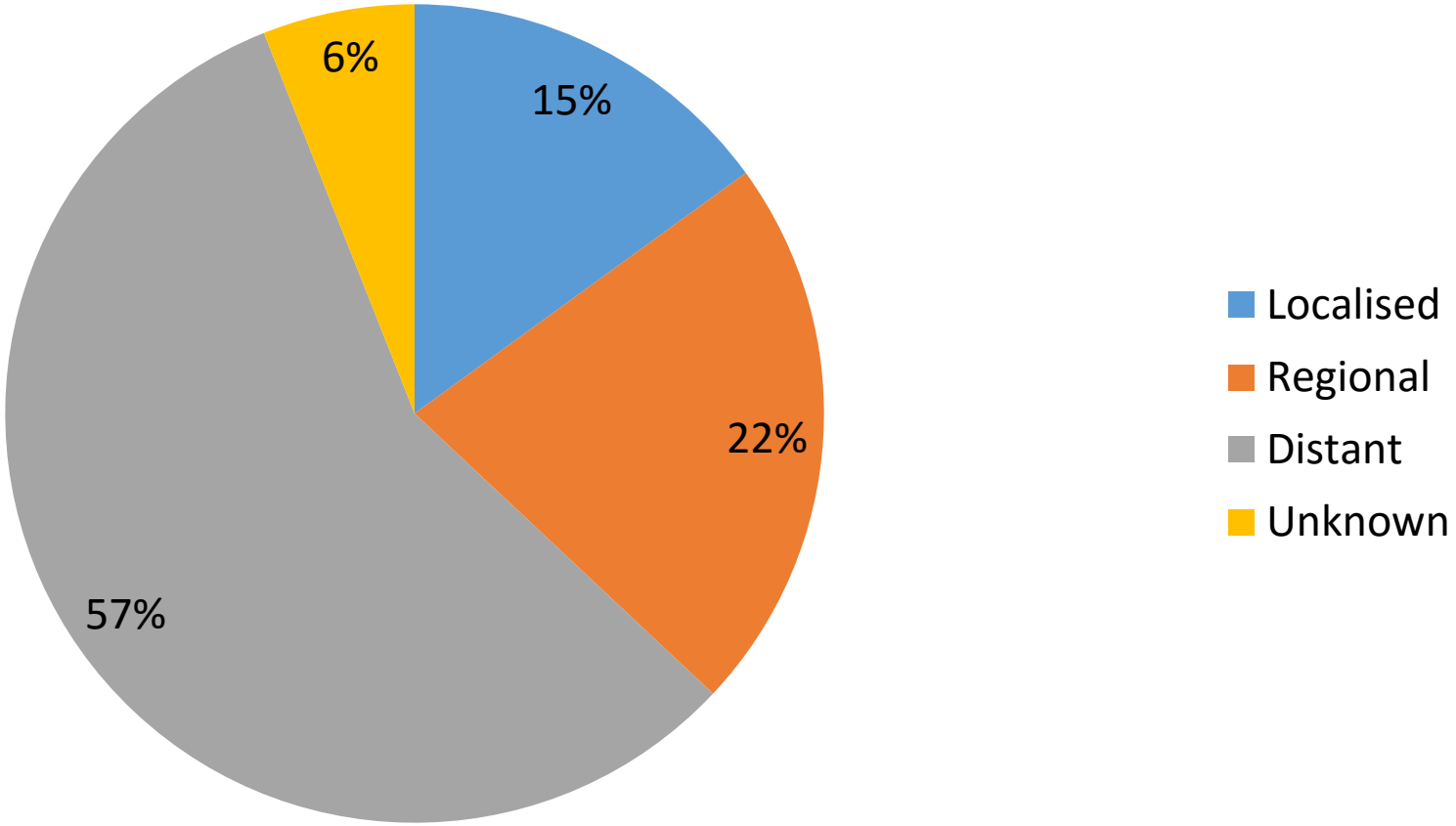
American Cancer Society, Surveillance Research 2013

Lung ca: 5-yr survival (by stage at diagnosis)



SEER (U.S. NCI) cancer statistics 2013

Lung ca: Stage at diagnosis



SEER (U.S. NCI) cancer statistics 2013

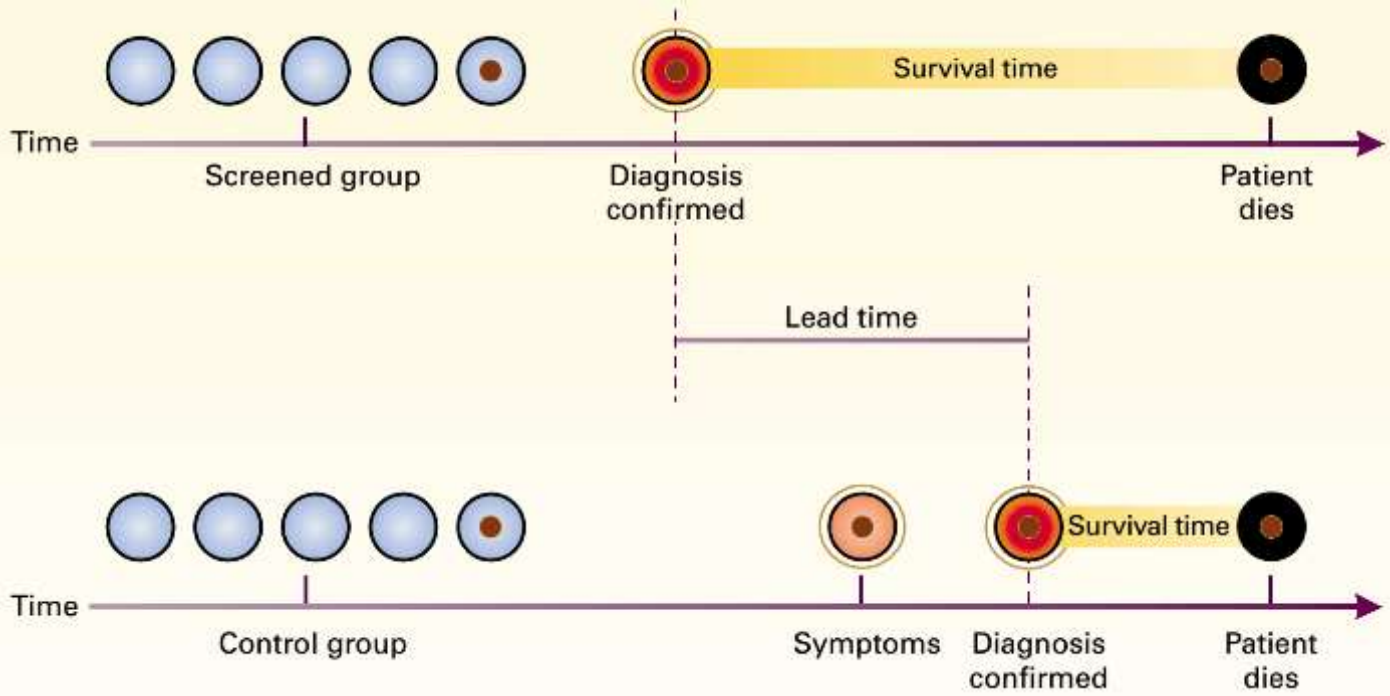
Is lung cancer suitable for screening?

- Is the burden of the disease significant?
  - Yes
- Does it cause significant mortality/morbidity?
  - Yes
- Is there a preclinical phase where early Dx and Rx produce better outcomes?
  - Yes

Screening test: Which outcome measure to use?

- Cancer detection rates
- Stage at detection
- Survival
- Disease-specific mortality
- Overall mortality

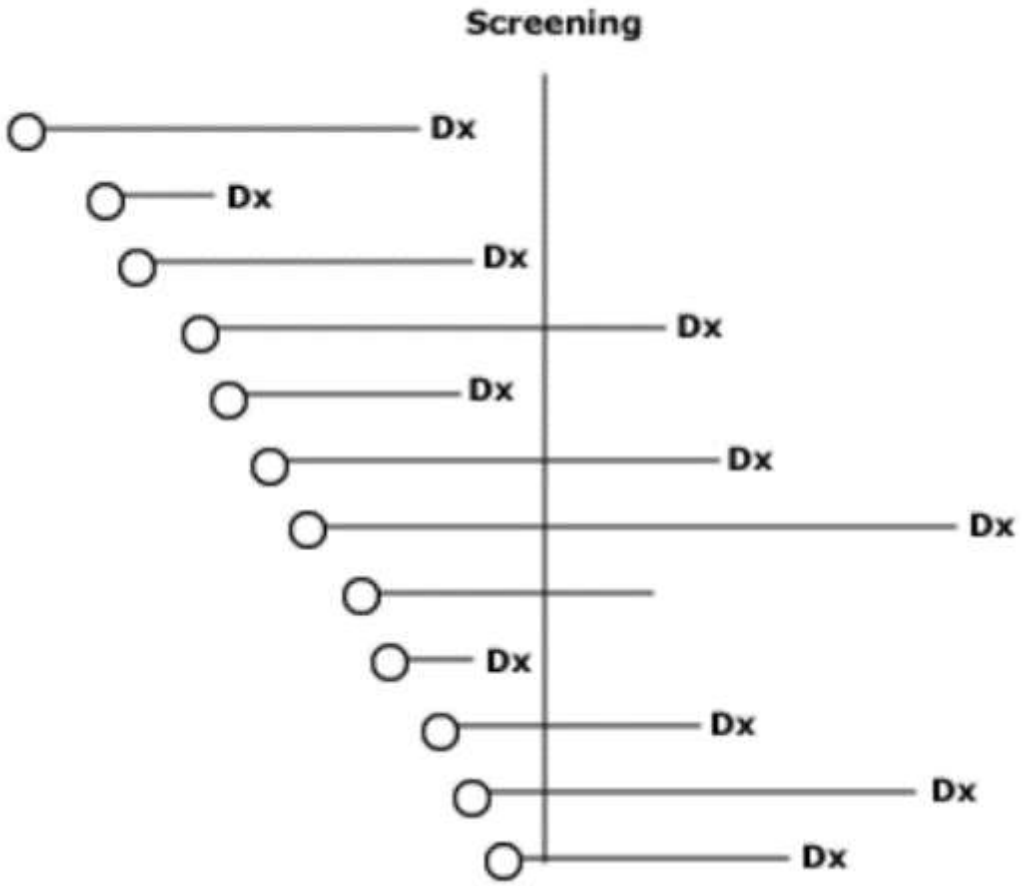
Lead time bias



- Dx of disease is made earlier in the screened group
- However, time of death is the same in both groups
- This results in an apparent increase in survival time

