Pulmonologist's Perspective

– Literature Review

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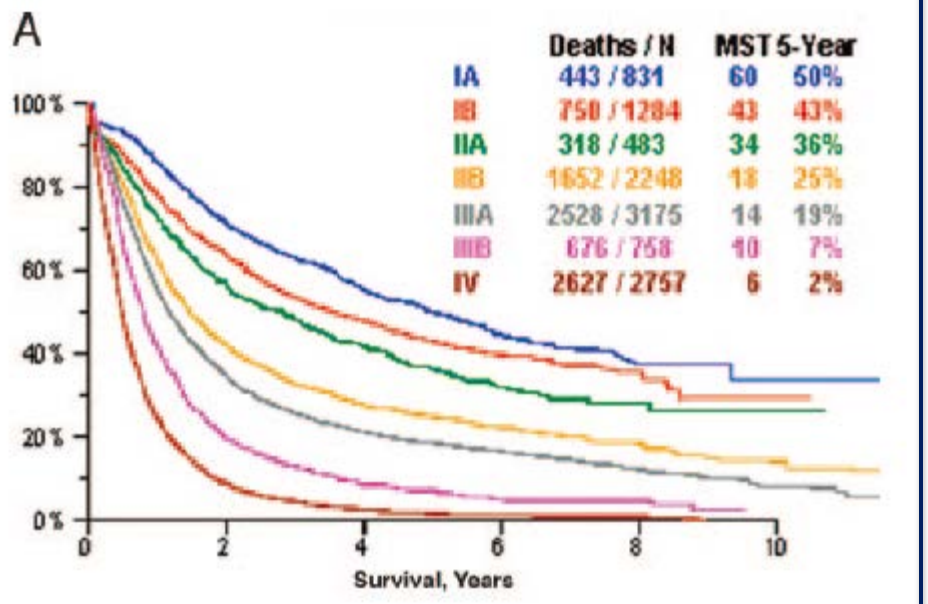
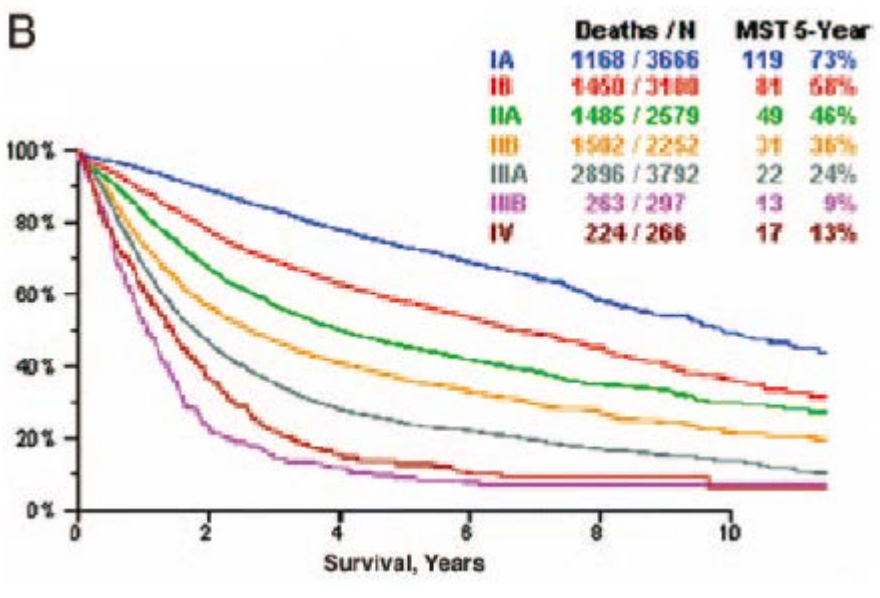
Local vs. Advanced NSCLC

5-year survival rate 15.9%

Clinical Staging



Pathologic Staging



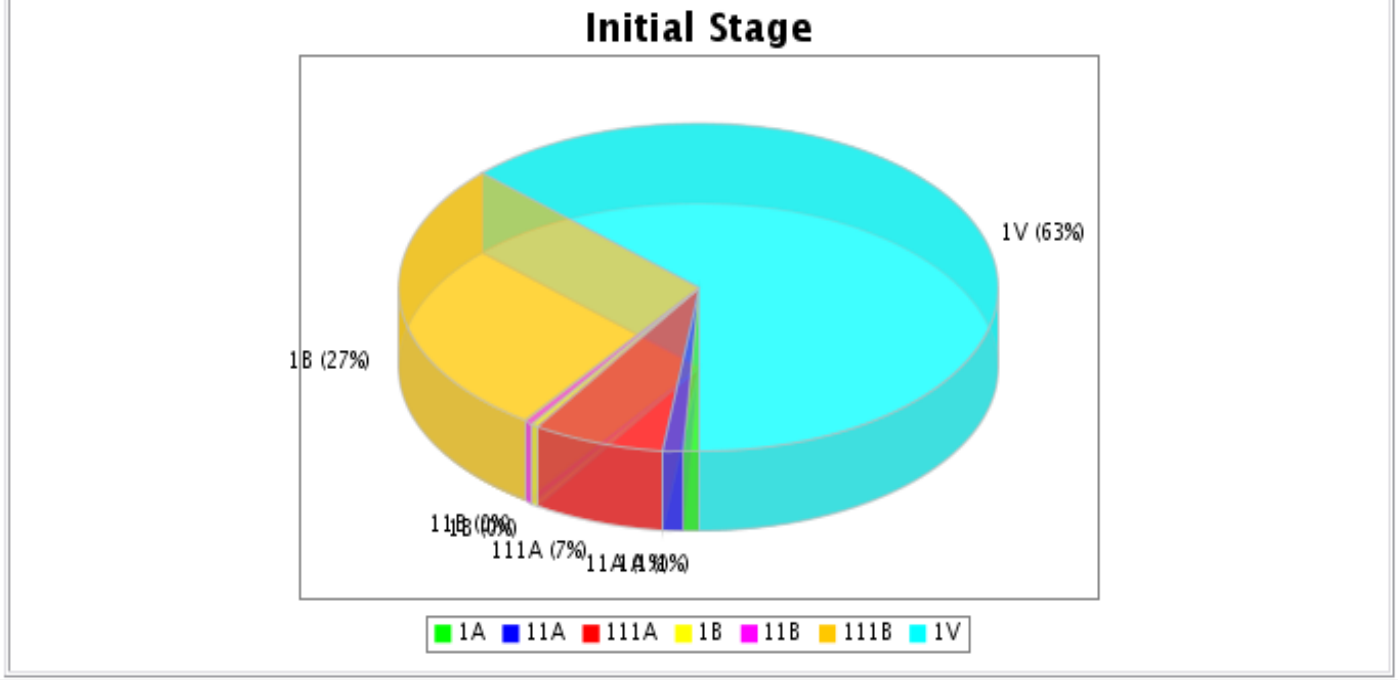
Detterbeck FC, Chest 2009;136;260-271

Late Stage Lung Cancer When Diagnosed in Taiwan

35.5%

62.7%

Initial Stage						
1A	1B	11A	11B	111A	111B	1V
(0.784%)	(0.392%)	(1.176%)	(0.392%)	(7.05%)	(27.45%)	(62.74%)



There has been a **70%** decrease in cervical cancer deaths between 1955 and 1972, largely as a result of the Pap test.

DEATH RATES FOR BREAST CANCER (1990–2008)

32.0% **N/A**

EST. 2012 INCIDENCE = **229,060** • DEATHS = **39,920**

DEATH RATES FOR CERVIX UTERI (1990–2008)

35.1% **N/A**

EST. 2012 INCIDENCE = **12,710** • DEATHS = **4,220**

DEATH RATES FOR PROSTATE (1990-2008)

N/A **40.9%**

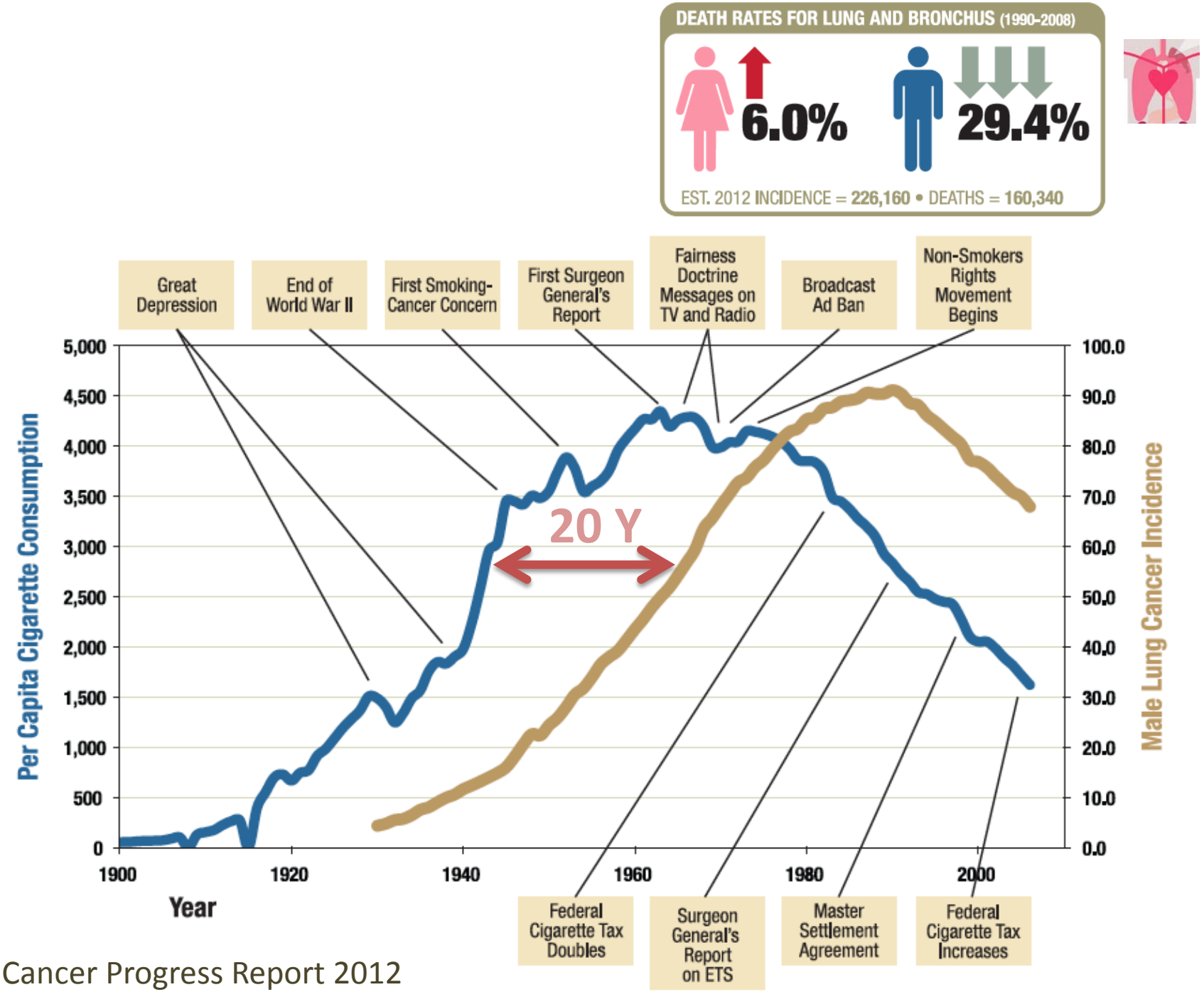
EST. 2012 INCIDENCE = **241,740** • DEATHS = **28,170**

DEATH RATES FOR COLORECTAL CANCER (1990–2008)

