NATIONAL CANCER INSTITUTE

Lung Cancer Screening Promise and Pitfalls

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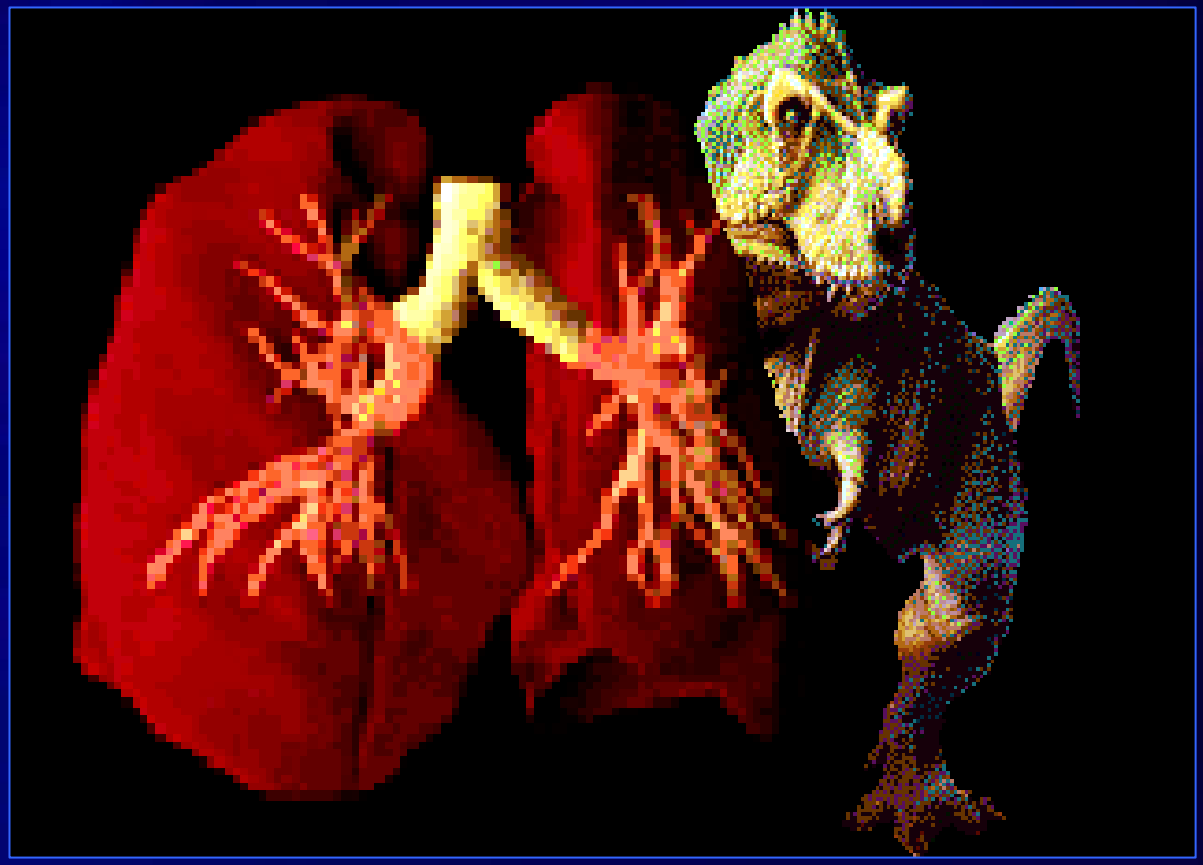
NATIONAL INSTITUTES OF HEALTH