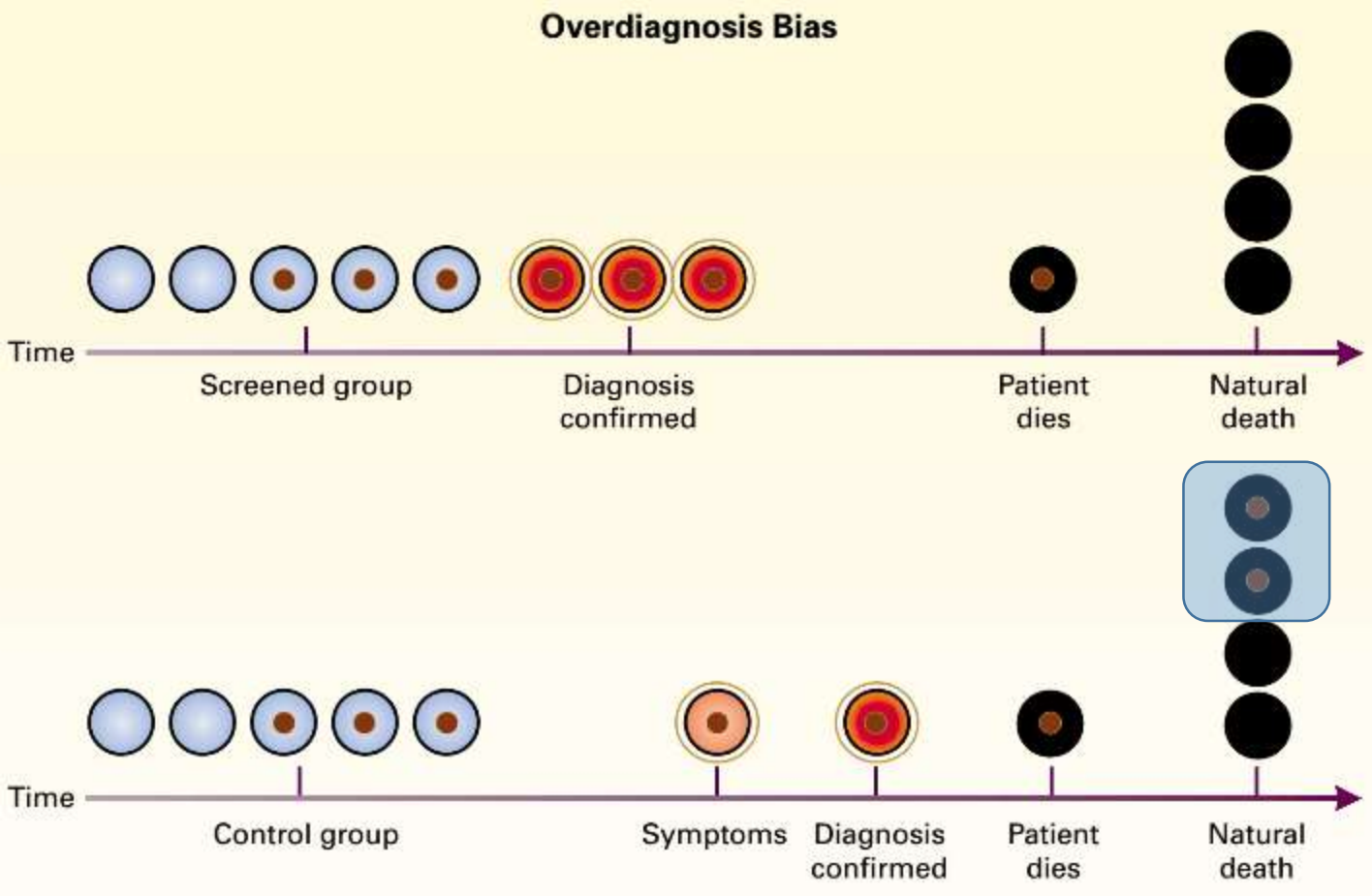
N Engl J Med. 2000 Nov 30;343(22):1627-33

Length-time bias



- Aggressive tumors that progress rapidly from onset (O) to symptoms and diagnosis (Dx) are less likely to be detected during a screening examination
- Indolent tumors have a longer potential screening period and are more likely to be detected
- As a result, a higher proportion of indolent tumors is found in the screened group, causing an apparent improvement in survival

Overdiagnosis bias



- Overdiagnosis is the detection of disease that, in the absence of screening, would never have been diagnosed
- An extreme form of length-time bias which occurs in very indolent tumors
- Screening produces an apparent increases in the number of cases of lung cancer (3 vs 1) and survival (1/3 vs 0/1)
- Actually, no effect on mortality (Two patients in the control group died with undiagnosed lung cancer)

N Engl J Med. 2000 Nov 30;343(22):1627-33

Overdiagnosis in lung cancer screening trials

Table 5. Cumulative lung cancer cases in the Mayo Lung Project (MLP) by study arm and follow-up time and by study arm and year of diagnosis*

	Intervention arm ($n = 491$), No.	Usual-care arm ($n = 422$), No.	Difference in cumulative No. of lung cancer cases
Follow-up time, years†			
5	132	88	44
10	256	204	52
15	338	276	62
20	425	360	65
25	486	418	68
27	491	422	69

- MLP was an RCT comparing lung cancer screening with CXR & sputum cytology every 4M (intervention) vs annually (control)
- Found no difference in mortality but more lung cancers were diagnosed in the intervention arm
- The number of cases of lung cancer in both control and intervention groups should have equalized over time, as cancers in the control group become clinically apparent
- Persistence of excess lung cancer in the screened group compared to controls in the extended follow-up suggests overdiagnosis

J Natl Cancer Inst. 2006 Jun 7;98(11):748-56

Stage shift

- Screening should increase detection of early-stage cancer
- Early detection and Rx of these early-stage cancers should cause a decrease in late-stage cancers
- If not, this could amount to overdiagnosis by the screening test

Volunteer bias

- Study volunteers may not be representative of the general population
- Subjects may volunteer because they are overly health-conscious or when they know that they are at an increased risk of a disease
- PLCO trial participants were better educated, more physically active, more likely to be married, and less likely to be current smokers (Compared to the general US population)
- NLST participants were younger, had a higher level of education, and were more likely to be former smokers (Compared to a US census survey of tobacco use who met NLST criteria)

Am J Epidemiol 2007;165:874–881
N Engl J Med 2011;365:395-409

Screening test: Which outcome measure to use?

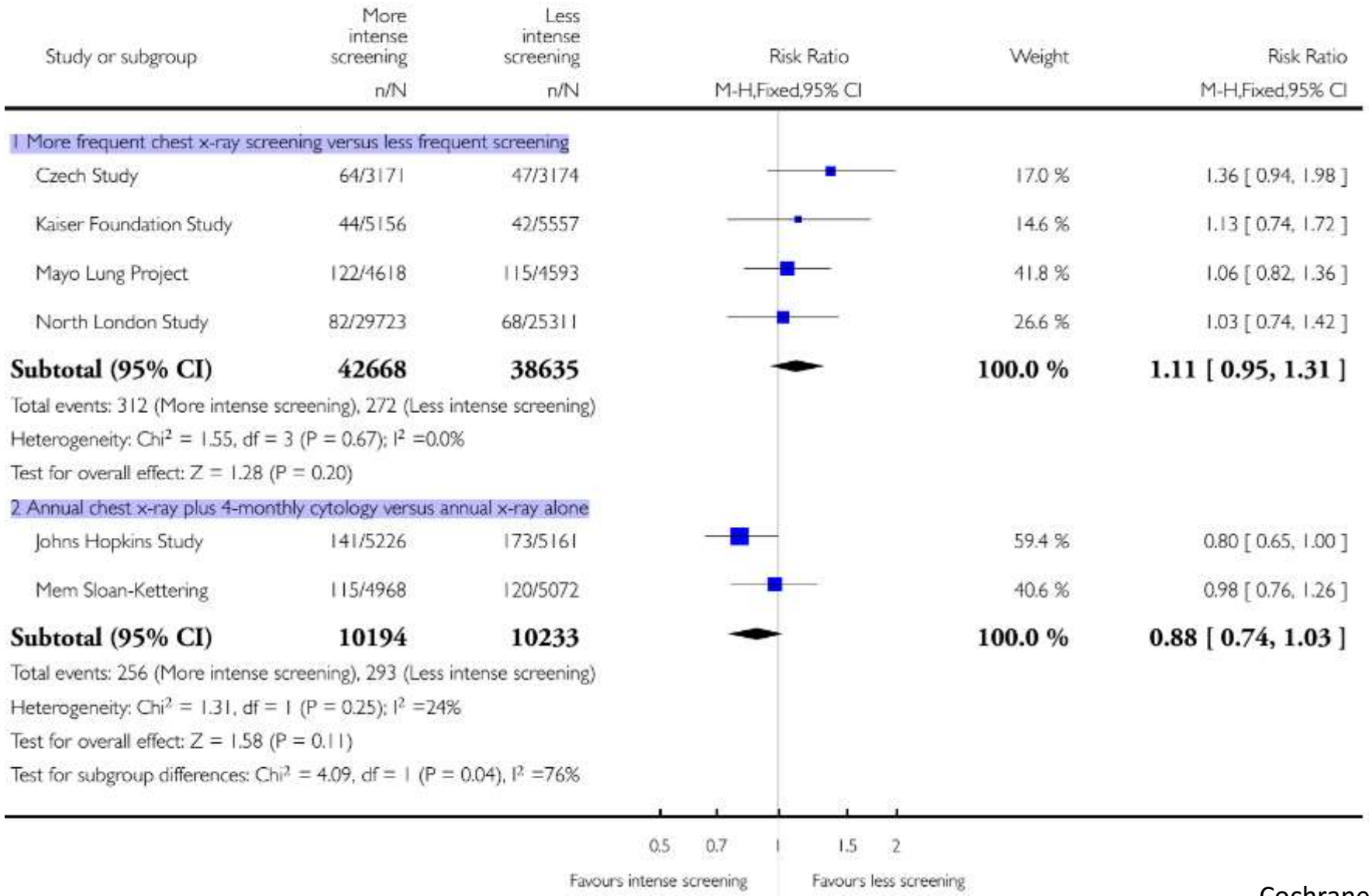
- Cancer detection rates
- **Stage at detection**
- Survival
- **Disease-specific mortality**
- **Overall mortality**

CXR

Simple & cheap. But, effective?