33.0% **36.0%**

EST. 2012 INCIDENCE = **143,460** • DEATHS = **51,690**

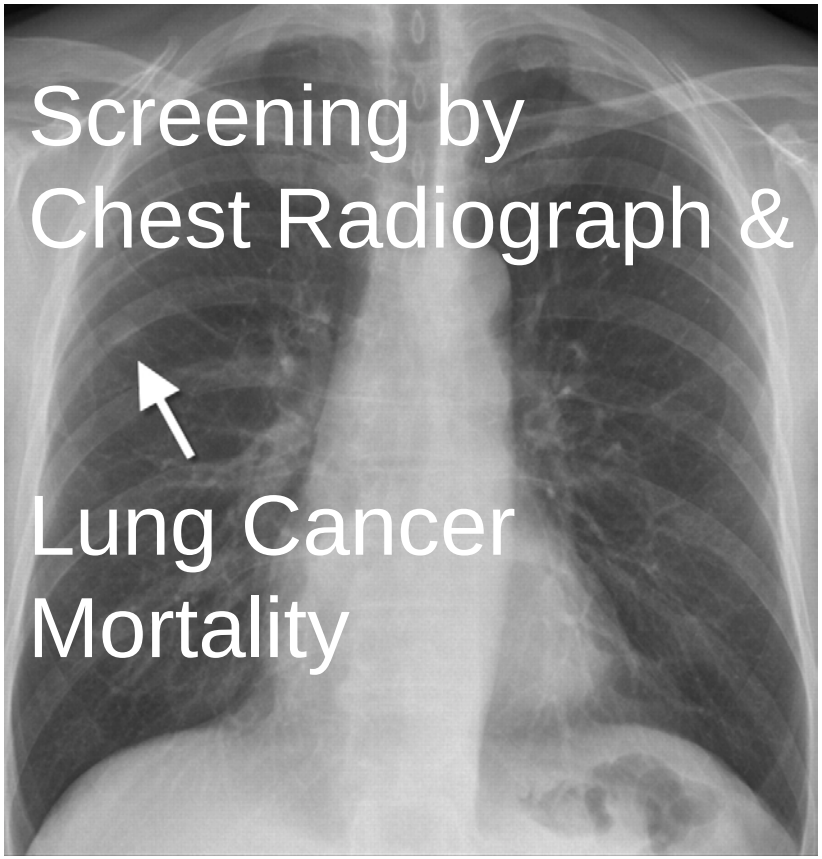
AACR Cancer Progress Report 2012



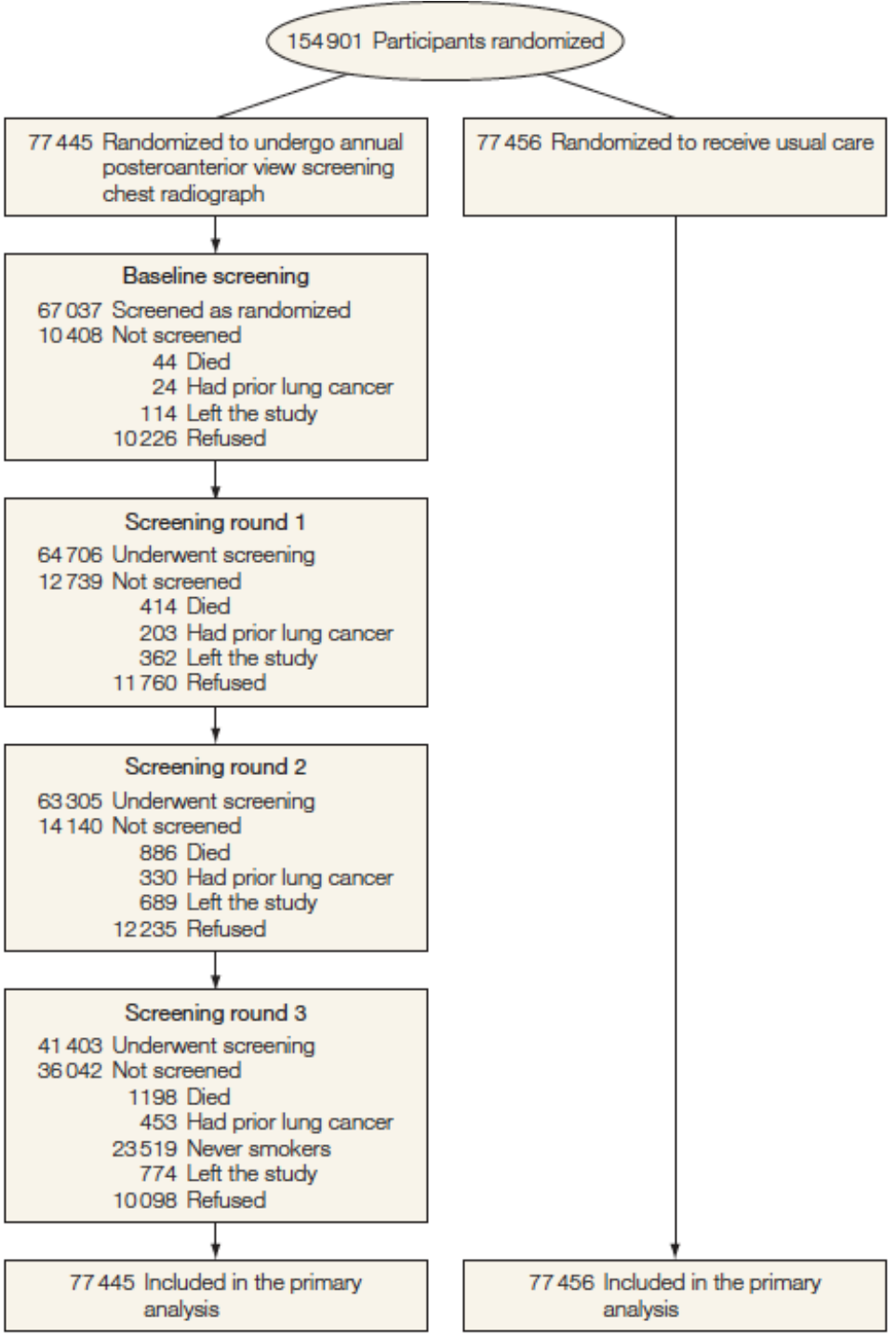
AACR Cancer Progress Report 2012

The PLCO Trial

The Prostate, Lung, Colorectal & Ovarian Randomized Trial



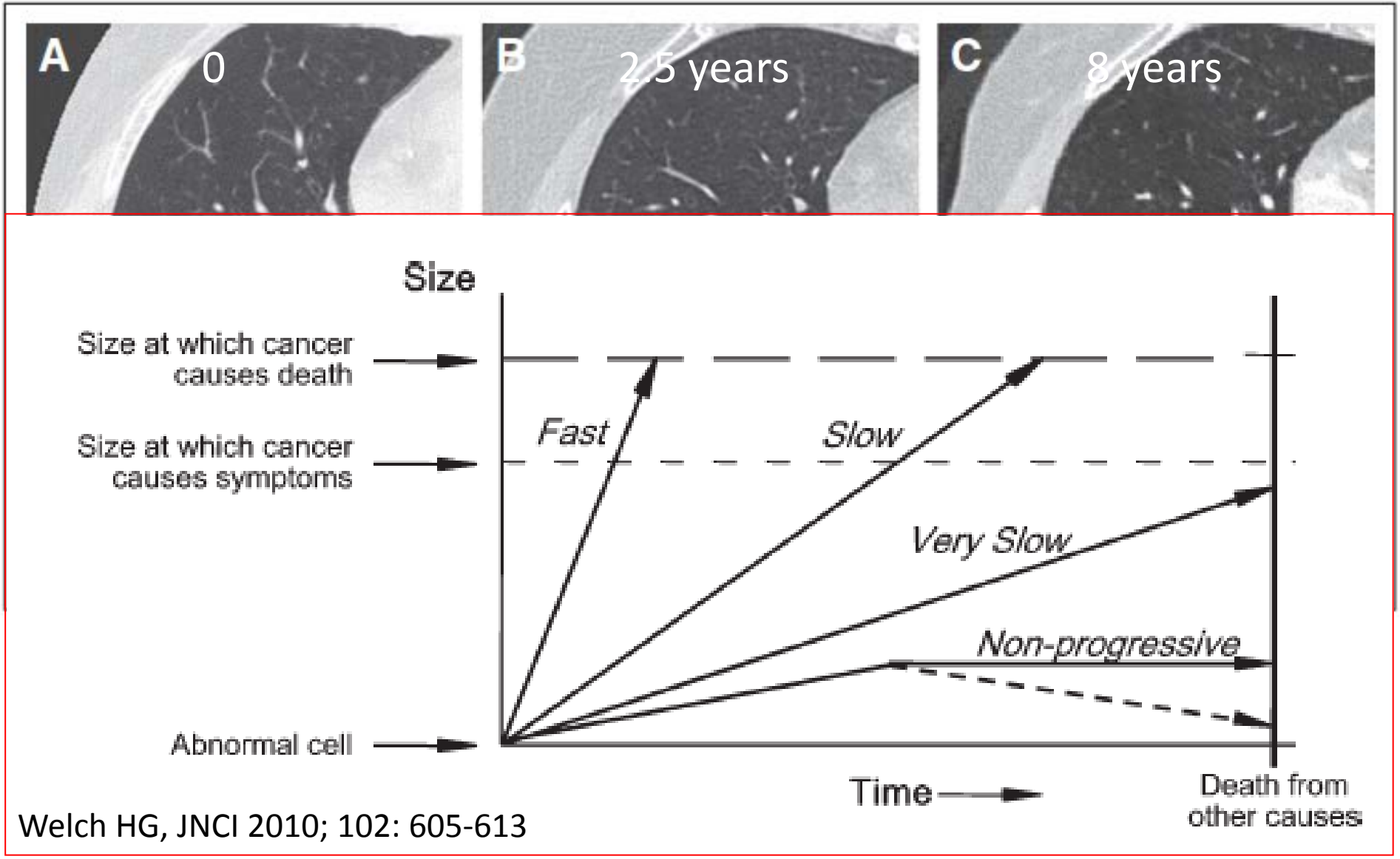
Men & women
aged 55 through 74 years



Oken MM, JAMA. 2011;306(17):1865-1873

Overdiagnosis in Cancer

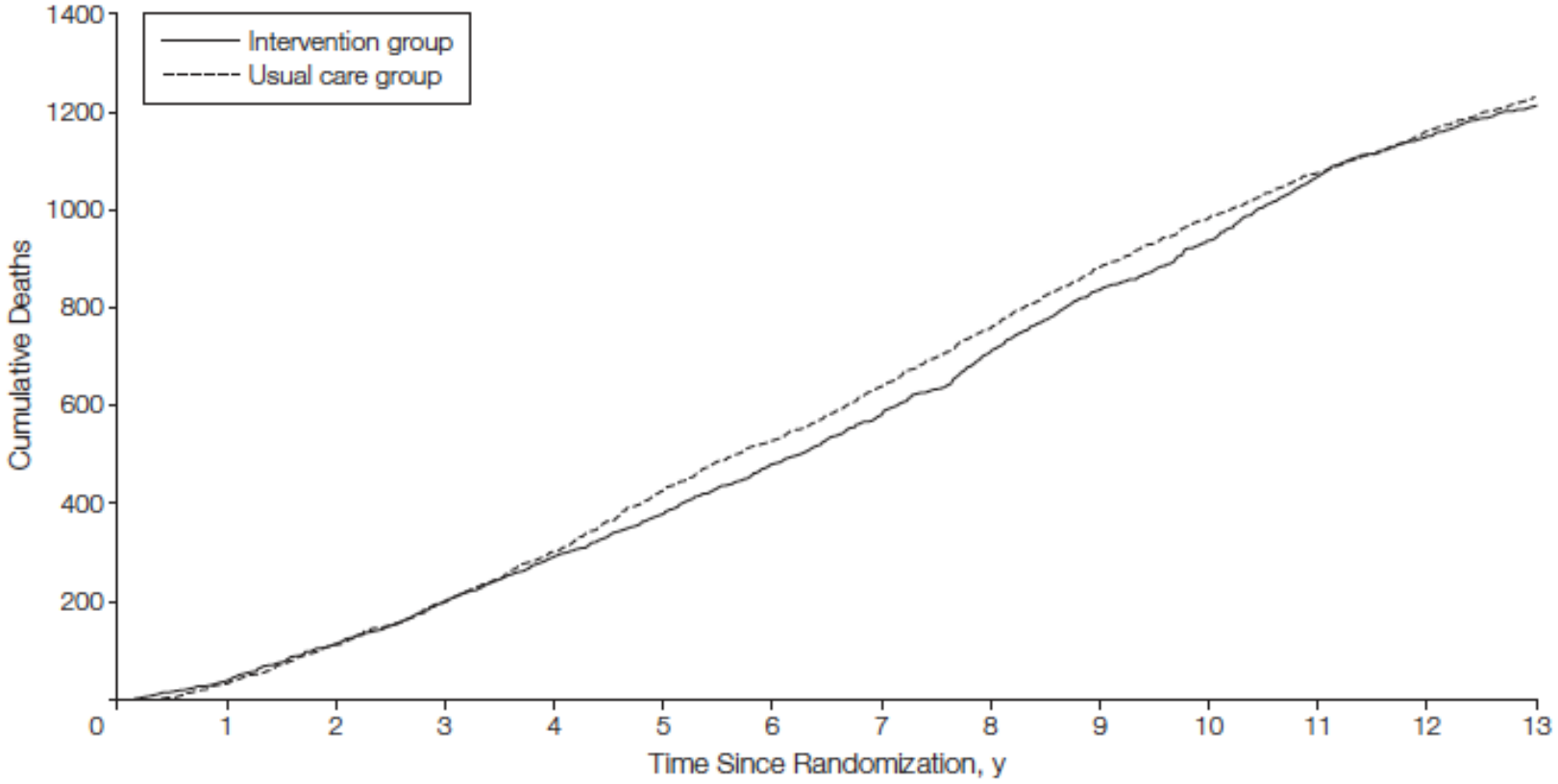
in addition to false positive



Welch HG, JNCI 2010; 102: 605-613

The PLCO Trial

Lung Cancer Mortality by Year

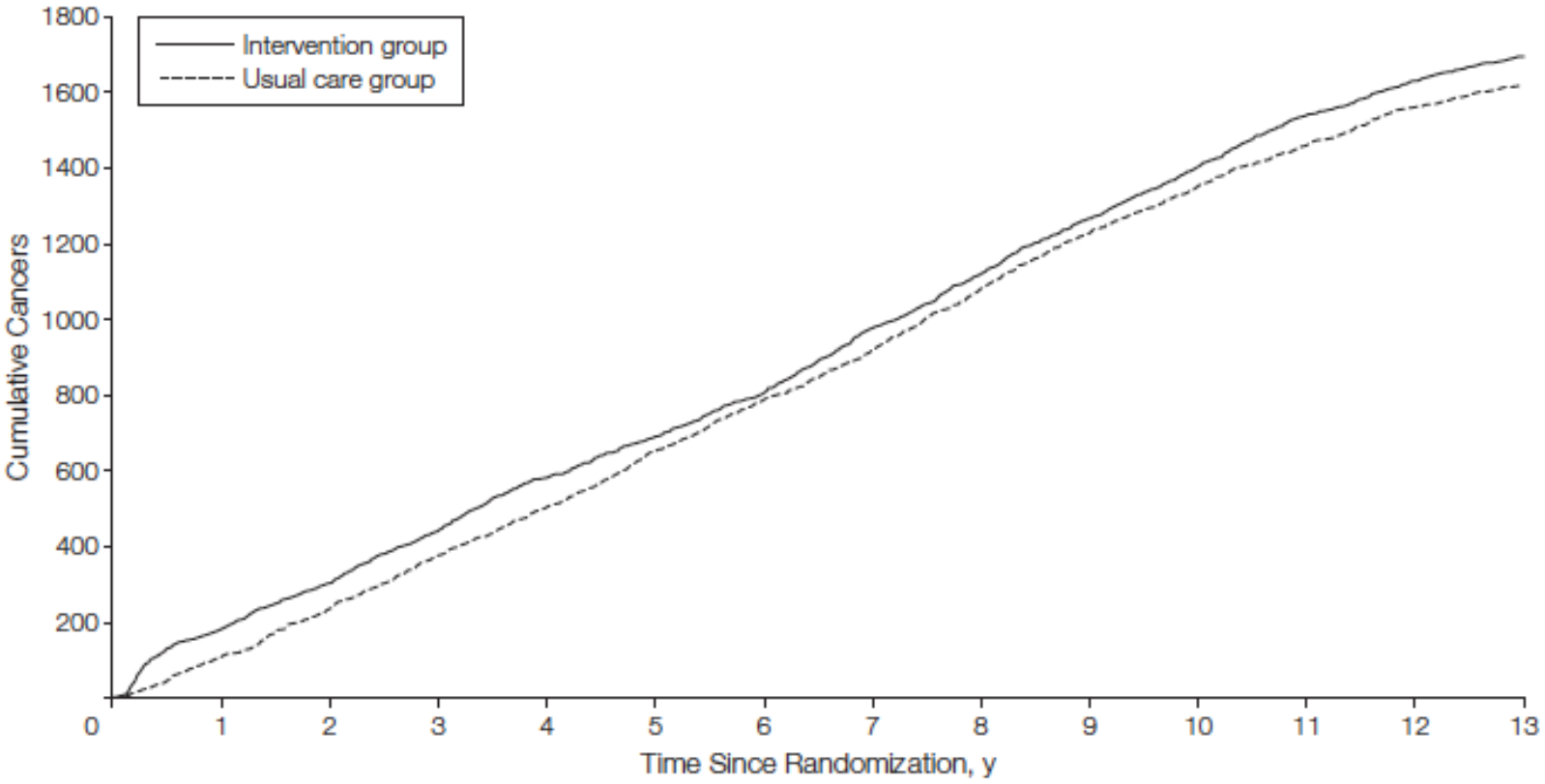


Intervention group													
Cumulative deaths	36	113	196	292	378	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77 268	154 053	230 270	305 833	380 691	454 773	527 937	600 004	670 274	735 098	789 540	832 441	864 227
Usual care group													
Cumulative deaths	30	111	198	301	426	527	639	761	884	987	1076	1162	1230
Cumulative person-years	77 286	154 116	230 348	305 902	380 725	454 719	527 804	599 790	669 955	734 523	788 854	831 678	863 330

Oken MM, JAMA. 2011;306(17):1865-1873

The PLCO Trial

Lung Cancer Incidence by Year

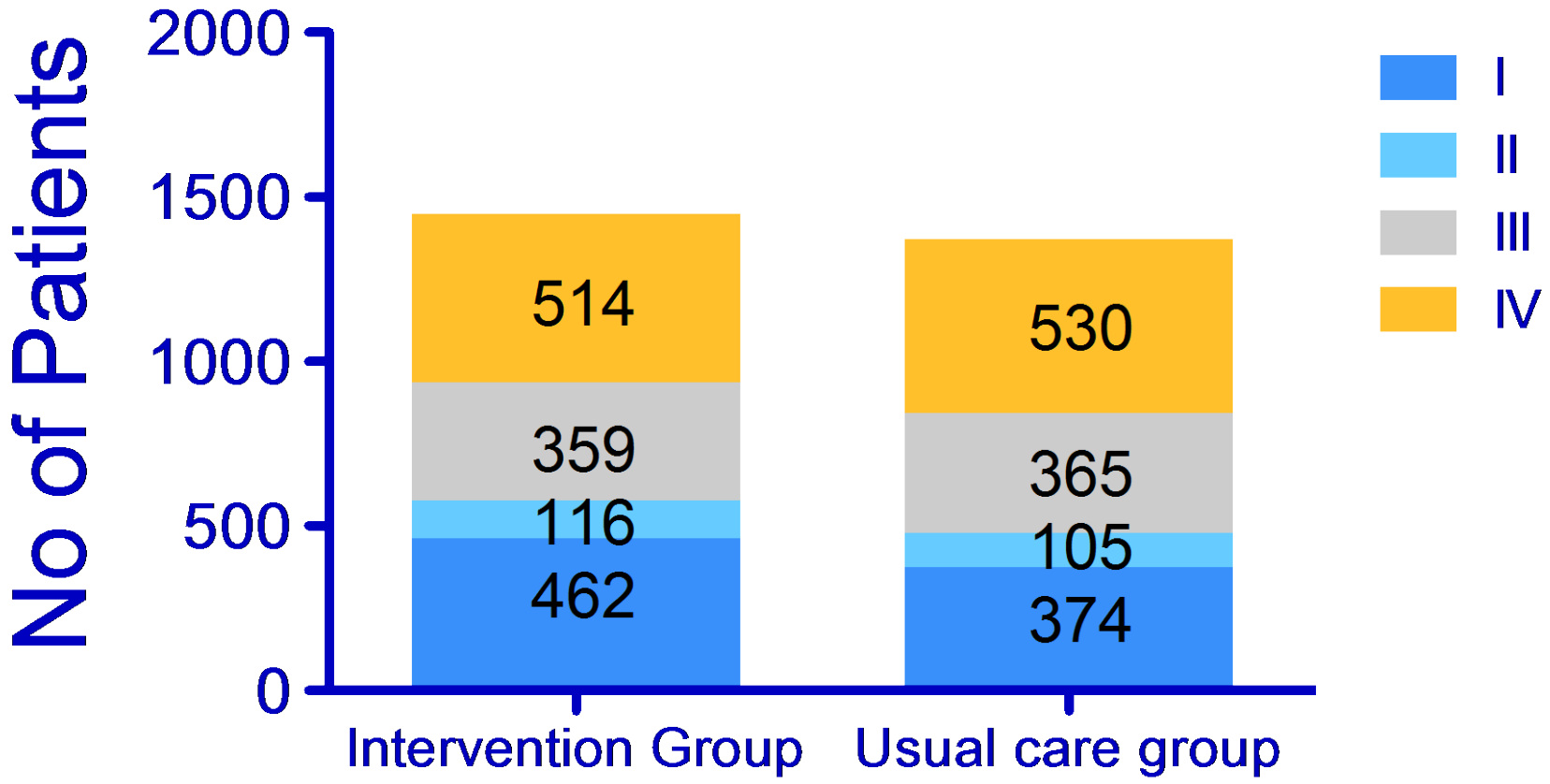


Intervention group													