Lung Cancer

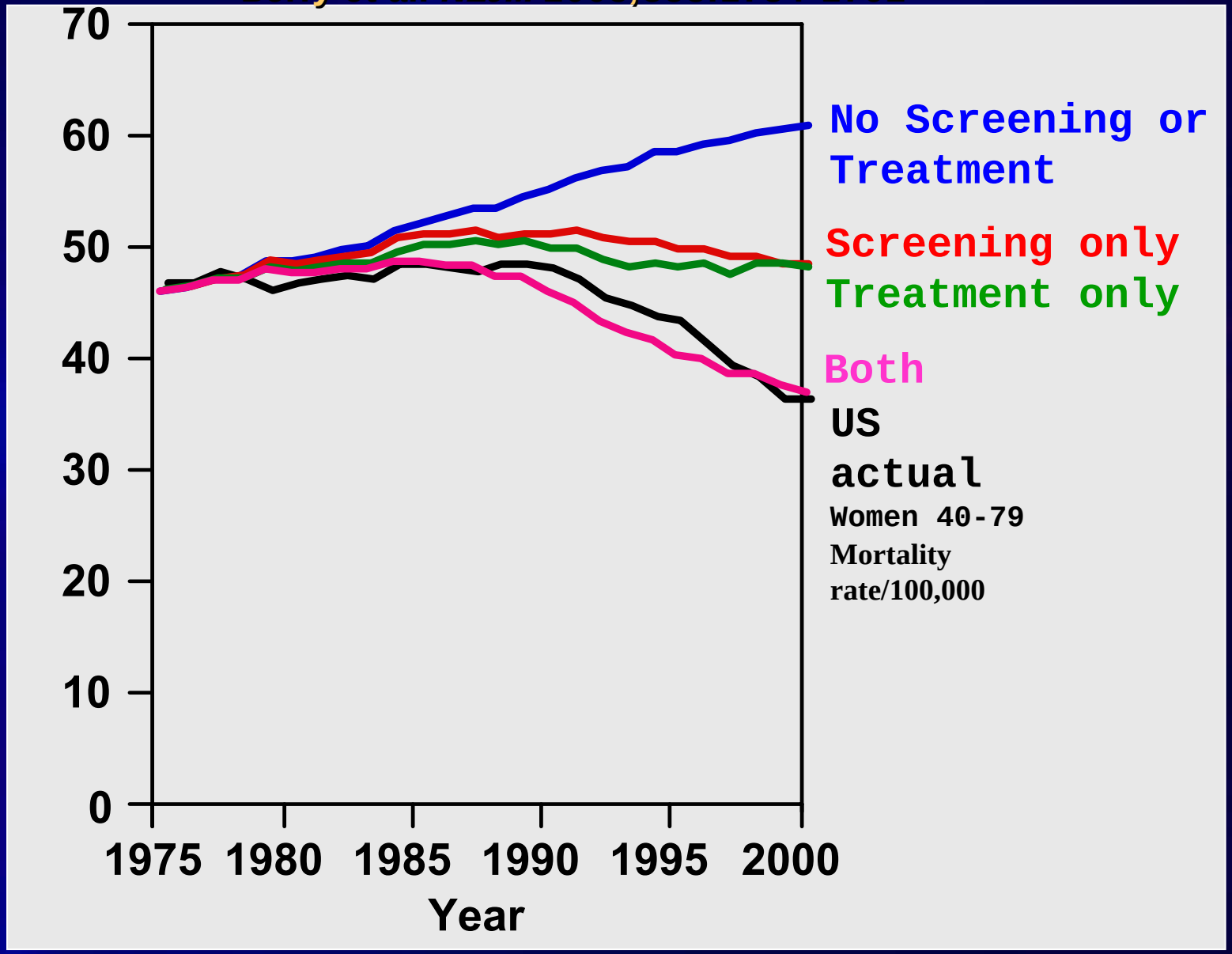


Only 7% cured in 1971: only 15% cured today.

What has helped with other solid tumors?

CISNET Breast Cancer Group
Impact of Screening and Treatment

Berry et al. *NEJM* 2005;353:1784-1792



What would help most for lung cancer?

SMOKING CESSATION

U.S. population with direct smoking exposure:

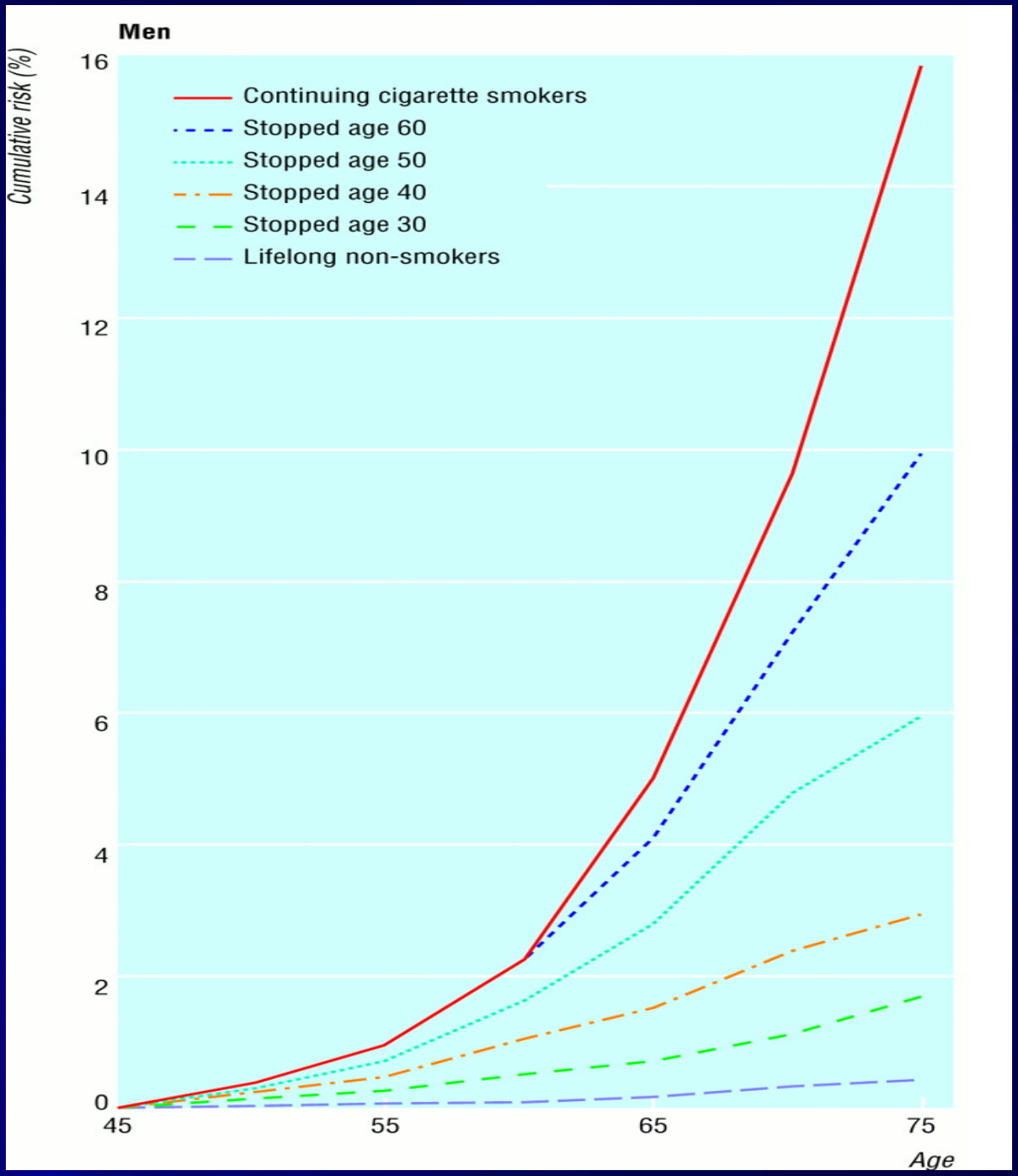
- 46.5 million former smokers
- 45.1 million current smokers

CDC MMWR 10/27/06

Percentage of persons age ≥18 years who were current cigarette smokers, by sex and age groups

Age groups (yrs)	Men	Women	Total
United States (2005)			
18-24	28.0 (±3.0)	20.7 (±2.4)	24.4 (±2.0)
25-44	26.8 (±1.4)	21.4 (±1.2)	24.1 (±1.0)
45-64	25.2 (±1.5)	18.8 (±1.1)	21.9 (±0.9)
≥65	8.9 (±1.3)	8.3 (±1.0)	8.6 (±0.8)
Total	23.9 (±1.0)	18.1 (±0.7)	20.9 (±0.6)
Maryland (2005)			
Total	19.7 (±1.9)	18.4 (±1.4)	19.0 (±1.2)

CDC MMWR 10/27/06



Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in UK in 1990. Nonsmoker rates were taken from US prospective study of mortality

Peto R, BMJ, 2000

Rationale for Lung Cancer Screening

- Smoking cessation helps, but residual risk remains
  - Quit at age 50 risk by age 75 is 6%
- Improved *survival* with early stage disease
  - 5-Yr Survival all comers: 15%
  - Resected clinical Stage I: 92% per I-ELCAP; 75 % SEER
- Why not start screening high-risk individuals now?
  - Dr. Henschke's estimate that CT screening could reduce deaths by 80 % is "an outrageous and implausible claim." But … "it really got people to pay attention."
    - Dr. Peter Bach, NYT Tuesday, October 31, 2006