Comparison: 1 Lung cancer screening with chest radiography +/- sputum cytology versus less intense screening

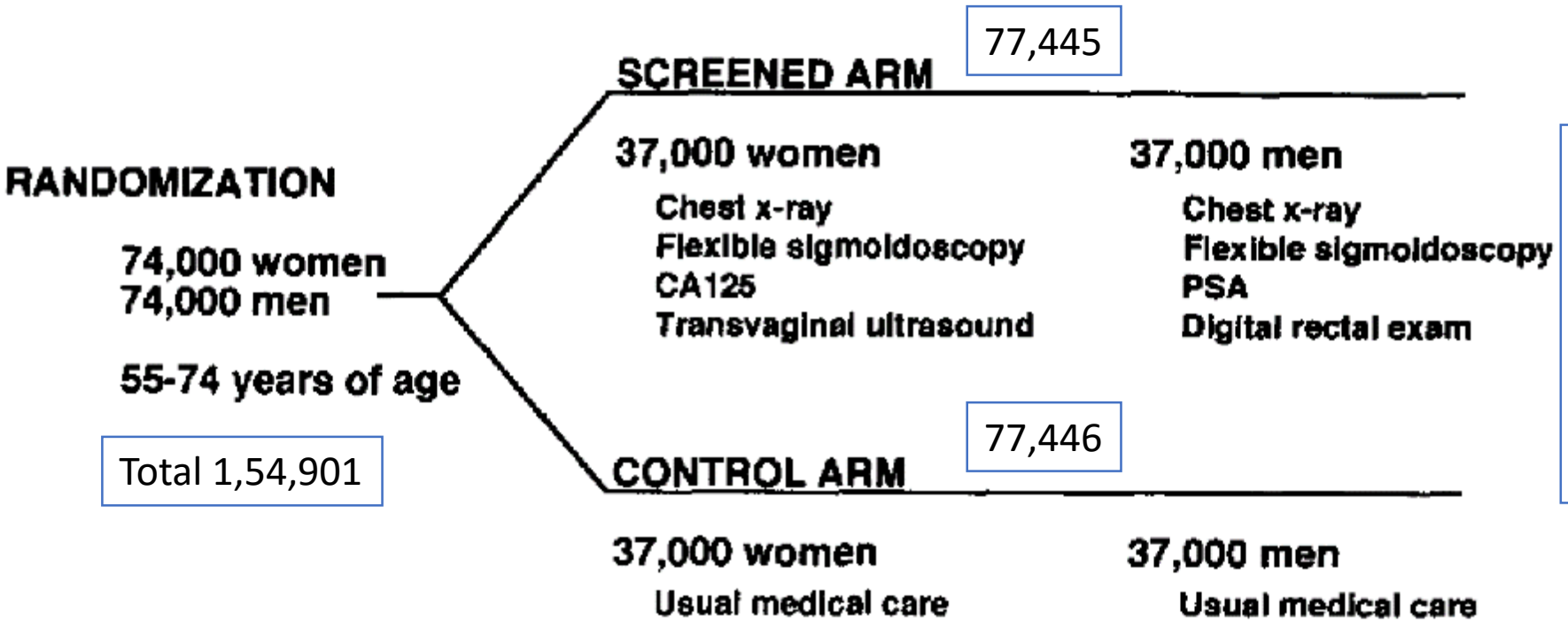
Outcome: 1 Lung cancer mortality



Cochrane Database Syst Rev. 2013 Jun 21;6:CD001991

Screening by Chest Radiograph and Lung Cancer Mortality

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial



- Annual CXRs for 3 years
- Follow-up: at least 13 years from randomization
- Because PLCO was a screening trial for multiple cancers, there was no eligibility requirement concerning smoking

JAMA. 2011;306(17):1865-1873
Control Clin Trials. 2000 Dec;21(6 Suppl):273S-309S

PLCO: Results

Comparison: 2 Annual chest x-ray screening versus usual care (no regular screening)

Outcome: 2 Lung cancer mortality at 13 years of follow up

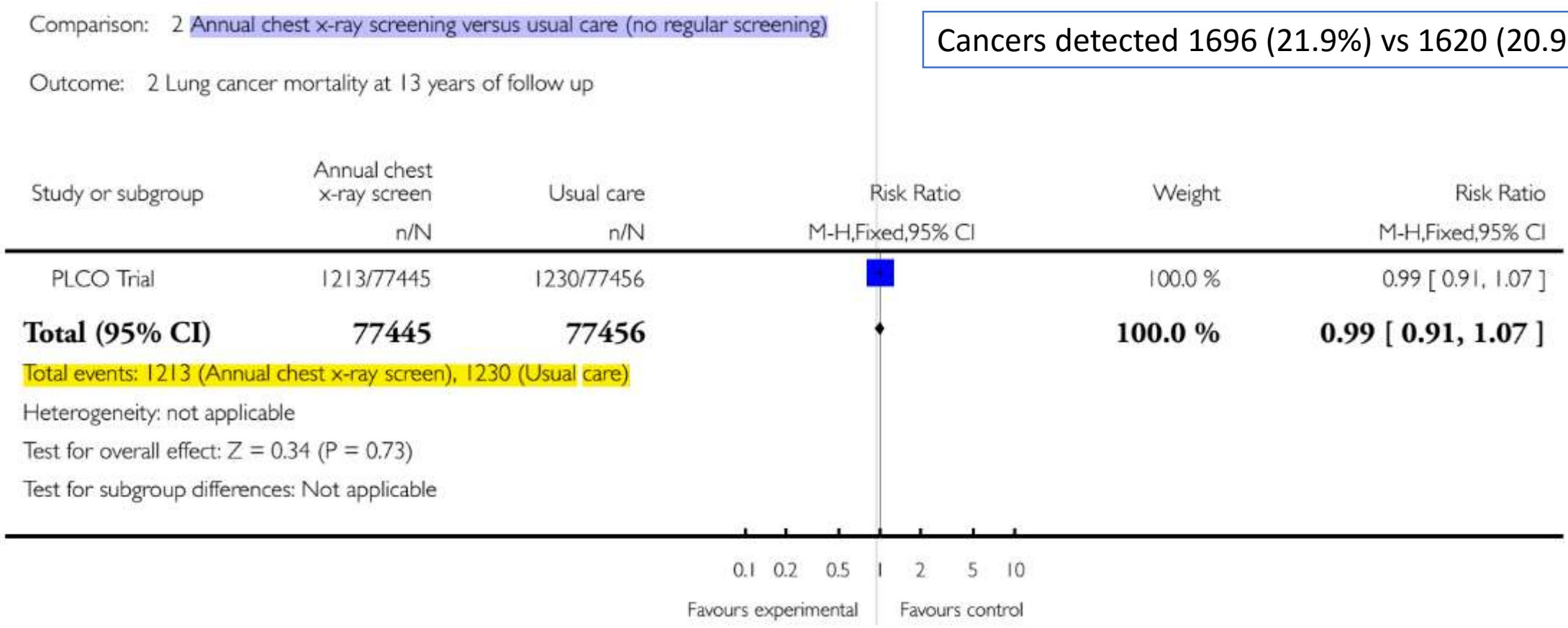
Study or subgroup	Annual chest x-ray screen n/N	Usual care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
PLCO Trial	1213/77445	1230/77456		100.0 %	0.99 [0.91, 1.07]
Total (95% CI)	**77445**	**77456**		**100.0 %**	**0.99 [0.91, 1.07]**

Total events: 1213 (Annual chest x-ray screen), 1230 (Usual care)

Heterogeneity: not applicable

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable



Cancers detected 1696 (21.9%) vs 1620 (20.9%)

Analysis of the subgroup of PLCO participants who met the NLST criteria for age and smoking history did not show a mortality benefit

Cochrane Database Syst Rev. 2013 Jun 21;6:CD001991

ACCP 2013: Screening for Lung Cancer

- In patients at risk for developing lung cancer, screening for lung cancer with chest radiograph (CXR) once or at regular intervals is not recommended (Grade 1A)

ACCP guidelines. Chest 2013; 143(5)(Suppl):e78S–e92S

Low-dose CT (LDCT)

TYPE OF EXAMINATION	EFFECTIVE DOSE (mSv)	NO. OF CHEST X-RAYS RESULTING IN SAME EFFECTIVE DOSE[a]
Radiography		
Skull AP or PA	0.015	1
Chest PA	0.013	1
L-spine AP	0.44	30
Abdomen AP	0.46	35
Pelvis AP	0.48	35
Mammography (4 views)[b]		
Screening	0.2	15
Dental radiography[c]		
Intraoral	0.013	1
Panoramic	0.012	1
Diagnostic fluoroscopy procedures		
Barium swallow[d]	1	70
Barium enema[d]	5	350
Angiography: cardiac[c]	7	500
CT[e]		
Head	2	150
Chest	10	750
Abdomen	10	750
Pelvis	7	500
Abdomen/pelvis	15	1100

Low-dose CT

- Acquisition variables during scanning chosen to reduce exposure to an average effective dose of **1.5 mSv** (NLST)
- 1 low-dose CT = Approximately 100 CXRs

CA Cancer J Clin 2012;62:75-100

LDCT: Scan parameters (NLST)

- Spiral CT scan obtained with a multi-channel helical CT scanner (minimum of four channels)
- X-ray tube voltage: 120-140 kVp
- X-ray tube-current time product: 40-80 mAs (Effective mAs: 20-60)
- Scan time: ≤ 1 second
- Collimation: 2.5mm (maximum effective slice thickness 3.2)
- Pitch: 1.25-2.0

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

NLST: Methodology

- Smokers aged 55-74 years with a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years were eligible
- Enrolment from August 2002 to April 2004; Screening from August 2002 to September 2007; Follow-up till December 31, 2009
- 53,454 persons were enrolled from 33 US medical centres:
  - 26,722 were randomly assigned to screening with LDCT and
  - 26,732 to screening with CXR-PA
- Annual screening at 0, 1 & 2 years

NLST: Classification of nodules on CT

Benign: Lesions with the following characteristics: calcification of central, rim, uniform, or other benign distribution; fat attenuation; linear morphology; and lesions documented to be stable for two or more years. The presence of micronodules < 4 mm diameter will be documented on screening CT but will not result in a positive screen.