Cumulative cancers	181	304	441	583	692	808	981	1124	1268	1405	1544	1633	1696
Cumulative person-years	76617	152416	227322	301309	374374	446481	517521	587405	655538	718389	771188	812963	844011
Usual care group													
Cumulative cancers	109	235	377	504	653	790	923	1084	1232	1358	1465	1563	1620
Cumulative person-years	76597	152495	227549	301699	374873	446975	517940	587701	655718	718398	771147	812834	843762

Oken MM, JAMA. 2011;306(17):1865-1873

The PLCO Trial

Annual screening with chest radiograph is not useful for lung cancer screening in low risk patients



Modified from Oken MM, JAMA. 2011;306(17):1865-1873

The PLCO Trial

Lung Cancer Mortality by Year

NLST (High risk group)

	Intervention Group (n = 15 183)	Usual Care Group (n = 15 138)	Rate Ratio (95% CI)
Men, No. (%)	9252 (60.9)	9110 (60.2)	
Current smoker, No. (%)	6146 (40.5)	6069 (40.3)	
Median pack-years	52.0	52.5	
Adherence with baseline screen, No. (%)[a]	13 035 (85.9)		
Overall adherence, No. (%)[a]	48 330 (81.4)		
Results through 6 y of follow-up			
Diagnosed cases, No.	518	520	1.00 (0.89-1.13)
Person-years for incidence	85 428	85 474	
Lung cancer deaths, No.	316	334	0.94 (0.81-1.10)
Person-years for death	87 473	87 198	

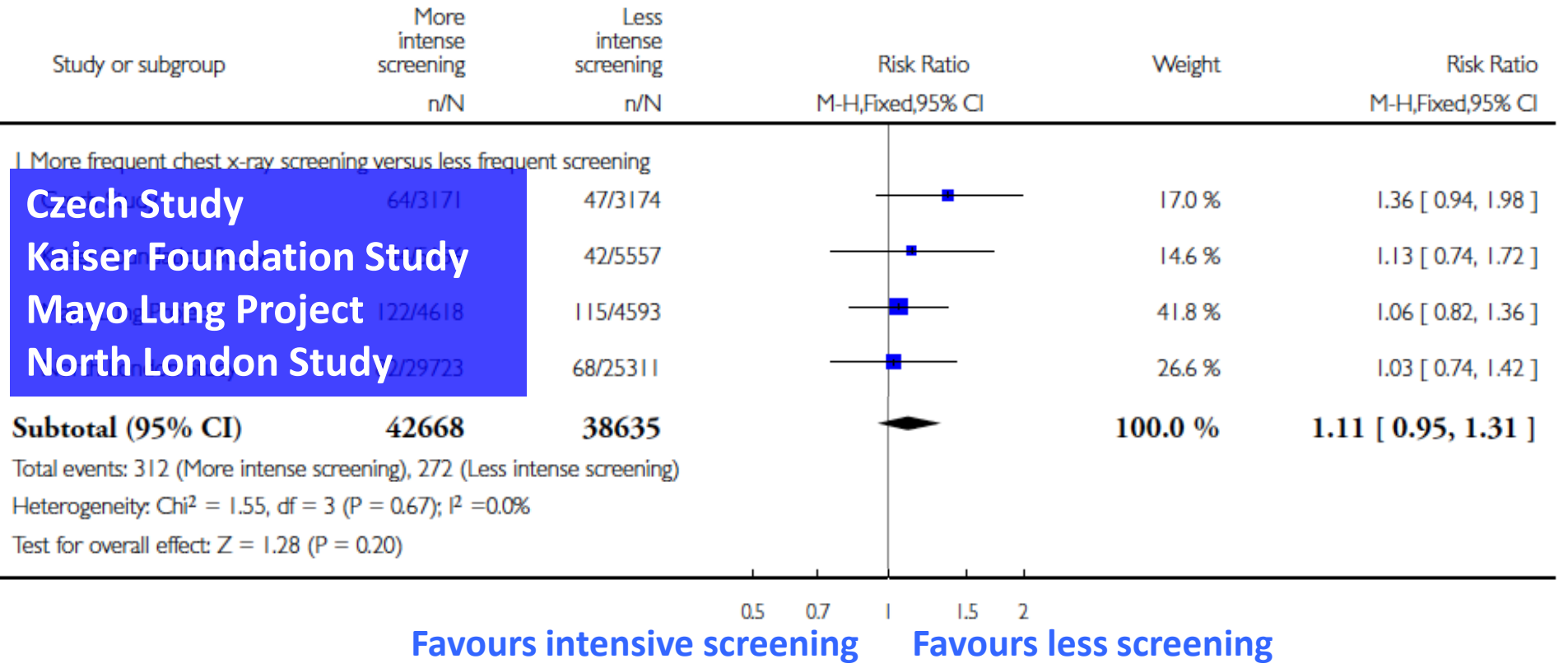
[a] Percentage of expected screens.