Distinguishing *Benefit* from *Bias*

- In screening, survival endpoints are confounded by:
  - Lead-time: Earlier detection prolongs survival independent of delay in death
  - Length : Screening selects for more indolent cancers
  - Overdiagnosis: Detecting cancer that is not lethal
- Prolonged survival $\neq$ mortality reduction

Current Data

from

CXR & CT Screening Studies

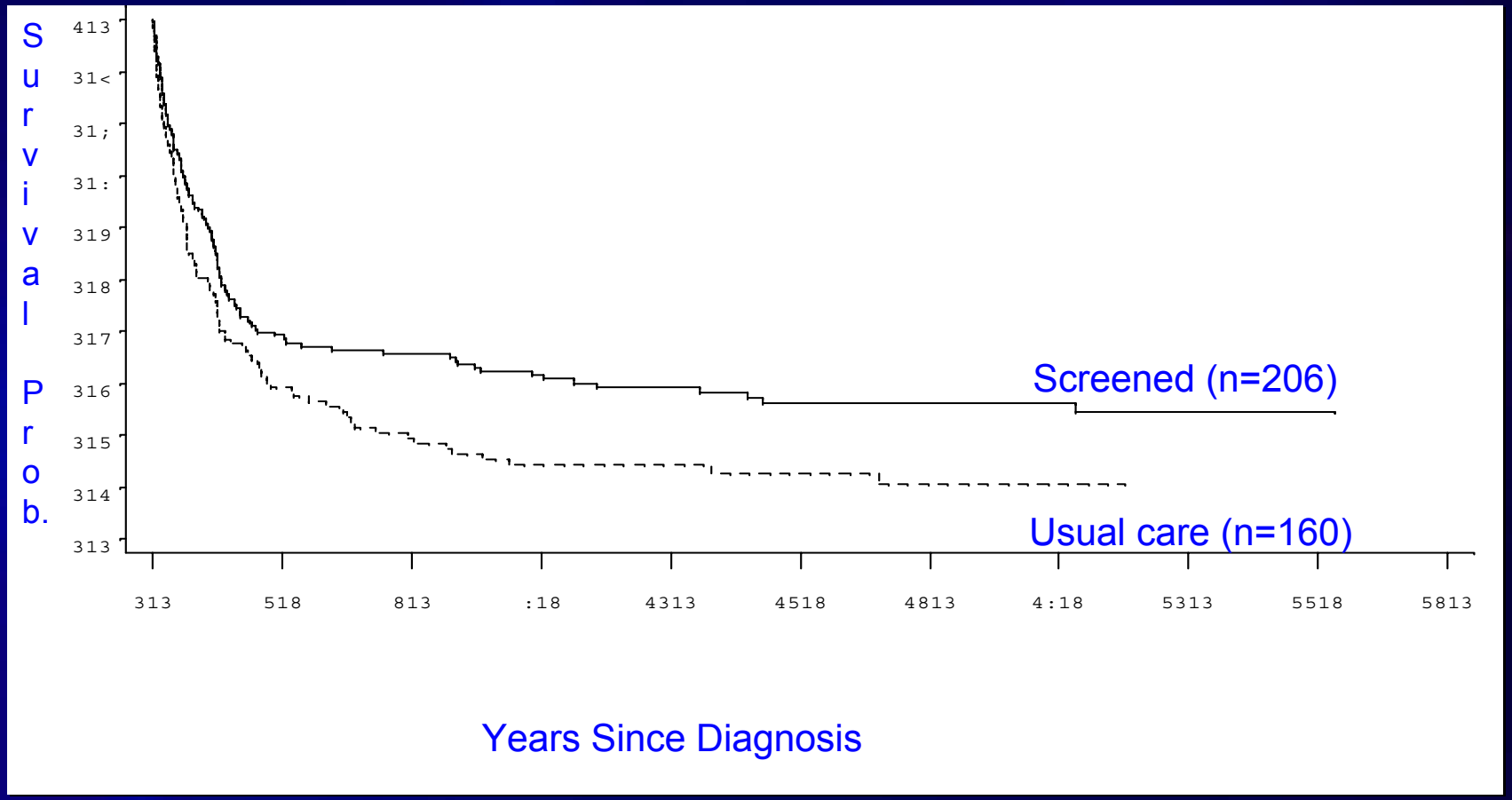
Mayo Lung Cancer Screening Project

9211 Study Participants

Screened Group CXR & pooled sputum q 4 months	Standard care recommendation at study entry
Lung Cancers=206 Stage I & II (resected) 83 (40%) Late-stage (unresected) 123 (60%)	Lung Cancers=160 Stage I & II (resected) 41 (25%) Late-stage (unresected) 119 (75%)