Abnormal: Any new nodules > 10 mm diameter or enlarging nodules ≥ 7 mm diameter not satisfying criteria for benign or related to a clinically documented non-neoplastic process *(e.g., newly positive fungal serology, etc.)*. Nodule characteristics such as longest axial perpendicular diameters, margin *(spiculated, smooth, poorly defined, other)* and attenuation *(soft tissue, ground glass, mixed, fluid, etc.)* will be recorded.

Indeterminate: New solitary or multiple micronodules 4-10 mm diameter or enlarging nodules < 7 mm diameter.

Screening Result	Observation	Recommended Management
Negative	▪ No significant abnormalities ▪ Benign nodule*(s)* ▪ Noncalcified micronodule*(s)* < 4 mm ▪ Minor abnormalities, not suspicious for lung cancer	Continue annual screening CT
Negative	Significant abnormalities **not suggestive of cancer**	▪ Evaluation for condition unrelated to lung cancer *(Recommendations exceed the scope of trial)* ▪ Continue annual screening CT
Positive	▪ Nodule*(s)* 4 -10 mm diameter ▪ Enlarging nodules < 7 mm diameter ▪ Other suspicious change in nodule	▪ Repeat low dose helical CT or limited TSCT at 3, 6, (3 to 6), 12, or 24 months from the date of the [+] screening CT, depending upon lesion size and level of suspicion for lung cancer
Positive	▪ Nodule*(s)* >10 mm diameter ▪ Enlarging nodules ≥ 7 mm diameter ▪ Other suspicious change in nodule ▪ Mass ▪ Nonspecific findings suspicious for lung cancer	Additional diagnostic tests, which may include: ▪ Repeat low dose helical CT or limited thin-section CT of nodule*(s)* at 3, 6, (3 to 6), 12, or 24 months, depending upon lesion size and level of suspicion for lung cancer ▪ Diagnostic chest CT with nodule densitometry pre- and post-contrast administration ▪ FDG-PET or Technetium-99m depreotide scintigraphy ▪ Biopsy (percutaneous, bronchoscopic, thoracoscopic, open, etc.) ▪ Other, specify

NLST: Results

Screening Round	Low-Dose CT				Chest Radiography			
	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality
			no. (% of screened)				*no. (% of screened)*	
T0	26,309	7191 (27.3)	2695 (10.2)	16,423 (62.4)	26,035	2387 (9.2)	785 (3.0)	22,863 (87.8)
T1	24,715	6901 (27.9)	1519 (6.1)	16,295 (65.9)	24,089	1482 (6.2)	429 (1.8)	22,178 (92.1)
T2	24,102	4054 (16.8)	1408 (5.8)	18,640 (77.3)	23,346	1174 (5.0)	361 (1.5)	21,811 (93.4)

Overall positivity 24.2% vs 6.9%

Positive results by LDCT more than 3-times that of CXR

NLST: Cancer detection by stage

Stage and Histologic Type	LDCT	CXR
	Total (N=1060)	Total (N=941)
	number/total	
Stage		
IA	416/1040 (40.0)	196/929 (21.1)
IB	104/1040 (10.0)	93/929 (10.0)
IIA	35/1040 (3.4)	32/929 (3.4)
IIB	38/1040 (3.7)	42/929 (4.5)
IIIA	99/1040 (9.5)	109/929 (11.7)
IIIB	122/1040 (11.7)	122/929 (13.1)
IV	226/1040 (21.7)	335/929 (36.1)

LDCT: NLST

Comparison: 3 Annual low dose CT screening versus annual chest x-ray

Outcome: 1 Lung cancer mortality

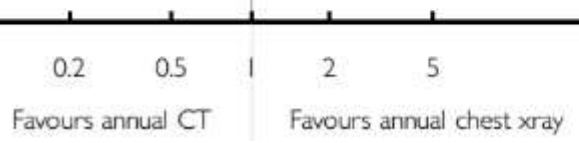
Study or subgroup	Annual ow dose CT n/N	Annual chest x-ray n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
North American NLST	356/26722	443/26732		100.0 %	0.80 [0.70, 0.92]
Total (95% CI)	**26722**	**26732**		**100.0 %**	**0.80 [0.70, 0.92]**

Total events: 356 (Annual ow dose CT), 443 (Annual chest x-ray)

Heterogeneity: not applicable

Test for overall effect: Z = 3.09 (P = 0.0020)

Test for subgroup differences: Not applicable



20% reduction in relative risk of death due to lung ca

Cochrane Database Syst Rev. 2013 Jun 21;6:CD001991

Table 3. Diagnostic Follow-up of Positive Screening Results in the Three Screening Rounds.*

Variable	Low-Dose CT				Chest Radiography			
	T0	T1	T2	Total	T0	T1	T2	Total
	number (percent)							
Total positive tests	7191 (100.0)	6901 (100.0)	4054 (100.0)	18,146 (100.0)	2387 (100.0)	1482 (100.0)	1174 (100.0)	5043 (100.0)
Lung cancer confirmed	270 (3.8)	168 (2.4)	211 (5.2)	649 (3.6)	136 (5.7)	65 (4.4)	78 (6.6)	279 (5.5)
Lung cancer not confirmed†	6921 (96.2)	6733 (97.6)	3843 (94.8)	17,497 (96.4)	2251 (94.3)	1417 (95.6)	1096 (93.4)	4764 (94.5)
Positive screening results with complete diagnostic follow-up information	7049 (100.0)	6740 (100.0)	3913 (100.0)	17,702 (100.0)	2348 (100.0)	1456 (100.0)	1149 (100.0)	4953 (100.0)
Any diagnostic follow-up	6369 (90.4)	3866 (57.4)	2522 (64.5)	12,757 (72.1)	2176 (92.7)	1078 (74.0)	957 (83.3)	4211 (85.0)
Clinical procedure	5089 (72.2)	3190 (47.3)	2151 (55.0)	10,430 (58.9)	1414 (60.2)	723 (49.7)	658 (57.3)	2795 (56.4)
Imaging examination	5717 (81.1)	2520 (37.4)	2009 (51.3)	10,246 (57.9)	2010 (85.6)	968 (66.5)	906 (78.9)	3884 (78.4)
Chest radiography	1284 (18.2)	613 (9.1)	650 (16.6)	2,547 (14.4)	867 (36.9)	381 (26.2)	365 (31.8)	1613 (32.6)
Chest CT	5153 (73.1)	2046 (30.4)	1608 (41.1)	8,807 (49.8)	1546 (65.8)	745 (51.2)	712 (62.0)	3003 (60.6)
FDG PET or FDG PET–CT	728 (10.3)	350 (5.2)	393 (10.0)	1,471 (8.3)	179 (7.6)	105 (7.2)	113 (9.8)	397 (8.0)
Percutaneous cytologic examination or biopsy	155 (2.2)	74 (1.1)	93 (2.4)	322 (1.8)	83 (3.5)	37 (2.5)	52 (4.5)	172 (3.5)
Transthoracic	120 (1.7)	60 (0.9)	74 (1.9)	254 (1.4)	67 (2.9)	31 (2.1)	43 (3.7)	141 (2.8)
Extrathoracic	39 (0.6)	17 (0.3)	24 (0.6)	80 (0.5)	20 (0.9)	6 (0.4)	13 (1.1)	39 (0.8)
Bronchoscopy	306 (4.3)	178 (2.6)	187 (4.8)	671 (3.8)	107 (4.6)	56 (3.8)	62 (5.4)	225 (4.5)
With neither biopsy nor cytologic testing	126 (1.8)	95 (1.4)	99 (2.5)	320 (1.8)	45 (1.9)	19 (1.3)	32 (2.8)	96 (1.9)
With biopsy or cytologic testing	194 (2.8)	95 (1.4)	102 (2.6)	391 (2.2)	74 (3.2)	40 (2.7)	36 (3.1)	150 (3.0)
Surgical procedure	297 (4.2)	197 (2.9)	219 (5.6)	713 (4.0)	121 (5.2)	51 (3.5)	67 (5.8)	239 (4.8)
Mediastinoscopy or mediastinotomy	60 (0.9)	32 (0.5)	25 (0.6)	117 (0.7)	22 (0.9)	12 (0.8)	21 (1.8)	55 (1.1)
Thoracoscopy	82 (1.2)	56 (0.8)	96 (2.5)	234 (1.3)	22 (0.9)	11 (0.8)	20 (1.7)	53 (1.1)
Thoracotomy	197 (2.8)	148 (2.2)	164 (4.2)	509 (2.9)	96 (4.1)	44 (3.0)	44 (3.8)	184 (3.7)
Other procedures	168 (2.4)	96 (1.4)	63 (1.6)	327 (1.8)	55 (2.3)	33 (2.3)	34 (3.0)	122 (2.5)

11.6% of false +ve

NLST: Complications after invasive procedures

	Lung Ca confirmed	Lung Ca not confirmed	Total
LDCT			
+ve screening tests with invasive diagnostic test*	618	457	1075
At least one complication	179 (30%)	44 (9.6%)	323 (30.5%)
CXR			
+ve screening tests with invasive diagnostic test*	264	115	379
At least one complication	64 (24.2%)	8 (7%)	72 (20%)

*Not all patients who underwent invasive diagnostic procedures had full diagnostic information. Hence the numbers shown here are lower than the actual number of patients who underwent invasive diagnostic procedures

NLST

	T0	T1	T2
Sensitivity	93.8%	94.4%	93%
Specificity	73.4%	72.6%	83.9%
PPV	3.8%	2.4%	5.2%
NPV	99.9%	99.9%	99.9%

N Engl J Med 2013;368:1980-91
N Engl J Med 2013;369:920-31

NLST: Overall

	Lung Ca +	Lung Ca -	
LDCT +	649 (True +ve 3.6%)	17497 (False +ve 96.4%)	18146
LDCT -	44 (False –ve 0.5%)	8532 (True –ve 99.5%)	8576
	693	26029	26722

- Sensitivity = TP/TP+FN = (649/693) = 93.7%
- Specificity= TN/TN+FP = (8532/26029) = **32.8%**
- PPV = TP/TP+FP = (649/649+18146) = 3.58%
- NPV = TN/TN+FN = (8532/8576) = 99.5%

(due to decrease in true negatives during follow-up)

NLST: Are the results generalizable?