Oken MM, JAMA. 2011;306(17):1865-1873

More frequent CXR screening vs. less frequent screening

Lung cancer mortality

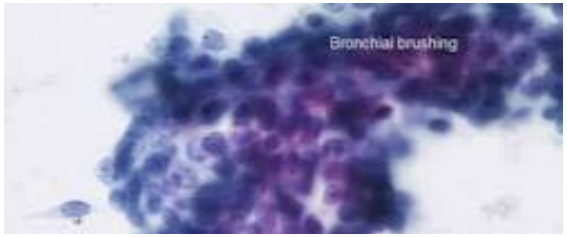
More frequent chest radiograph screening is not useful



Manser R, Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001991.

Annual CXR+4-monthly cytology vs. annual CXR alone

Lung cancer mortality



Study or subgroup	More intense screening n/N	Less intense screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Annual chest x-ray plus 4-monthly cytology versus annual x-ray alone					
Johns Hopkins Study	141/5226	173/5161		59.4 %	0.80 [0.65, 1.00]
Mem Sloan-Kettering	136/4968	120/5072		40.6 %	0.98 [0.76, 1.26]
Subtotal (95% CI)	**10194**	**10233**		**100.0 %**	**0.88 [0.74, 1.03]**
Total events: 256 (More intense screening), 293 (Less intense screening)					
Heterogeneity: $Chi^2 = 1.31$, df = 1 (P = 0.25); I^2 =24%					
Test for overall effect: Z = 1.58 (P = 0.11)					
Test for subgroup differences: $Chi^2 = 4.09$, df = 1 (P = 0.04), I^2 =76%					

0.5 0.7 1 1.5 2

Favours intensive screening **Favours less screening**

Manser R, Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001991.

The NLST

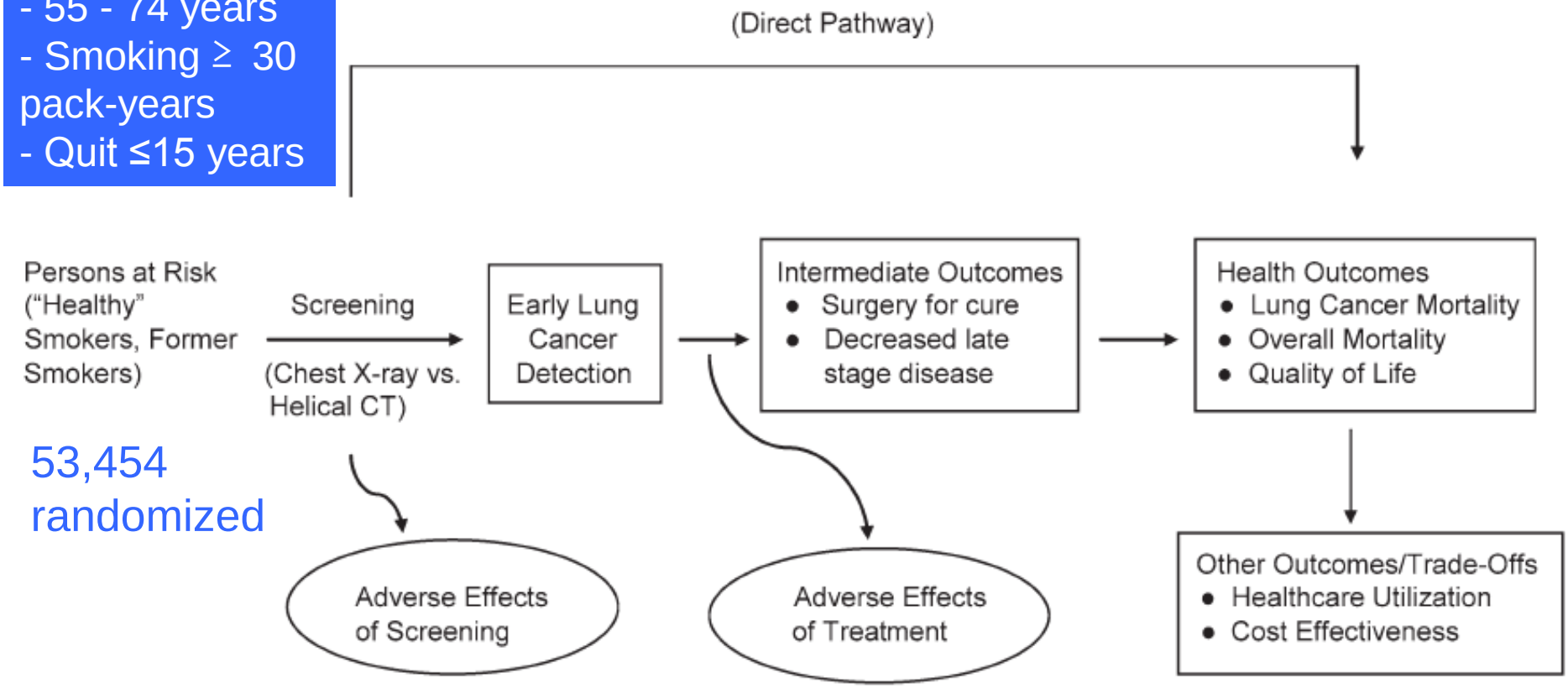
Annual LDCT VS. annual CXR

The National Lung Screening Trial (NLST)

The primary endpoint : lung cancer mortality

High risk
- 55 - 74 years
- Smoking ≥ 30 pack-years
- Quit ≤15 years

August 2002 through April 2004



53,454 randomized

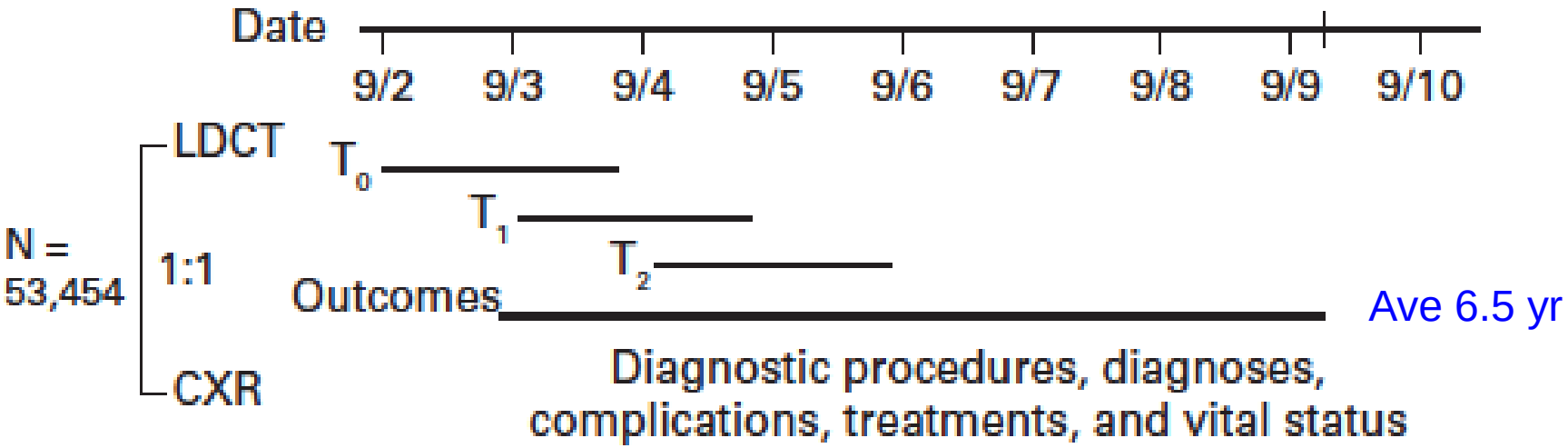
Process and outcomes in the NLST. (Adapted and reprinted, with permission, from reference 1).

Radiology 2011; 258 (1): 243-253

The NLST

Annual LDCT VS. annual CXR

The National Lung Screening Trial (NLST)



Radiology 2011; 258 (1): 243-253

The NLST

Positive

LDCT

a nodule at least 4 mm in any diameter or
other abnormalities suspicious for lung cancer

24.2% positive
23.3% false positive

Chest radiography

a nodule or mass of any size or
other abnormalities suspicious for lung cancer

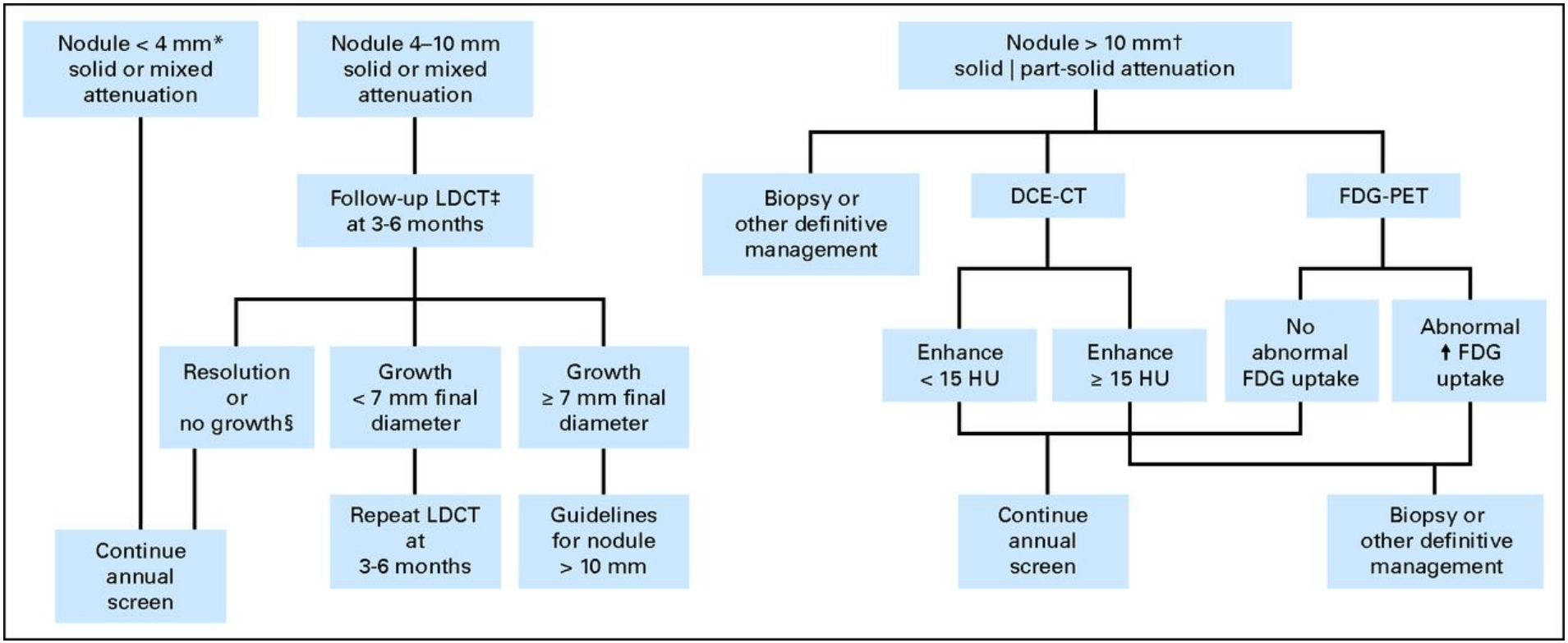
6.9% positive
6.5% false positive

Table 2. Results of Three Rounds of Screening.*

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)

N Engl J Med 2011;365:395-409.

The original guidelines for the management of CT–detected nodules in the NLST

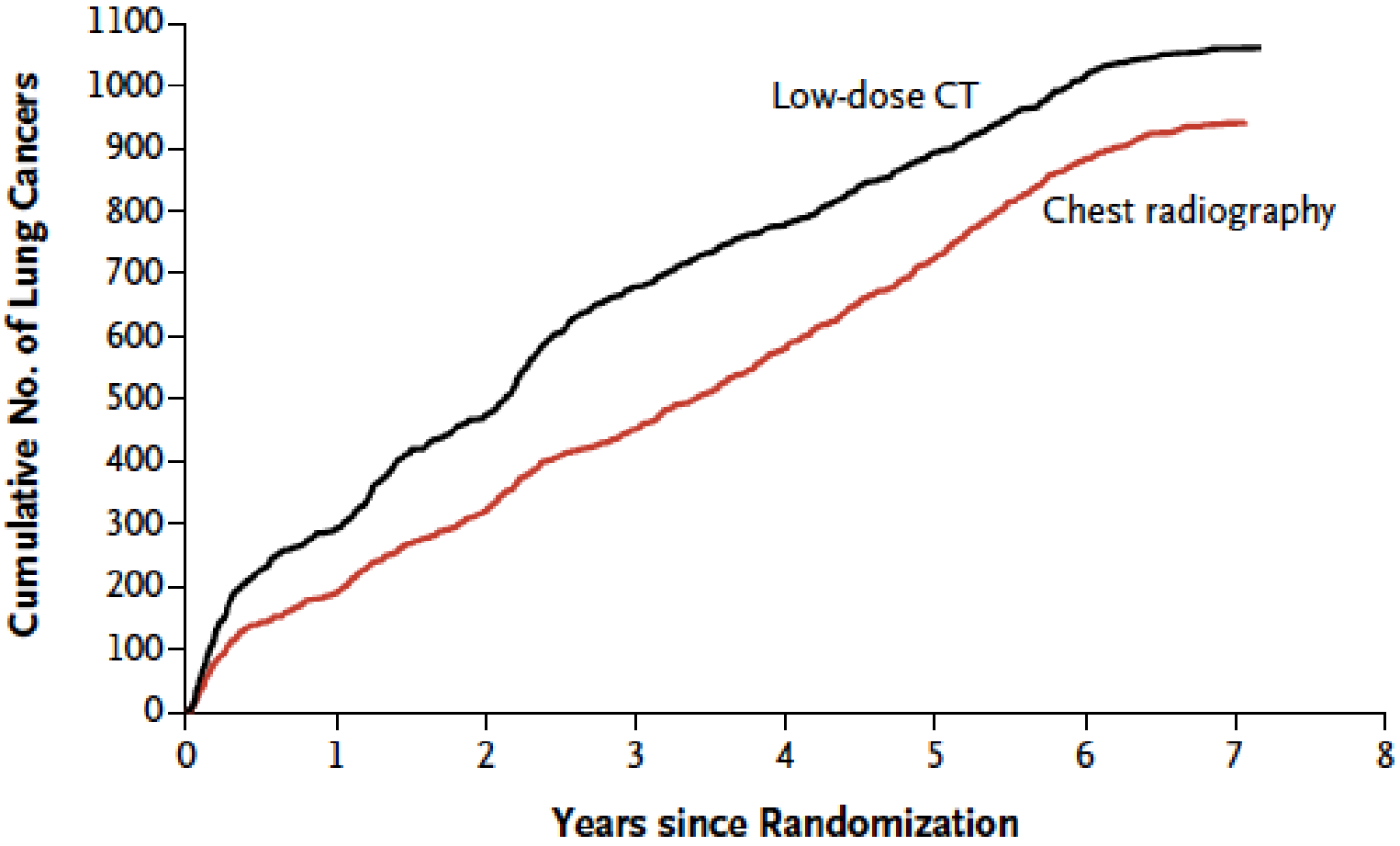


Pure ground-glass nodules < 10 mm can be followed with LDCT at 6 to 12 months

Aberle D R et al. JCO 2013;31:1002-1008

The NLST

Cumulative Numbers of Lung Cancers

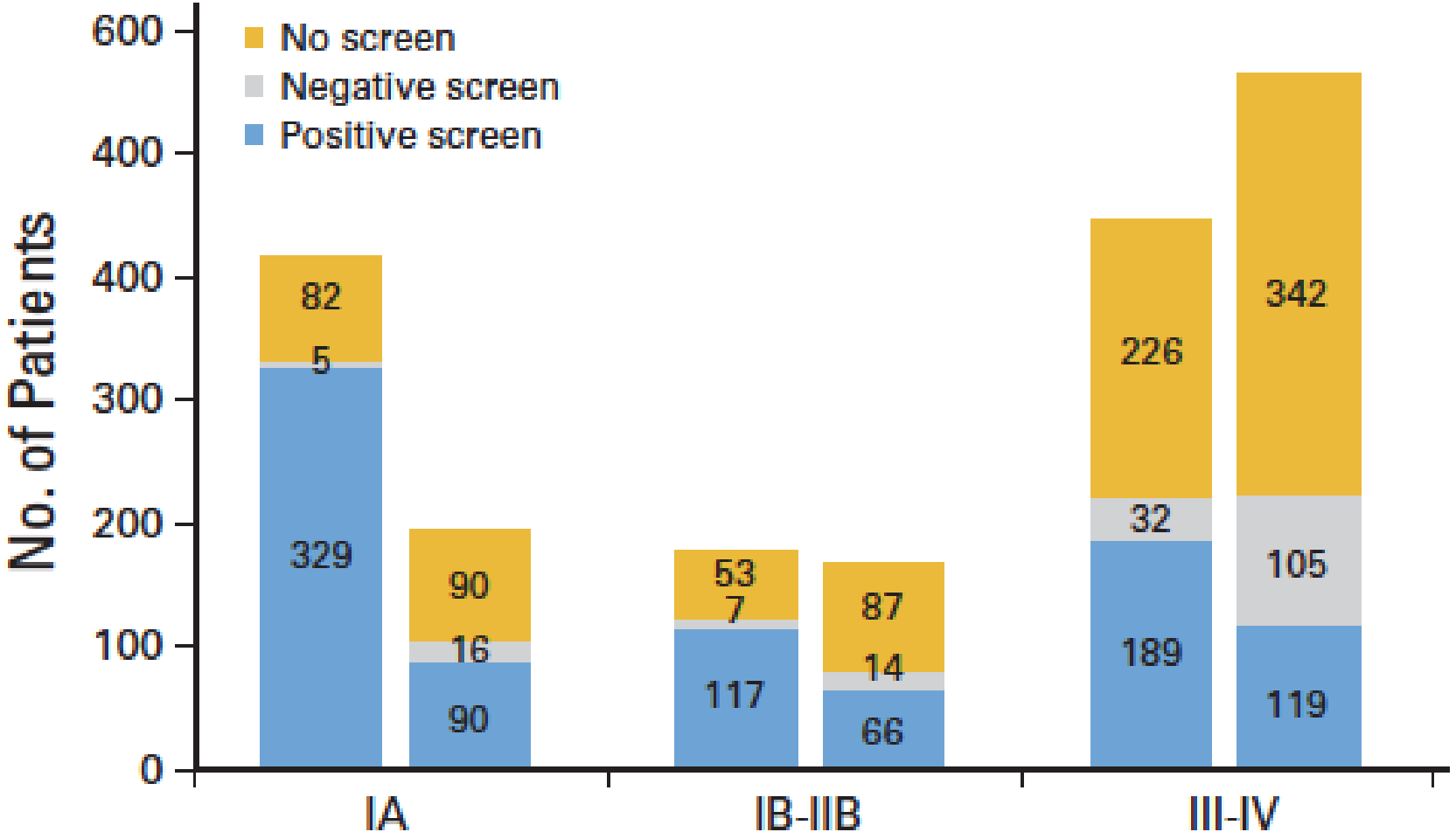


N Engl J Med 2011;365:395-409.

The NLST

Stage of lung cancers in the two screening arms

More stage IA, less III-IV in the LDCT arm



Aberle DR, J Clin Oncol 31:1002-1008.

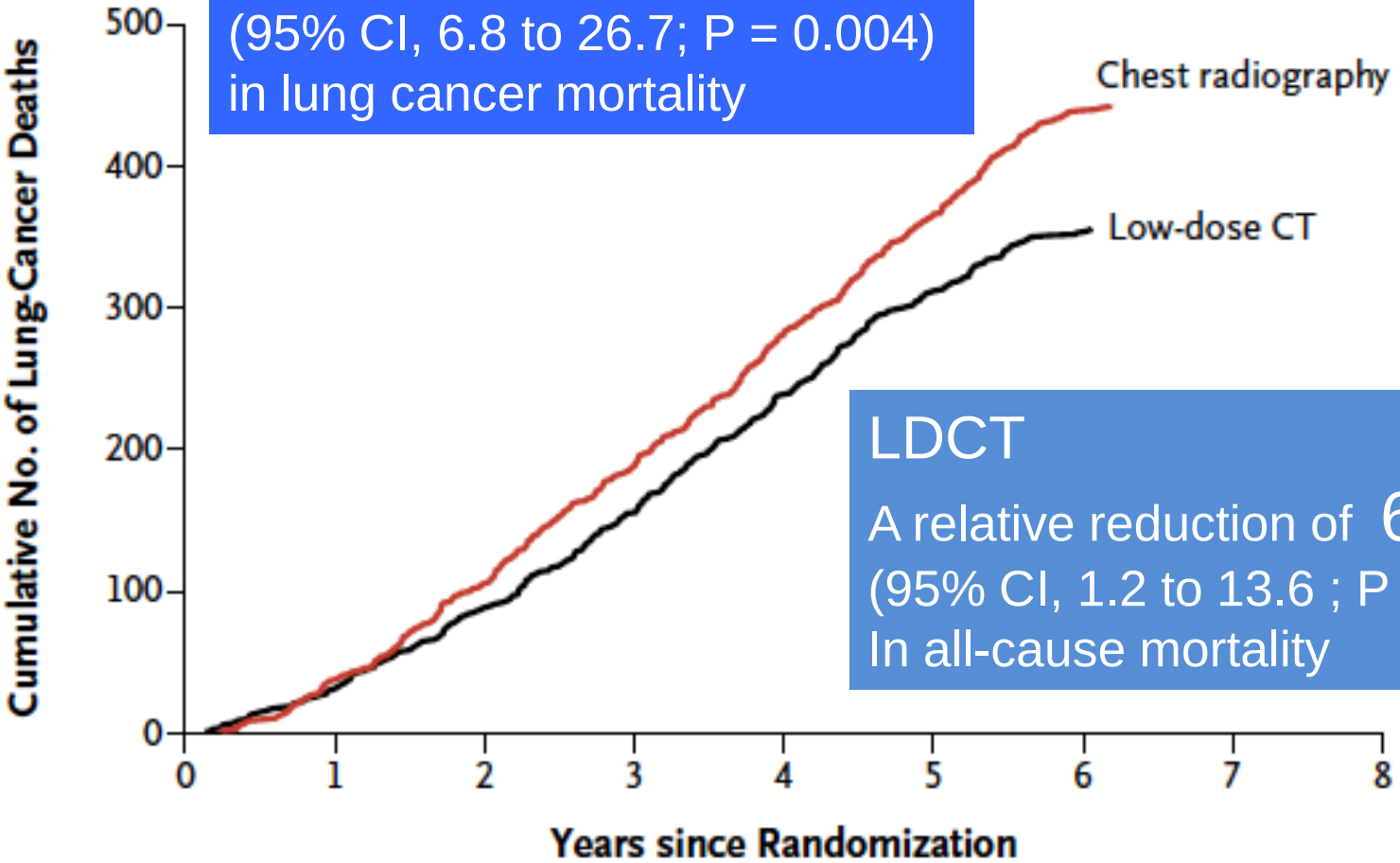
N Engl J Med 2011;365:395-409.

The NLST

Cumulative Numbers of Deaths from Lung Cancer

LDCT

A relative reduction of 20.0%
(95% CI, 6.8 to 26.7; P = 0.004)
in lung cancer mortality



LDCT

A relative reduction of 6.7%
(95% CI, 1.2 to 13.6 ; P = 0.02)
In all-cause mortality

N Engl J Med 2011;365:395-409.

Number needed to be screened

LDCT
for lung cancer

302
needed to be screened
to save a life

N Engl J Med 2011;365:395-409.
Aberle DR, J Clin Oncol 31:1002-1008.