- NLST participants were younger, had a higher level of education, and were more likely to be former smokers: Community results may be different
- Current scanners more advanced than those used in NLST: Possibility of higher false positive rates
- Done in institutions with significant expertise in radiology, dx and Rx of cancer: May not be applicable in community setting

RCTs	Country	Enrolment	Screening	Follow-up	n	Age	Male	Smoking	Results
Garg 2002 (Feasibility study)	USA	2001	2 annual rounds	N/A	92 vs 98 (190)	50-80	97.4%	30 PY	+vity 33% at baseline
ITALUNG 2009 (Feasibility study)	Italy	2004-2006	4 annual rounds	N/A	1613 vs 1593 (3206)	55-69	64.7%	20 PY; Current/Quit <10y	+vity 30.3% at baseline
DLCST 2009	Denmark	2004-2006	5 annual rounds	Till March 2010	2052 vs 2052 (4104)	50-70	55.2%	20 PY; Current/Quit <10y	LC 69 vs 24; P = 0.002 Stage I-IIB 47 (2.3%) vs 7 (0.3%) Advanced 19 (0.9%) vs 10 (0.5%) LC mortality 15 (0.7%) vs 11 (0.5%); P=NS
DANTE 2009	Italy	2001-2006	5 annual rounds	Till Jan 2008 (Median 33.7M)	1276 vs 1196 (2472)	60-74	100%	20 PY	LC 60 (4.7%) vs 34 (2.8%); P=0.016 Stage I 33 (2.6%) vs 12 (1%); P=0.004 Stage IIIB, IV 17 (1.3%) vs 17 (1.4%) P=NS LC mortality 20 (1.6%) vs 20 (1.7%); P=NS
NELSON (Final results awaited)	Netherlands & Belgium	2004-2006	3 rounds at years 0, 1, 3	10 years	7907 vs 7915 (15,822)	50-74	84%	>15 cig/d for >25y >10 cig/d for >30y Current/Quit <10y	Overall +vity 2.7% vs N/A LC 127 (1.6% vs N/A)
MILD 2012	Italy	2005-2011	Annual Biennial	Till Nov 2011	1190 annual, 1186 bi vs 1723 (4099)	>48	66%	20 PY; Current/Quit <10y	LC 34 vs 25 vs 20 (P=0.04) Stage I, II: 15 (75%) vs 20 (69%) vs 35 (71.4%) Stage III, IV: 5 (25%) vs 9 (31%) vs 14 (28.6%) LC mortality 12 vs 6 vs 7 (P=NS)
LSS 2005 (Pilot trial for NLST)	USA	2000	2 annual rounds	None	1660 vs 1658 (3318)	55-74	59%	30 PY; Current/Quit <10y	+vity 25.8% vs 8.7% at 1 year
Depiscan 2007 (Pilot trial)	France	2002-2004	3 annual rounds	None	385 vs 380 (765)	50-75	71%	>15 cig/d for >20y; Current/Quit <15y	+vity 45.2% vs 7.4% at baseline
NLST 2011	USA	2002-2004	3 annual rounds	Till 2009 (Mean 6.9y, Max 7.4y)	26,722 vs 26,732 (53,454)	55-74	59%	30 PY; Current/Quit <15y	LC 1060 (4%) vs 941 (3.5%) Stage I, II: 55.9% vs 38.6% Stage IV: 21.7% vs 36.1% LC mortality 356 (1.3%) vs 443 (1.7%)

Red = LDCT vs No screening; Blue = LDCT vs CXR

Nodule detection: High false positive rates

Source	No. Screened	Adherence, %[a]	Round of Screening[b]	No. of Participants (%)				
				Noncalcified Lung Nodules Over Study Threshold[c]	Lung Cancer Nodules	Benign Nodules	Nodules Not Lung Cancer	Diagnosed With Lung Cancer Over Entire Study Period[d]
LDCT vs Usual Care (No Screening)								
NELSON,[18] 2009	7557	95	Baseline	1570 (21)	70 (0.9)	1500 (20)	1500 (96)	124 (1.6)
	7289	92	Year 1	570 (8)	54 (0.7)	516 (7)	516 (91)	
DLCST,[19,20] 2009	2047	100	Baseline	179 (9)	17 (0.8)	162 (8)	162 (91)	70 (3.4)
	1976	96	Year 1	NR	11 (0.6)	NR	NR	
	1944	95	Year 2	NR	13 (0.7)	NR	NR	
ITALUNG,[21] 2009	1406	87	Baseline	426 (30)	20 (1.5)	406 (29)	406 (95)	20 (1.5)
DANTE,[22] 2009	1276	91	Baseline	226 (18)	47 (3.7)	179 (14)	179 (79)	60 (4.7)
Garg et al,[16] 2002	92	100	Baseline	3 (3)	2 (2.2)	1 (1)	1 (33)	2 (2.2)
LDCT vs Chest Radiographs								
NLST,[23,24] 2011	26 309	98	Baseline	6561 (25)	270 (1.0)	6291 (24)	6291 (96)	1060 (4.0)
	24 715	92	Year 1	6901 (28)	168 (0.6)	6733 (27)	6733 (98)	
	24 102	90	Year 2	4054 (17)	211 (0.9)	3843 (16)	3843 (95)	
LSS,[25,26] 2005	1629	96	Baseline	316 (19)	30 (1.8)	286 (18)	286 (91)	40 (2.5)
	1398	86	Year 1	360 (26)	8 (0.6)	352 (25)	352 (98)	
Dépiscan,[27] 2007	336	87	Baseline	81 (24)	7 (2.4)	74 (22)	74 (91)	8 (2.4)

JAMA. 2012;307(22)

Follow-up imaging/invasive procedures

Source	No. Randomized	No. of Screened Group Participants (%)						
		Had Nodules at Baseline	Additional Diagnostic CT	Additional PET	Nonsurgical Biopsy/Procedure		Surgical Biopsy/Procedure	
					Had Procedure	Benign Result	Had Procedure	Benign Result
LDCT vs Usual Care (No Screening)								
NELSON,[18] 2009	15 822[a]	1570 (21)	NR	0	257 (3.4)	138 (54)	153 (2.0)	45 (30)
DLCST,[20] 2009	4104	179 (9)	NR	NR	NR[b]	NR[b]	25 (1.2)[b]	8 (32)[b]
ITALUNG,[21] 2009	3206	426 (30)	NR	59 (4.2)	16 (1.1)	1 (6)	16 (1.1)	1 (6)
DANTE,[22] 2009	2811[c]	226 (18)	NR	57 (4.5)	NR	NR	72 (5.6)	17 (24)
Garg et al,[16] 2002	190	3 (3)	3 (3.3)	NR	NR	NR	NR	NR
LDCT vs Chest Radiographs								
NLST,[23] 2011	53 454	6561 (25)	8807 (33)	1471 (5.5)	402 (1.5)	293 (73)	673 (2.6)	164 (24)
LSS,[25,26] 2005	3318	316 (19)	NR	NR	NR[b]	NR[b]	30 (3.3)[b]	23 (43)[b]
Dépiscan,[27] 2007	765	81 (24)	NR	NR	3 (0.9)	NR	9 (2.7)	4 (45)

NR = Not reported

JAMA. 2012;307(22)

RCTs with data on lung cancer mortality

Source	Compared With	No. of Participants Screened or Followed Up		Median Follow-up, mo	*P* Value on End Point	Mortality Events, No. (%)	
		LDCT	Control			LDCT	Control
All-Cause Mortality							
DANTE,[22] 2009	Usual care	1276	1196	34	.84	46 (3.6)	45 (3.8)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.02	1877 (7.0)	2000 (7.5)
DLCST,[19] 2012	Usual care	2052	2052	58	.43	61 (3.0)	42 (2.0)
Lung Cancer–Specific Mortality							
DANTE,[22] 2009	Usual care	1276	1196	34	.83	20 (1.6)	20 (1.7)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.004	356 (1.3)	443 (1.7)
DLCST,[19] 2012	Usual care	2052	2052	58	.06	15 (0.7)	11 (0.5)
Mortality Not Due to Lung Cancer							
DANTE,[22] 2009	Usual care	1276	1196	34	.93	26 (2.0)	25 (2.1)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.51	1521 (5.7)	1557 (5.8)
DLCST,[19] 2012	Usual care	2052	2052	58	.08	46 (2.2)	31 (1.5)

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography.