Mammography
for breast cancer

465 - 601
needed to be screened
to save a life

Tabar L, J Med Screen 11:126-129, 2004
Richardson A, J Med Screen 8:125-127, 2001

The NLST

Complication	Lung Cancer Confirmed				
	Thoracotomy, Thoracoscopy, or Mediastinoscopy	Bron-choscopy	Needle Biopsy	No Invasive Procedure	Total
	number (percent)				
Low-dose CT group					
Positive screening results for which diagnostic information was complete	509 (100.0)	76 (100.0)	33 (100.0)	31 (100.0)	649 (100.0)
No complication	344 (67.6)	69 (90.8)	26 (78.8)	26 (83.9)	465 (71.6)
At least one complication	165 (32.4)	7 (9.2)	7 (21.2)	5 (16.1)	184 (28.4)
Most severe complication classified as major	71 (13.9)	2 (2.6)	0	2 (6.5)	75 (11.6)
Most severe complication classified as intermediate	81 (15.9)	5 (6.6)	7 (21.2)	2 (6.5)	95 (14.6)
Most severe complication classified as minor	13 (2.6)	0	0	1 (3.2)	14 (2.2)
Death within 60 days after most invasive diagnostic procedure†	5 (1.0)	4 (5.3)	1 (3.0)	0	10 (1.5)
Radiography group					
Positive screening results for which diagnostic information was complete	189 (100.0)	46 (100.0)	29 (100.0)	15 (100.0)	279 (100.0)
No complication	130 (68.8)	42 (91.3)	28 (96.6)	14 (93.3)	214 (76.7)
At least one complication	59 (31.2)	4 (8.7)	1 (3.4)	1 (6.7)	65 (23.3)
Most severe complication classified as major	22 (11.6)	1 (2.2)	0	1 (6.7)	24 (8.6)
Most severe complication classified as intermediate	32 (16.9)	2 (4.3)	1 (3.4)	0	35 (12.5)
Most severe complication classified as minor	5 (2.6)	1 (2.2)	0	0	6 (2.2)
Death within 60 days after most invasive diagnostic procedure†	4 (2.1)	5 (10.9)	1 (3.4)	1 (6.7)	11 (3.9)

N Engl J Med 2011;365:395-409.

The NLST

Lung Cancer Not Confirmed				
Thoracotomy, Thoracoscopy, or Mediastinoscopy	Bronchoscopy	Needle Biopsy	No Invasive Procedure	Total
number (percent)				
164 (100.0)	227 (100.0)	66 (100.0)	16,596 (100.0)	17,053 (100.0)
138 (84.1)	216 (95.2)	59 (89.4)	16,579 (99.9)	16,992 (99.6)
26 (15.9)	11 (4.8)	7 (10.6)	17 (0.1)	61 (0.4)
9 (5.5)	2 (0.9)	0	1 (<0.1)	12 (0.1)
13 (7.9)	9 (4.0)	6 (9.1)	16 (0.1)	44 (0.3)
4 (2.4)	0	1 (1.5)	0	5 (<0.1)
2 (1.2)	4 (1.8)	0	5 (<0.1)	11 (0.1)
45 (100.0)	46 (100.0)	24 (100.0)	4,559 (100.0)	4,674 (100.0)
38 (84.4)	46 (100.0)	23 (95.8)	4,551 (99.8)	4,658 (99.7)
7 (15.6)	0	1 (4.2)	8 (0.2)	16 (0.3)
1 (2.2)	0	0	3 (0.1)	4 (0.1)
6 (13.3)	0	1 (4.2)	2 (<0.1)	9 (0.2)
0	0	0	3 (0.1)	3 (0.1)
0	0	0	3 (0.1)	3 (0.1)

N Engl J Med 2011;365:395-409.

The NLST

Results of Initial LDCT Screening for Lung Cancer

Sensitivity	93.8% (95% CI, 90.6 - 96.3)	73.5% (95% CI, 67.2 - 79.8)
Specificity	73.4% (95% CI, 72.8 - 73.9)	91.3% (95% CI, 91.0 - 91.6)

Table 2. Frequency and Positive Predictive Value of Positive Screening Results, According to Study Group.*

Positive predictive value

Finding at Initial Screening	Low-Dose CT						Chest Radiography					
	Confirmed Lung Cancer			Total	PPV	PPV Range	Confirmed Lung Cancer			Total	PPV	PPV Range
	yes	no	unknown		percent		yes	no	unknown		percent	
Patients												
Positive screening	270	6911	10	7191	3.8	3.3–4.2	136	2243	8	2387	5.7	4.8–6.6
With subsequent biopsy	265 (98.1)	236 (3.4)	0	501 (7.0)	52.9	48.4–57.4	132 (97.1)	56 (2.5)	0	188 (7.9)	70.2	64.0–76.8
With noncalcified nodule or mass	267 (98.9)	6765 (97.9)	9 (90.0)	7041 (97.9)	3.8	3.3–4.2	123 (90.4)	1982 (88.4)	7 (87.5)	2112 (88.5)	5.8	4.9–6.9
Size of nodule or mass†												
<4 mm	0	1 (<1)	0	1 (<1)	0.0	0.0–0.0	1 (0.7)	40 (1.8)	1 (12.5)	42 (1.8)	2.4	0.0–7.9
≥4 mm	267 (98.9)	6743 (97.6)	9 (90.0)	7019 (97.6)	3.8	3.4–4.3	115 (84.6)	1807 (80.6)	6 (75.0)	1928 (80.8)	6.0	4.9–7.1
4–6 mm	18 (6.7)	3642 (52.7)	8 (80.0)	3668 (51.0)	0.5	0.3–0.7	5 (3.7)	491 (21.9)	2 (25.0)	498 (20.9)	1.0	0.2–2.0
7–10 mm	35 (13.0)	2079 (30.1)	1 (10.0)	2115 (29.4)	1.7	1.1–2.2	12 (8.8)	692 (30.9)	2 (25.0)	706 (29.6)	1.7	0.8–2.9
11–20 mm	111 (41.1)	821 (11.9)	0	932 (13.0)	11.9	9.8–13.9	38 (27.9)	481 (21.4)	2 (25.0)	521 (21.8)	7.3	5.1–9.7
21–30 mm	58 (21.5)	137 (2.0)	0	195 (2.7)	29.7	23.7–36.4	27 (19.9)	92 (4.1)	0	119 (5.0)	22.7	15.2–30.4
>30 mm	45 (16.7)	64 (0.9)	0	109 (1.5)	41.3	32.1–51.0	33 (24.3)	51 (2.3)	0	84 (3.5)	39.3	28.6–50.6
Unknown	0	21 (0.3)	0	21 (0.3)	0.0	0.0–0.0	7 (5.1)	135 (6.0)	0	142 (5.9)	4.9	1.8–8.7
Other findings												
Atelectasis, segmental or more extensive‡	3 (1.1)	69 (1.0)	0	72 (1.0)	4.2	0.0–9.0	4 (2.9)	24 (1.1)	0	28 (1.2)	14.3	3.4–29.5
Noncalcified hilar or mediastinal adenopathy or mass	51 (18.9)	225 (3.3)	1 (10.0)	277 (3.9)	18.5	14.1–23.4	8 (5.9)	78 (3.5)	0	86 (3.6)	9.3	3.8–15.8
Consolidation‡	7 (2.6)	80 (1.2)	0	87 (1.2)	8.0	2.6–14.4	3 (2.2)	41 (1.8)	1 (12.5)	45 (1.9)	6.8	0.0–14.4
Pleural thickening or effusion	16 (5.9)	439 (6.4)	1 (10.0)	456 (6.3)	3.5	1.9–5.3	10 (7.4)	161 (7.2)	1 (12.5)	172 (7.2)	5.8	2.5–9.4

N Engl J Med 2013;368:1980-91.

Targeting of LDCT Screening According to the Risk of Lung-Cancer Death

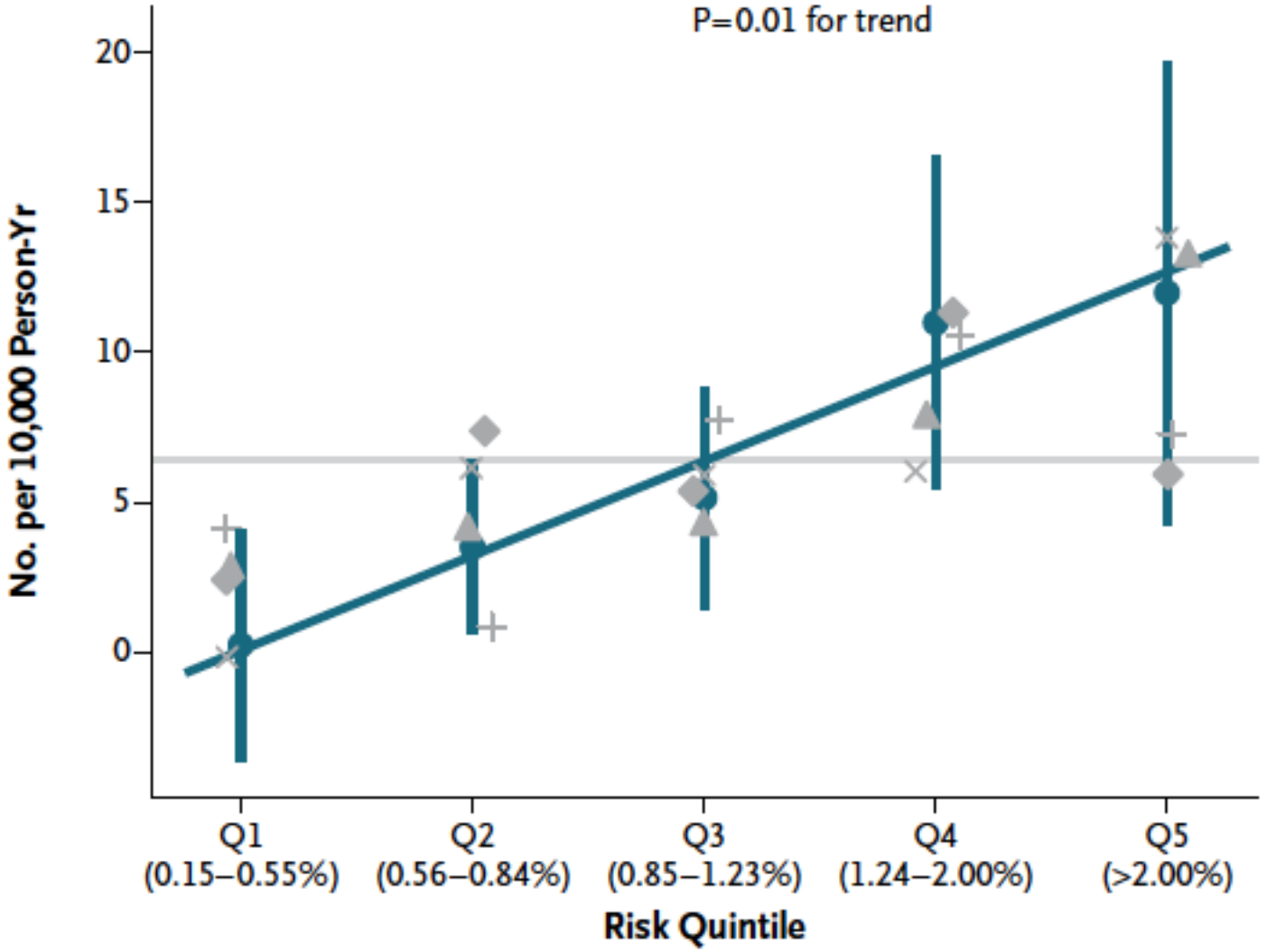
Table 2. Cause-Specific Hazard Models Used in the Risk-Prediction Model for Lung-Cancer Death in the Radiography Group of the NLST.*

Factor	Coding	Death from Lung Cancer	Death from Another Cause
		hazard ratio (95% CI)	
Age	Continuous	1.08 (1.06–1.10)	1.09 (1.08–1.10)
Female sex	Binary	NA†	0.50 (0.44–0.58)
Race	Categorical	NA†	
Non-Hispanic white			1.00 (reference)
Non-Hispanic black			2.22 (1.78–2.76)
Hispanic			1.34 (0.89–2.03)
Other			1.21 (0.91–1.60)
Body-mass index‡			
Linear term	Continuous	0.75 (0.66–0.86)	0.89 (0.82–0.97)
Quadratic term	Continuous	1.05 (0.99–1.11)	1.06 (1.04–1.09)
Pack-years of smoking	Continuous	1.02 (1.01–1.02)	1.01 (1.01–1.01)
Years since smoking cessation	Trend§	0.62 (0.55–0.70)	0.76 (0.70–0.81)
Presence of emphysema	Binary	1.56 (1.20–2.04)	1.52 (1.28–1.80)
First-degree relative with lung cancer	Trend¶	1.27 (1.00–1.62)	NA‖

Kovalchik SA, N Engl J Med 2013;369:245-54.