MILD trial (2012) LC mortality: 12 vs 6 vs 7 (P=NS)

JAMA. 2012;307(22)

RCTs with data on lung cancer mortality: Relative risk

Source	Events, No. (%)		Rate of Events per 100 000 Person-years		Relative Risk (95% CI)	Rate Ratio	Absolute Difference, %	No. Needed to Screen to Prevent 1 Event
	LDCT	Control	LDCT	Control				
All-Cause Mortality								
DANTE,[22] 2009	46 (3.6)	45 (3.8)	NR	NR	0.97 (0.80-1.20)[a,b]	NR	0.2	635
NLST,[23] 2011	1877 (7.0)	2000 (7.5)	1303[b]	1395[b]	0.93 (0.86-0.99)	0.93[b]	0.5	219
DLCST,[19] 2012	61 (3.0)	42 (2.0)	NR	NR	1.19 (1.01-1.40)	NR	−1.0	NR
Lung Cancer–Specific Mortality								
DANTE,[22] 2009	20 (1.6)	20 (1.7)	NR	NR	0.97 (0.71-1.32)[a,b]	NR	0.1	954
NLST,[23] 2011	356 (1.3)	443 (1.7)	247	309	0.80 (0.73-0.93)	0.80[b]	0.3	320
DLCST,[19] 2012	15 (0.7)	11 (0.5)	NR	NR	1.15 (0.83-1.61)	NR	−0.2	NR
Mortality Not Due to Lung Cancer								
DANTE,[22] 2009	26 (2.0)	25 (2.1)	NR	NR	0.99 (0.75-1.30)[b]	NR	0.1[b]	1898[b]
NLST,[23] 2011	1521 (5.7)	1557 (5.8)	1056[b]	1086[b]	0.99 (0.95-1.02)[b]	0.97[b]	0.1[b]	755[b]
DLCST,[19] 2012	46 (2.2)	31 (1.5)	NR	NR	1.20 (1.00-1.44)[b]	NR	−0.7[b]	NR

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography; NR, not reported.
[a] Based on count data.
[b] Calculated by authors.

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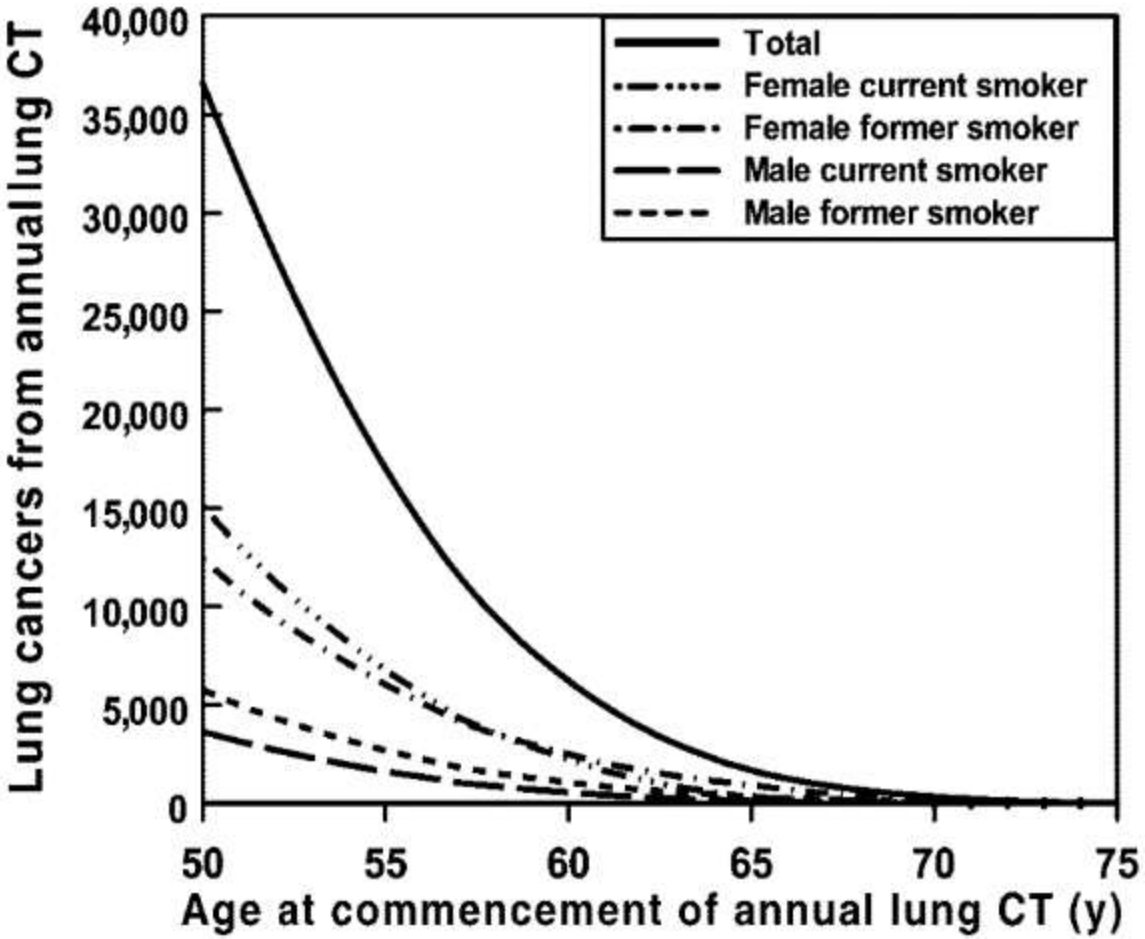
LDCT: Benefits & risks

Benefits	Risks
Reduced mortality from lung cancer	Radiation exposure
Reduced morbidity from lung cancer treatment	Overdiagnosis
Reduced morbidity and mortality from other diseases discovered incidentally (eg, chronic obstructive pulmonary disease, coronary artery calcification, extrapulmonary malignancy)	Risks associated with working up positive findings: either false positive or true positive
Increased awareness of harms of smoking	Potential for continued/renewed smoking behavior
Reduced anxiety when screen is negative	Increased anxiety from positive test results Financial costs of screening and subsequent evaluations False-negative test results

Radiol Clin N Am 52 (2014) 27–46

LDCT: Radiation risk



Radiology. 2004 May;231(2):440-5

- Radiation risk from LDCT calculated using the excess risk of lung cancer noted in the Japanese atomic bomb survivors exposed to similar amounts of radiation
- If 50% of all current and former smokers in the U.S. population aged 50 –75 years received annual CT screening (NLST dose), the estimated number of lung cancers associated with radiation from screening would be approximately 36,000, a **1.8% increase** over the otherwise expected number
- Radiation exposure due to further imaging studies for false-positive findings not included in this calculation

Is the LDCT a suitable screening test?

- Does it have good sensitivity and specificity?
  - Good sensitivity, but poor specificity (high false positive rates)
- Does it detects disease at an early stage where effective Rx is available?
  - Yes
- How safe is it?
  - Radiation hazard of screening and subsequent imaging
  - Invasive procedures following false positive diagnoses
- Is it cost-effective?
  - Yet to be seen (Additional imaging/invasive procedures of false +ves to be taken into account)
- Is it affordable?
  - ? In Indian set-up
- Is it easily available?
  - ? In peripheral settings in India (esp. the expertise in radiology, and subsequent Dx & Rx)

	ACCP/ASCO 2013	USPSTF 2013	ALA 2012	NCCN 2012	AATS 2012	ACS 2013
Age group	55-74	55-80	55-74	55-74	55-79	55-74
Smoking status	Smokers/Former smokers who quit <15yrs with at least 30 pack-years	Smokers/Former smokers who quit <15yrs with at least 30 pack-years	30 pack-years	Smokers/Former smokers who quit <15yrs with at least 30 pack-years	30 pack-years	Smokers/Former smokers who quit <15yrs with at least 30 pack-years
Interval	Annual	Annual	Not mentioned	Annual for 3y/till 74y age	Annual	Annual
Comments	Only in settings that can deliver the comprehensive care provided in NLST	Discontinue screening when the patient has not smoked for 15 y	-	Additional recommendations for smokers with 20 pack-years*	Additional recommendations for Rx lung cancer and smokers with 20 pack-years**	Physician-patient discussion with informed, shared decision making
Level of evidence & Strength of recommendation	Grade 2B (Weak recommendation, moderate-quality evidence)	B recommendation (High certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial)		Category 1 (High level evidence and uniform consensus)	Level 1 (i.e RCTs)	-

*NCCN 2012 also recommends screening for those aged ≥50y with ≥20 pack-years of smoking with one additional risk factor for lung cancer (Category 2: lower level of evidence with NCCN consensus)

**AATS 2012 (Additional recommendations)

- Annual lung cancer LDCT screening should be performed in patients who have been treated for a primary bronchogenic carcinoma and have completed 4 years of radiographic surveillance without evidence for recurrence (level 3 evidence i.e concensus)
- Patients aged 50 to 79 years with a 20 pack-year smoking history and other factors that produce a cumulative risk of developing lung cancer that is 5% or more over the following 5 years (level 2 evidence i.e non-randomized and case-control trials)

Table. **Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened***

Participant	Risk Factors	Deaths From Lung Cancer (Without Screening) per 1000 Persons, *n*	Deaths From Lung Cancer (With Screening) per 1000 Persons, *n*	Lung Cancer Deaths Averted per 1000 Persons, *n*	Persons Needed to Be Screened Annually for 3 y to Prevent 1 Death From Lung Cancer Over 6 y, *n*
"Typical" participant in the NLST	62-year-old male current 1.5-PPD smoker for 35 y	19.5	15.6	3.9	256
Minimum eligible participant in the NLST	55-year-old female former 1-PPD smoker for 30 y who just quit	4.0	3.2	0.8	1236
High-risk participant eligible for the NLST	70-year-old current 2-PPD smoker for 55 y	60.9	48.7	12.2	82
Minimum eligible participant by NCCN guidelines	50-year-old male former 1-PPD smoker for 20 y who quit 10 y ago with an occupational asbestos exposure history	1.6	1.3	0.3	3180
Low-risk eligible participant for Sequoia Hospital lung screening program	40-year-old female former 1-PPD smoker for 10 y who quit 15 y ago	0.10	0.08	0.02	35 186

NCCN = National Comprehensive Cancer Network; NLST = National Lung Screening Trial; PPD = packs per day.
* Assuming the program includes 3 y of annual screening.

Ann Intern Med. 2012 Oct 16;157(8):571-3

Indian scenario

No data on lung cancer screening (incl. LDCT screening) available from India

- Extrapolation of results difficult
  - Cultural & economic differences
  - Difference in health care resources/setting
- Variable priorities
  - Infective diseases vs Cancer
  - Smoking cessation vs screening

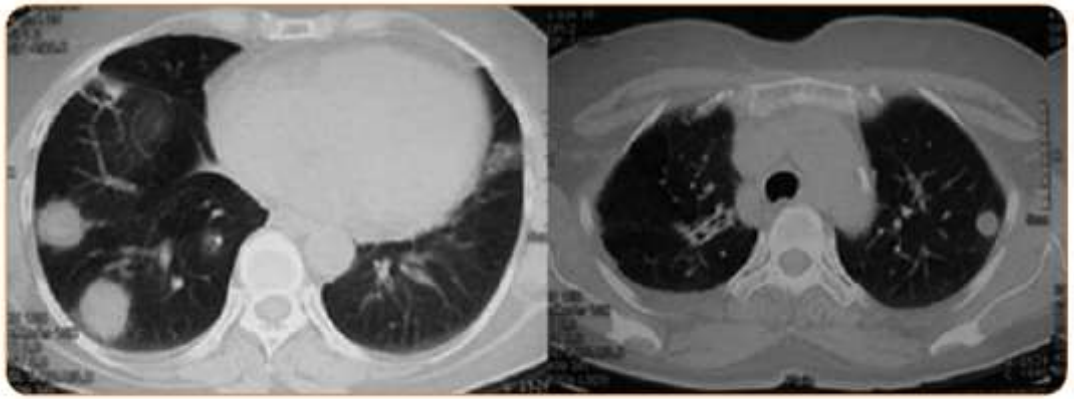


Figure 3: CT scan of a 62 years non-smoker female showing multiple and bilateral nodular opacities in right lower and left upper lobe which turned out to be pulmonary tuberculosis on histopathological examination done on CT guided biopsy

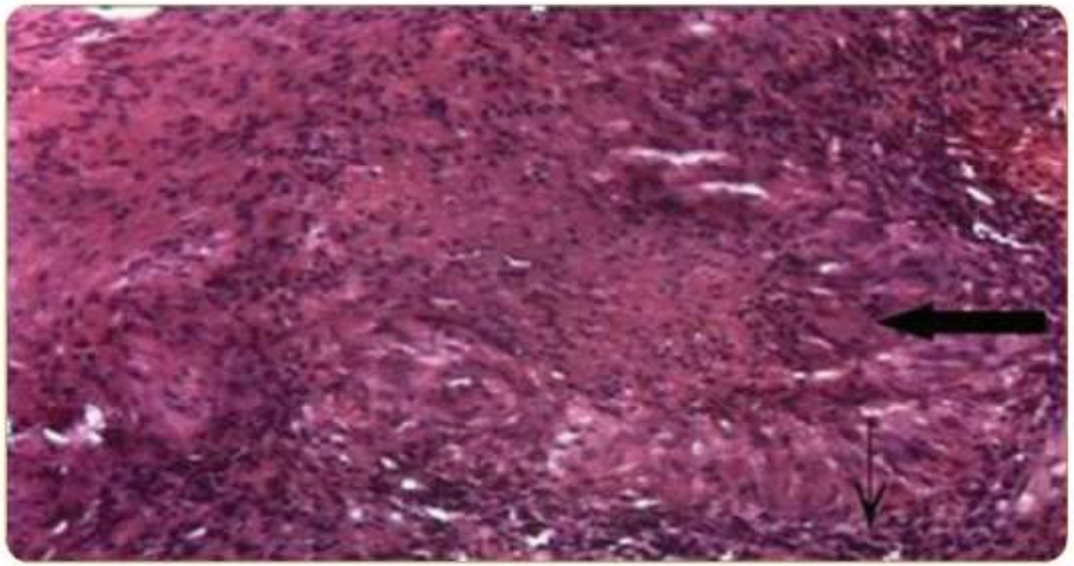


Figure 4: CT guided biopsy of right lower lobe nodule of same patient (Figure 3) showing epitheloid granuloma with langhan's giant cell (thick arrow) and wall of epitheloid cells (small arrow) around a central area of necrosis

HRCT findings of patients with active and inactive pulmonary tuberculosis

Findings	*Active tuberculosis (n = 32)*		*Inactive tuberculosis (n = 34)*	
Centrilobular nodule and/or branching linear structure*	29	(91)	0	(0)
Tree-in-bud appearance*	23	(71)	0	(0)
Macronodule*	22	(69)	0	(0)
Cavity*	16	(50)	4	(12)
Consolidation*	14	(44)	0	(0)
Bronchial wall thickening	14	(44)	22	(65)
Interlobular septal thickening	10	(34)	3	(9)
Ground glass opacity*	12	(38)	4	(11)
Bronchiectasis	18	(56)	24	(71)
Emphysema*	14	(44)	28	(82)
Bronchovascular distortion*	20	(63)	32	(94)
Fibrotic changes*	21	(66)	34	(100)
Calcified mediastinal lymph node enlargement*	7	(22)	15	(44)
Parenchymal calcification	14	(44)	18	(53)
Pleural thickening or retraction	20	(63)	24	(71)
Lymphadenopathy (>10 mm)	5	(16)	0	(0)
Pleural effusion	2	(6)	0	(0)
Miliary nodules	1	(3)	0	(0)

Values in parentheses are percentages. (Macronodule = Nodule 5-8mm in diameter)
* $p<0{\cdot}05$.

Bhatt MLB et al. South Asian J Cancer. 2012 Jul-Sep; 1(1): 36–42
Thorax 1996;51:397-402

Disease Profile (2012): USA vs. India

United States of America

Population 2012 **318 million**

Estimates of TB burden * 2012	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	0.44 (0.39–0.48)	0.14 (0.12–0.15)
Mortality (HIV+TB only)	0.13 (0.11–0.19)	0.04 (0.03–0.06)
Prevalence (includes HIV+TB)	15 (6.5–27)	4.7 (2–8.4)
Incidence (includes HIV+TB)	11 (10–13)	3.6 (3.2–4.1)
Incidence (HIV+TB only)	1.1 (0.96–1.2)	0.35 (0.3–0.39)
Case detection, all forms (%)	87 (77–99)	

Mortality due to TB: 530
Mortality due to lung cancer: 1,67,545 (ASR 28.6)

India

| High TB burden | High HIV burden | High MDR-TB burden |

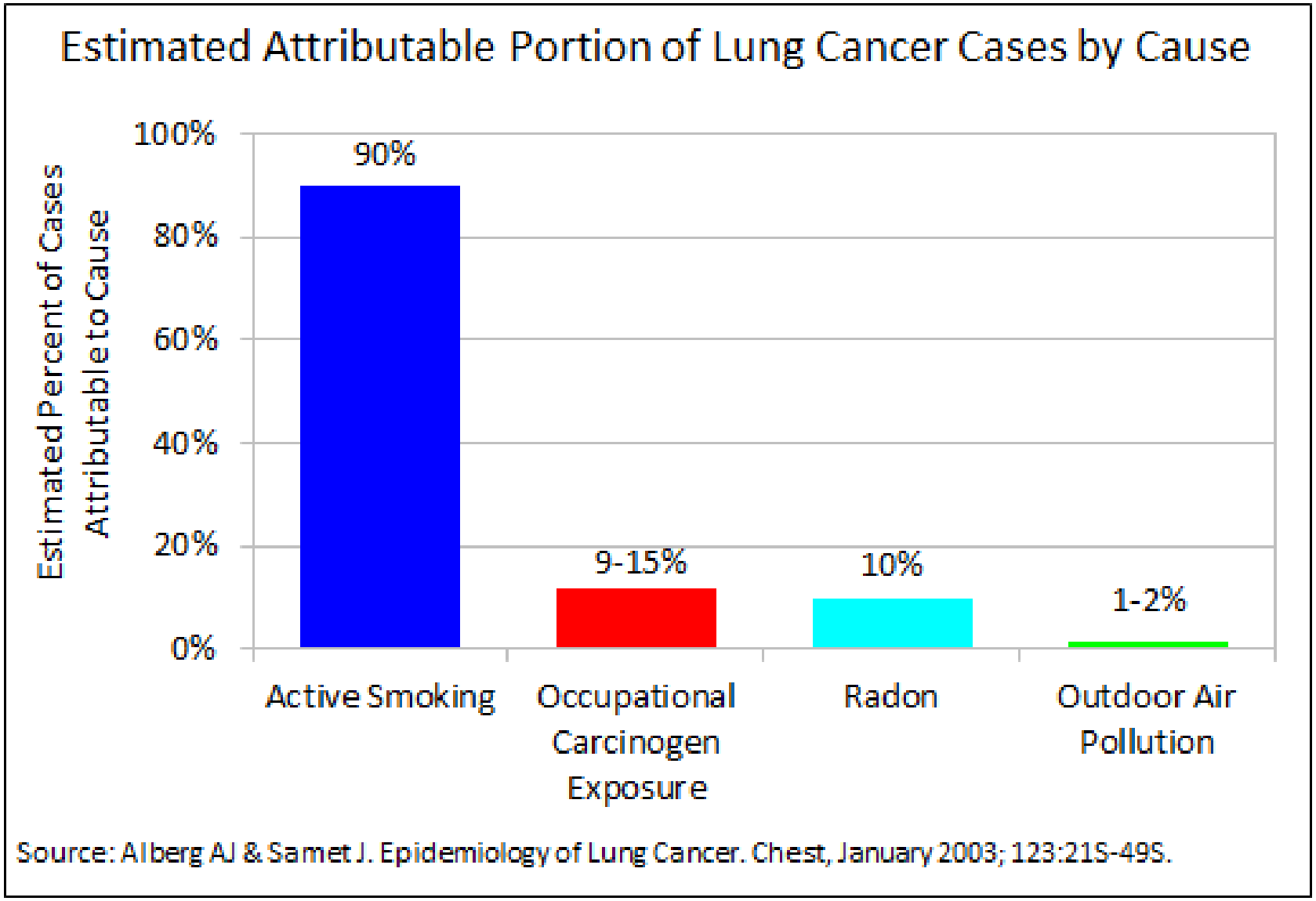
Population 2012 **1 237 million**

Estimates of TB burden * 2012	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	270 (170–390)	22 (14–32)
Mortality (HIV+TB only)	42 (37–48)	3.4 (3–3.9)
Prevalence (includes HIV+TB)	2 800 (1 900–3 900)	230 (155–319)
Incidence (includes HIV+TB)	2 200 (2 000–2 400)	176 (159–193)
Incidence (HIV+TB only)	130 (120–140)	10 (9.4–12)
Case detection, all forms (%)	59 (54–66)	