Targeting of LDCT Screening According to the Risk of Lung-Cancer Death

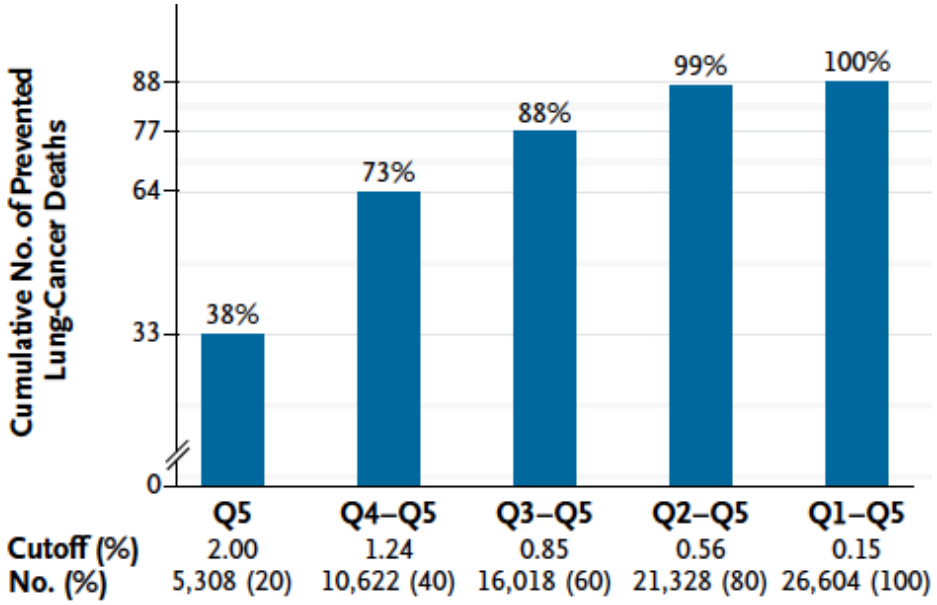
Lung-Cancer Deaths Prevented by LDCT



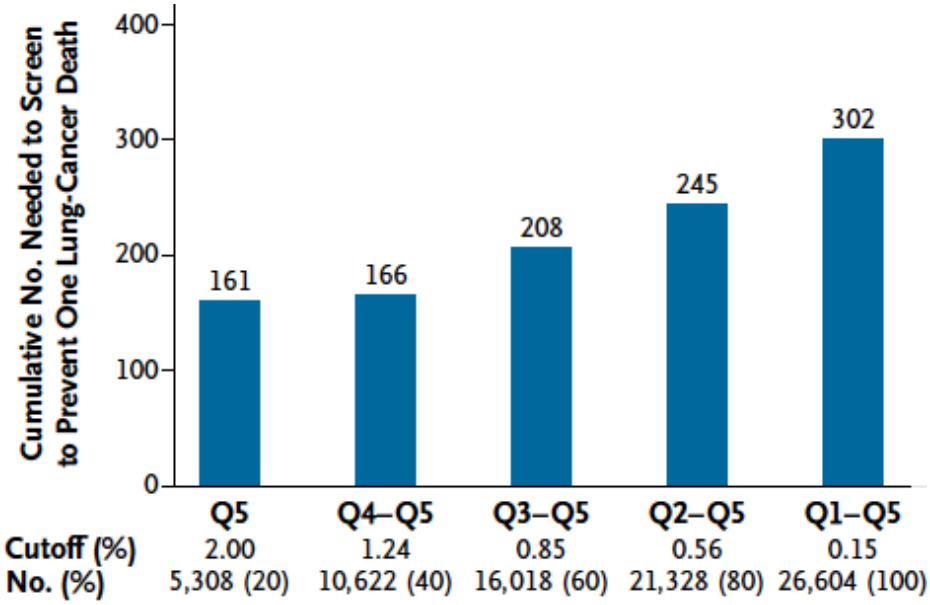
Kovalchik SA, N Engl J Med 2013;369:245-54.

Targeting of LDCT Screening According to the Risk of Lung-Cancer Death

Prevented Lung-Cancer Deaths



Number Needed to Screen



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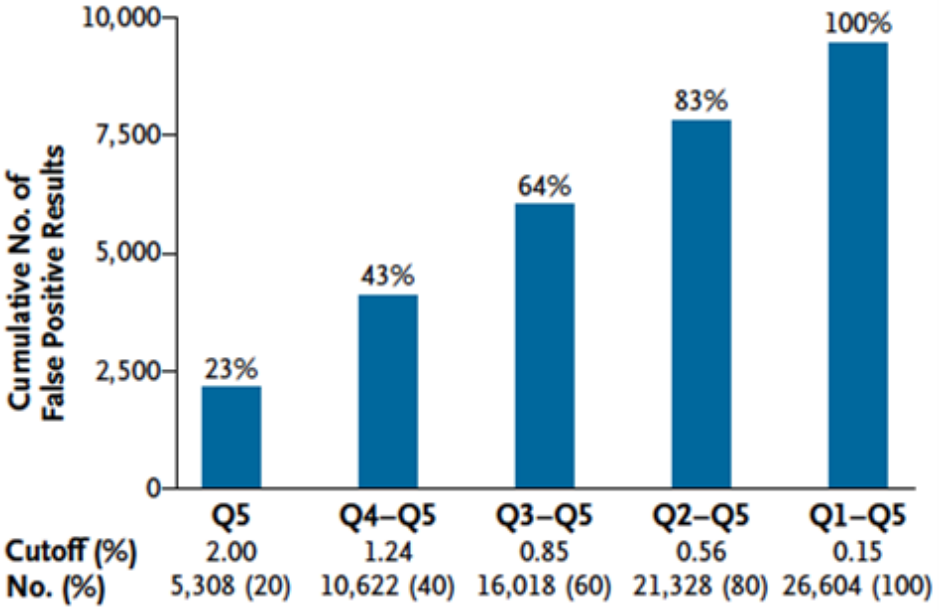
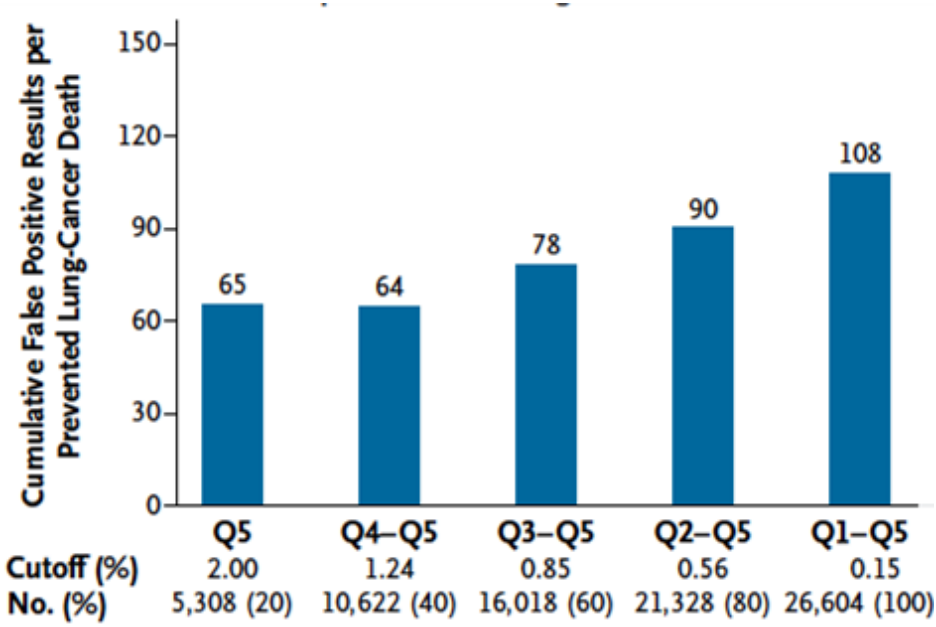
Targeting of LDCT Screening According to the Risk of Lung-Cancer Death

False Positive Results



False Positive Results
per Prevented Lung-Cancer Death



Kovalchik SA, N Engl J Med 2013;369:245-54.

Guidelines for lung caner screening

Organizations	Primary Population for Screening		Other Populations for Screening	
	Recommendations	AHA Level of Evidence[a]	Recommendations	AHA Level of Evidence[a]
American Association for Thoracic Surgery (AATS)	Aged 55-79 y ≥30 Pack-years of smoking	B	Aged ≥50 y ≥20 Pack-years of smoking Additional risk factor(s)[b] or Lung cancer survivor ≥5 y	B C
American College of Chest Physicians (ACCP) and American Society of Clinical Oncology (ASCO)	Aged 55-74 y ≥30 Pack-years of smoking Former smokers must have quit within past 15 y	B[c]	NR	NA
American Cancer Society	Aged 55-74 y ≥30 Pack-years of smoking Former smokers must have quit within past 15 y	B	NR	NA
National Comprehensive Cancer Network (NCCN)	Aged 55-74 y ≥30 Pack-years Former smokers must have quit within past 15 y	B	Aged ≥50 y ≥20 Pack-years of smoking Additional risk factor(s)[d]	B

Randomized Controlled Trials of CT Screening for Lung Cancer

	Screening Arm (n)	Screening Rounds (n)	Length of Screening Interval (yr)	Age Range (yr)	M / F (%:%)	Smoking Pack-Years	Years Since Quitting Smoking	Mortality Reduction, %
NLST	26,722	3	1	55-74	59.0:41.0	≥30	<15	20
NELSON	7,915	4	1, 2, 2.5	50-75	83.5:16.5	>15	≤10	NR
DLST	2,052	5	1	50-70	54.6:45.4	≥20	<10	NSD
ITALUNG	1,613	4	1	55-69	64.2:35.8	≥20	<10	NR
DANTE	1,276	4	1	60-74	100.0:0.0	≥20	<10	NSD
MILD	1,190 1,186	10 5	1 2	49-	68.4:31.6 68.5:31.5	≥20	<10	NR
LUSI	2,029	4	1	50-69	64.8:35.2	Heavy	NR	NR

CT vs. no screen, except NLST

The NELSON trial

(Nederlands Leuvens Longkanker Screenings Onderzoek)

Table 1 NELSON classification of the different non-calcified nodules according to size at baseline screening

NODCAT baseline	Definition
I	Benign nodule (fat/benign calcifications) or other benign characteristics
II	Any nodule, smaller than NODCAT III and no characteristics of NODCAT I
III	Solid: 50–500 mm^3 Solid, pleural based: 5–10 mm d_{min} Partial solid, non-solid component: ≥8 mm d_{mean} Partial solid, solid component: 50–500 mm^3 Non-solid: ≥8 mm d_{mean}
IV	Solid: >500 mm^3 Solid, pleural based: >10 mm d_{min} Partial solid, solid component: >500 mm^3