Mortality due to TB: 3,12,000
Mortality due to lung cancer: 63,759 (ASR 6.3)

ASR = Age-standardized rate per 100,000 population

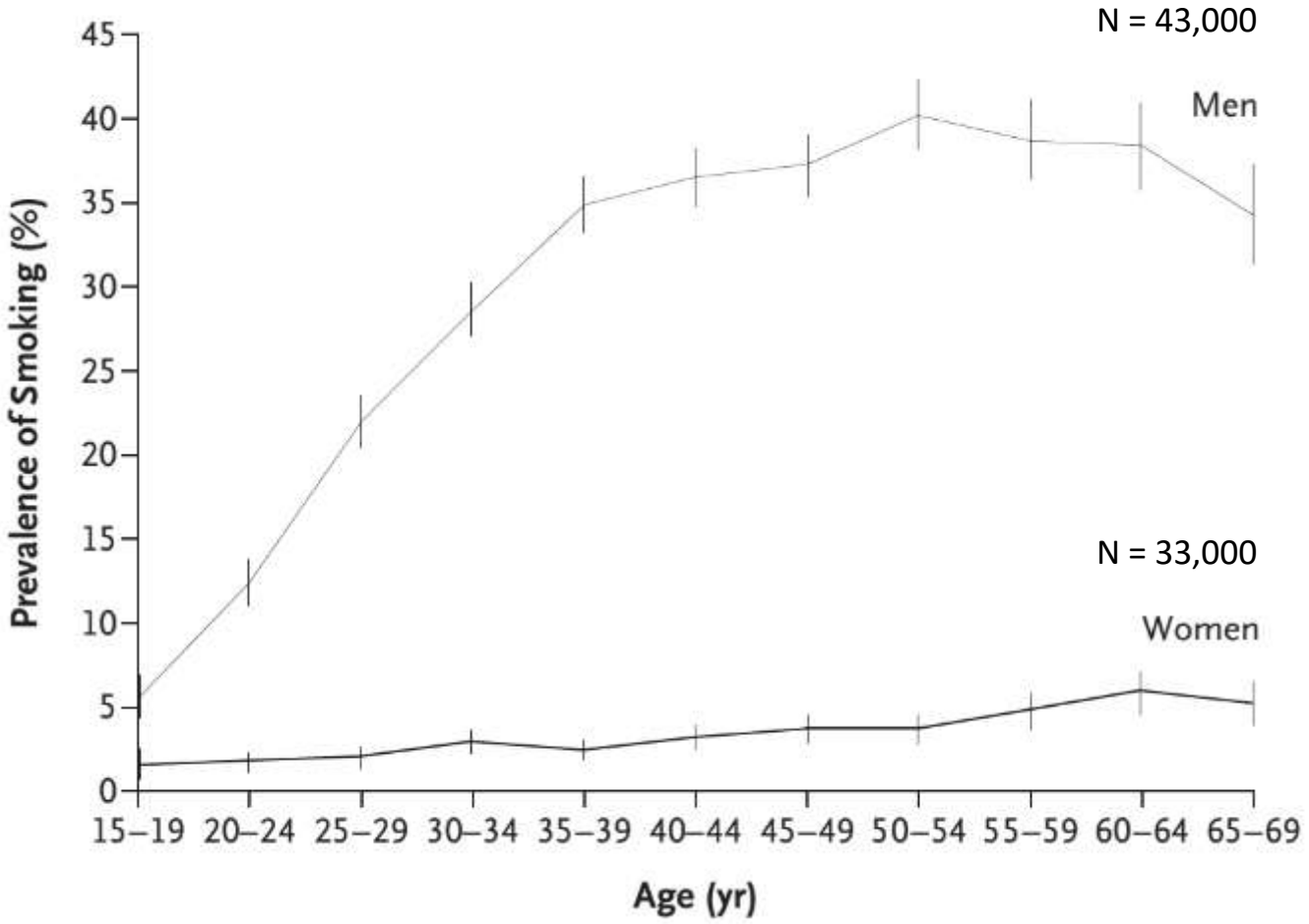
WHO Tuberculosis country profiles
GLOBOCAN 2012 (IARC)



"A single etiologic agent—cigarette smoking—is by far the leading cause of lung cancer, accounting for about 80% to 90% of lung cancer cases in countries where cigarette smoking is common"

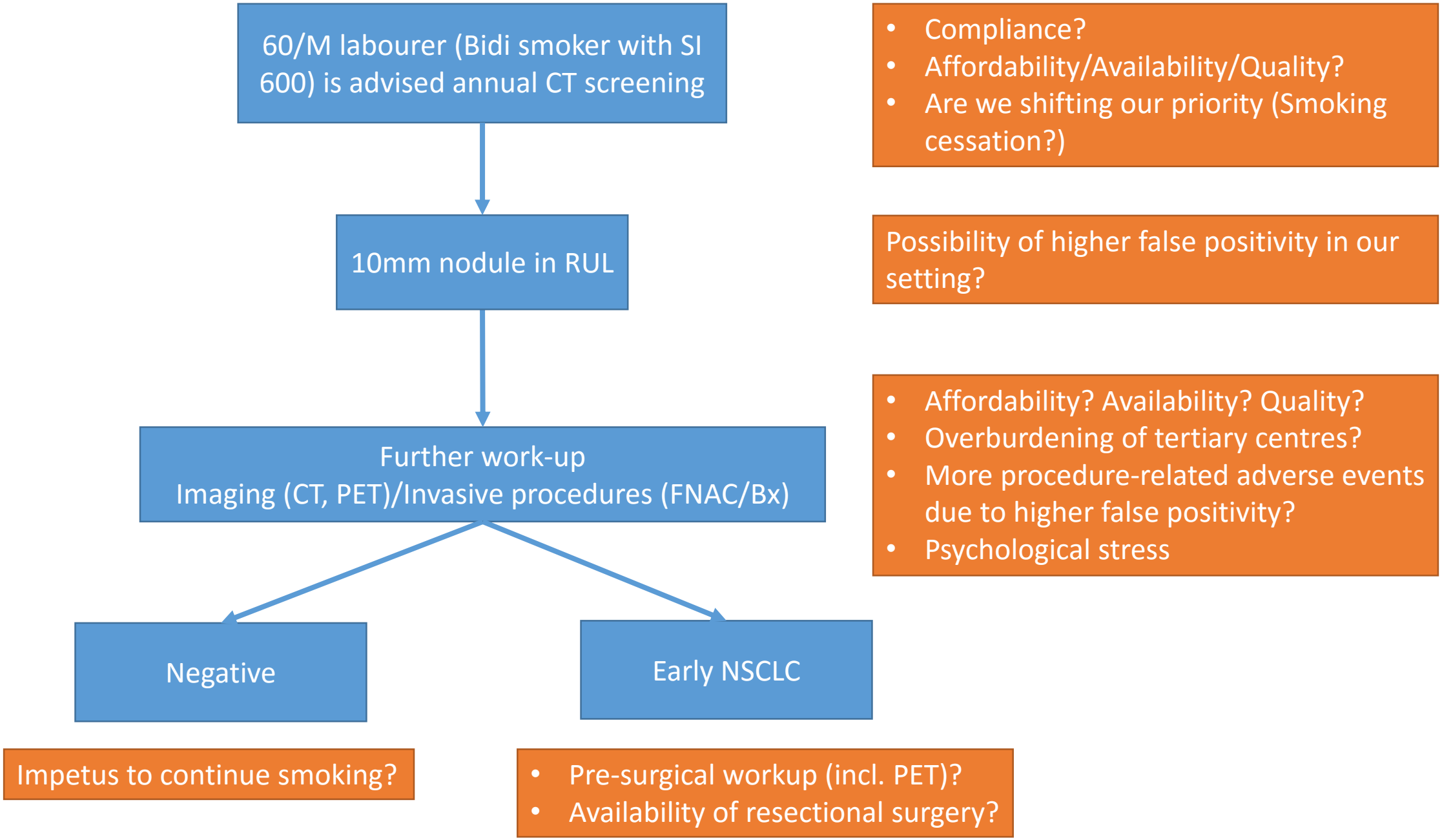
Chest 2013; 143(5)(Suppl):e1S–e29S

Prevalence of Smoking in India



- Study conducted in a nationally representative sample of 1.1 million homes in 6671 small areas chosen randomly from all parts of India
- Prevalence of smoking was **35 to 40%** for male subjects between the ages of 35 and 69 years

N Engl J Med 2008;358:1137-47


60/M labourer (Bidi smoker with SI 600) is advised annual CT screening
10mm nodule in RUL
Further work-up
Imaging (CT, PET)/Invasive procedures (FNAC/Bx)
Negative
Early NSCLC
Impetus to continue smoking?
Pre-surgical workup (incl. PET)?
Availability of resectional surgery?
Compliance?
Affordability/Availability/Quality?
Are we shifting our priority (Smoking cessation?)
Possibility of higher false positivity in our setting?
Affordability? Availability? Quality?
Overburdening of tertiary centres?
More procedure-related adverse events due to higher false positivity?
Psychological stress

Conclusion

- LDCT screening might be beneficial in selected individuals at high-risk of lung cancer
- Successful outcomes of LDCT in the western population cannot be extrapolated to the Indian population
- Efforts directed at smoking cessation rather than screening might prove to be more rewarding in our setting