→ Year 4

→ Year 3

→ Repeat scan 3-4 months later

volume-doubling time (VDT) < 400 days

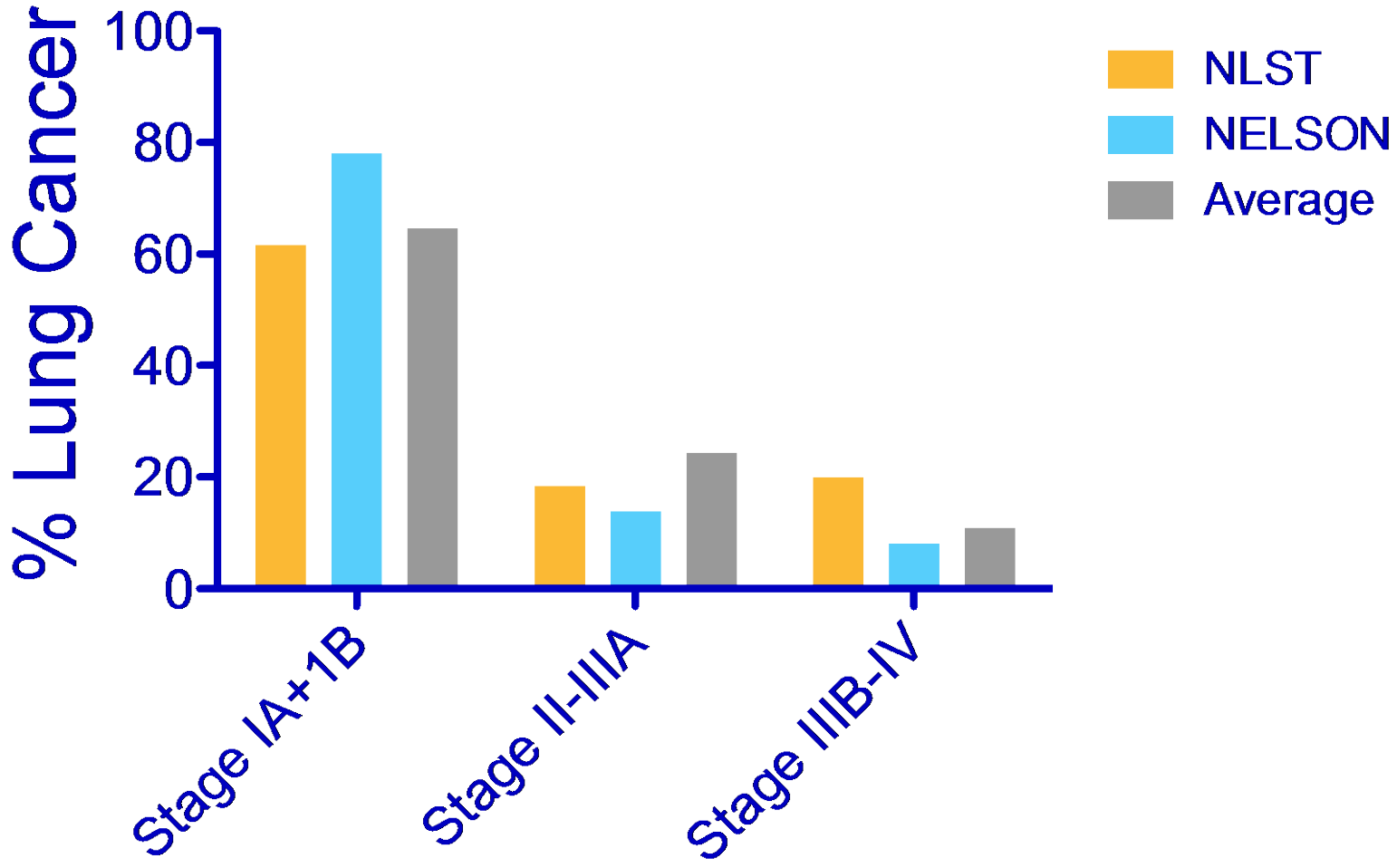
Positive

noncalcified nodules, a volume >500 mm^3 (about 9.8 mm in diameter)

Xu DM, Lung Cancer (2006) 54, 177—184

The NELSON trial

the cancer stage was significantly lower (P < 0.001) vs. NLST

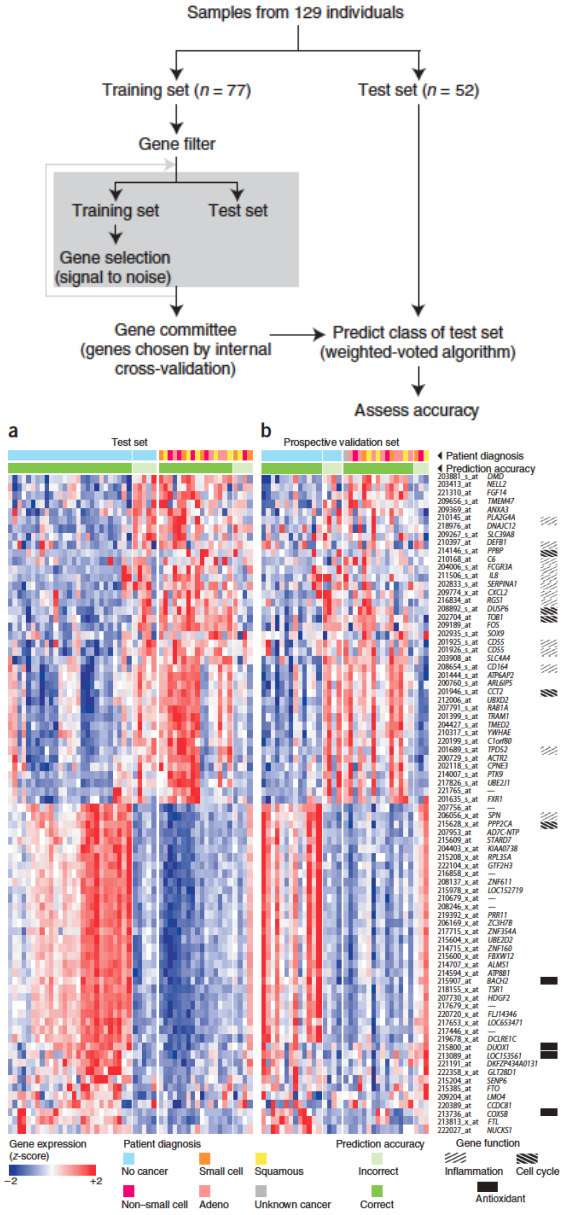


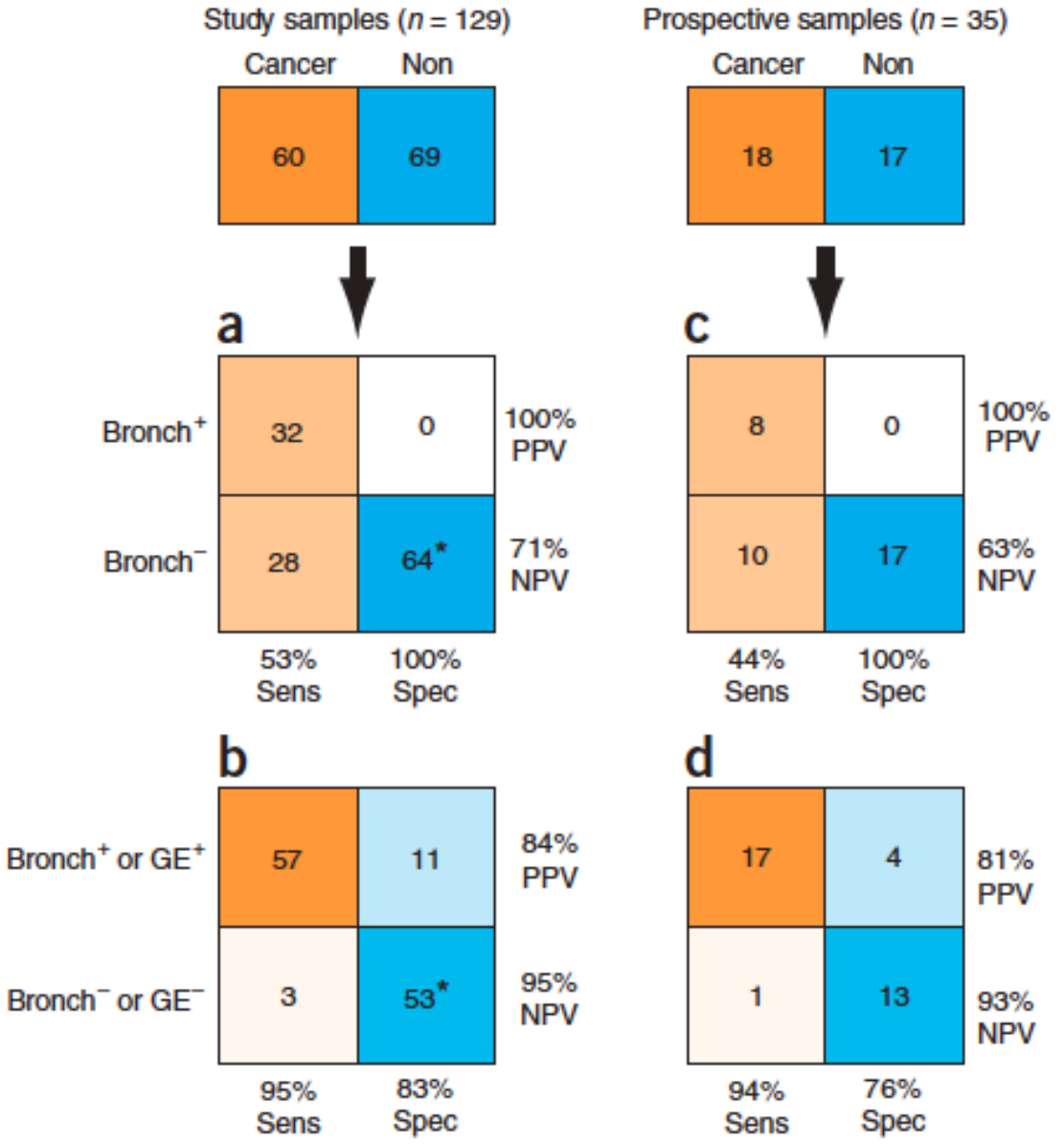
Adapted from Horeweg N, Am J Respir Crit Care Med Vol 187, Iss. 8, pp 848–854, Apr 15, 2013

nature medicine

Airway epithelial gene expression

in the diagnostic evaluation of smokers with suspect lung cancer





Spira A, Nat Med 2007; 13: 361–66.

A Novel Blood Biomarker

for Early Lung Cancer Detection-
Connective Tissue-Activating Peptide III

Improving the accuracy of a lung cancer risk prediction model

SELDI-TOF-MS followed by MS/MS (n = 16 matched pulmonary venous and radial artery sera)

Identification of

- CTAP III
- Haptoglobin

ELISA confirmation (n = 64 matched pulmonary venous and radial artery sera)

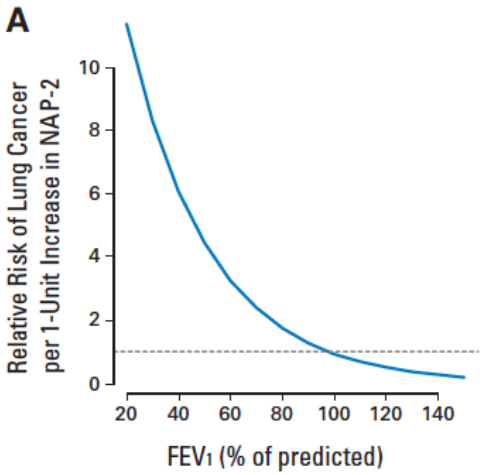
Effect of surgery on CTAP III/NAP-2 and haptoglobin (n = 28 matched samples pre- and postsurgery)

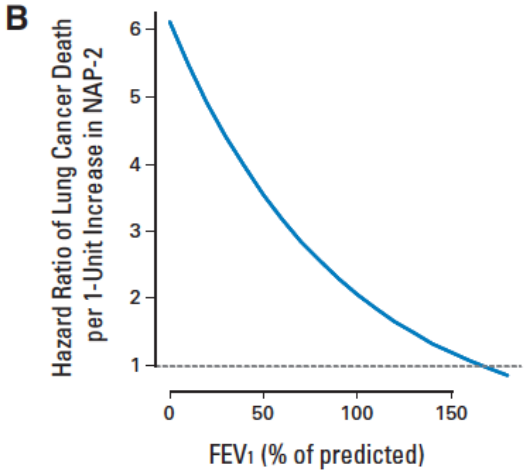
Validation of CTAP III/NAP-2 ar haptoglobin as biomarkers

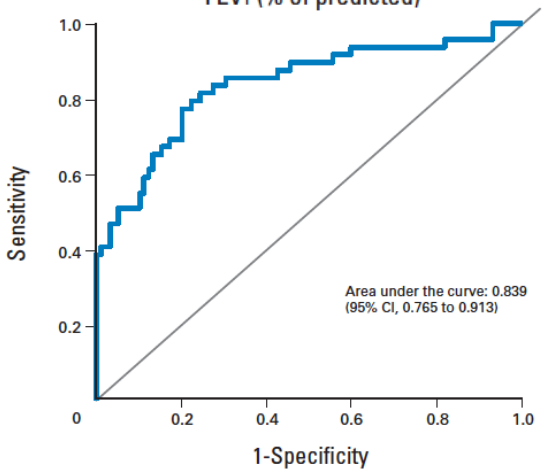
Lung Cancer Screening Program (N = 148)

Replication of CTAP III/NAP-2 a haptoglobin as biomarkers

Lung Health Study (N = 266)







Yee J, J Clin Oncol 2009, 27:2787-2792.

Take home message

- Screening with CXR +/- sputum cytology
  - no reduction in lung-cancer mortality
- Annual LDCT for 3 years (the NLST)
  - aged 55-74, smoking ≥30 pack-yrs, quit ≤ 15 yrs
  - 20% reduction in lung cancer mortality
  - screening 302, saving a life
  - People with higher risk?
  - More stringent criteria?
  - Longer screening interval?

Thank You for Your Attention