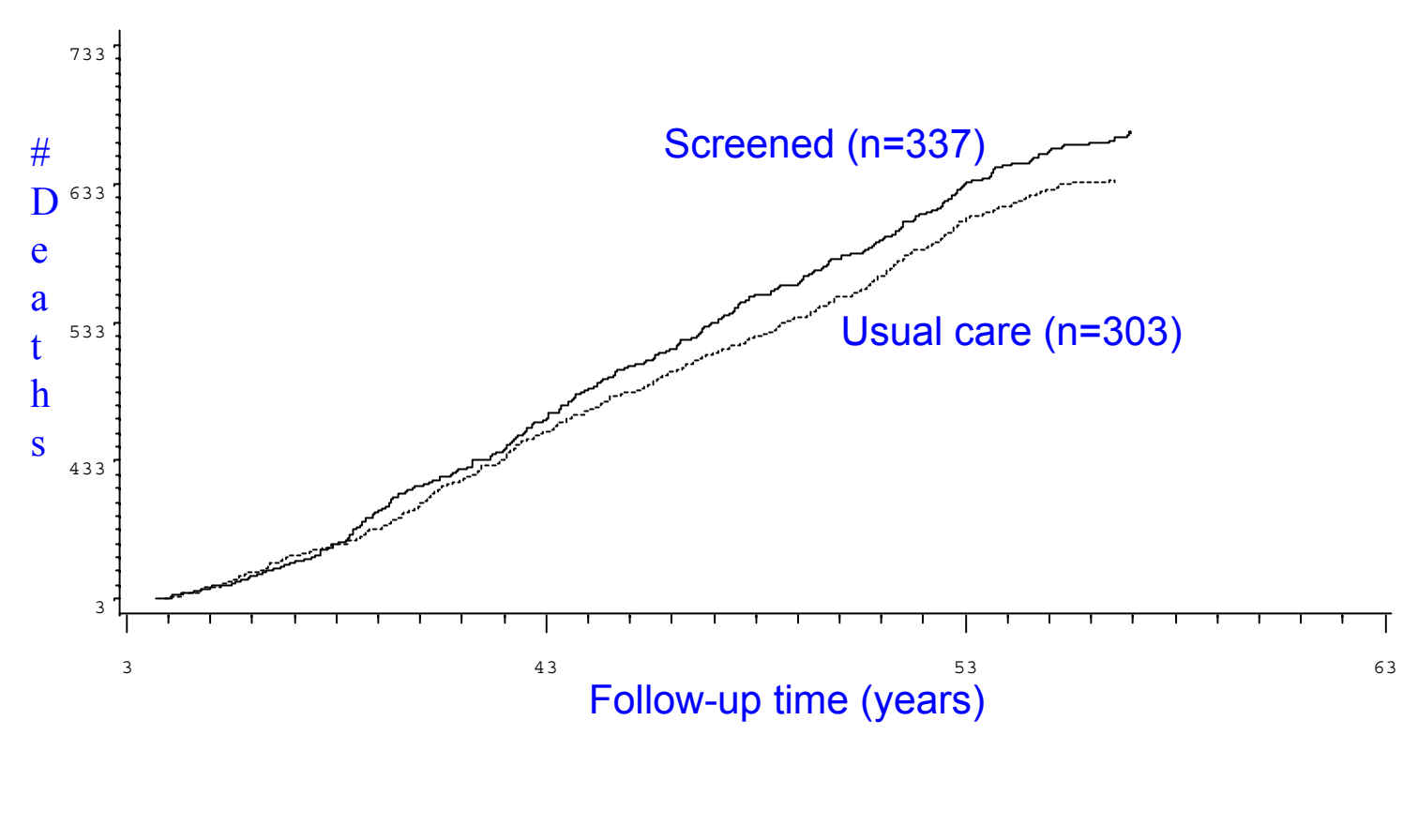
Marcus, JNCI, 2000

Mayo Lung Project
Lung Cancer Survival



Marcus, JNCI 2000

Mayo Lung Project
Cumulative Lung Cancer Deaths



Marcus, JNCI 2000

INTERPRETATION

- Overdiagnosis exists
- CXR not effective in reducing mortality
- Problems:
  - Study underpowered for a realistic result, 10% mortality decrease could have been missed
  - Contamination and compliance
- PLCO launched

Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial:
Screening vs. No Screening

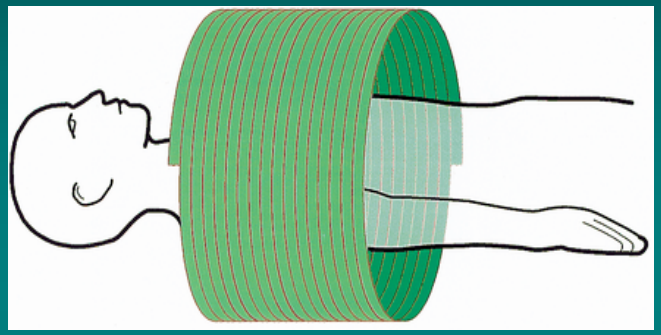
- Multicenter RCT involving 154,942 men and women aged 55-74
  - 1:1 randomization to CXR screening vs. no screening
  - Smokers: CXR at baseline and then annually for 3 screens
  - Non-smokers: CXR annually for 3 screens
- Primary endpoint: lung cancer-specific mortality

PLCO Prevalence Screen Results
(Oken, et al, *JNCI* 2005)

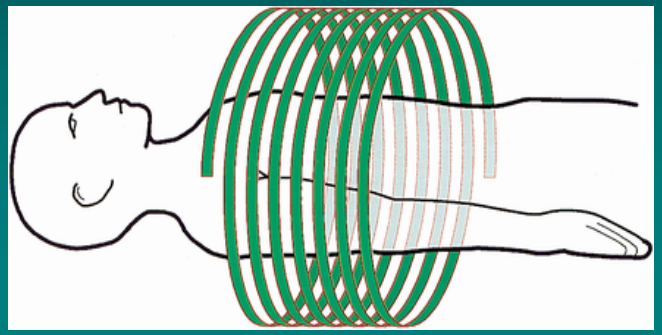
Participant group (n = 77,465)	Cancers per 1000 screens
Current smokers	6.3
Former smokers	Stratified
If smoked within prior 15 yrs	4.9
If did not smoke within prior 15 yrs	1.1
Never smokers	0.4

- 126 lung cancers were screen-diagnosed
  - 55 (44%) were Stage I, representing 52% of the 107 NSCLCs diagnosed
  - Of 14 cancers in never smokers, 12 = adenocarcinoma |12 in women
- Overall rates highest for older age groups, smokers and men
- Data re: mortality benefit from CXR screening are forthcoming

Spiral (Helical) CT



Pitch = 1



Pitch > 1

$$\text{Pitch} = \frac{\text{Table travel per revolution}}{\text{Collimation Width}}$$

$$\frac{\text{Acquired Slice Spacing (C to C)}}{\text{Slice Thickness}}$$

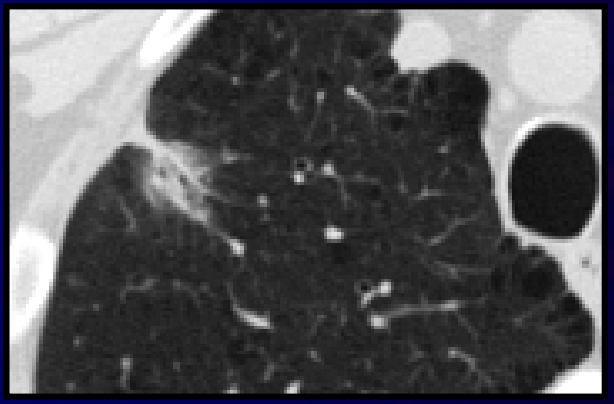
Low-Dose Helical CT

- Allows entire chest to be surveyed in a single breathhold
  - Time: approximately 7 - 15 seconds
  - Reduces motion artifact
  - Eliminates respiratory misregistration
- Narrower slice thickness
- Hourly throughput - 4 patients per hour
- Radiation dose one tenth of diagnostic CT

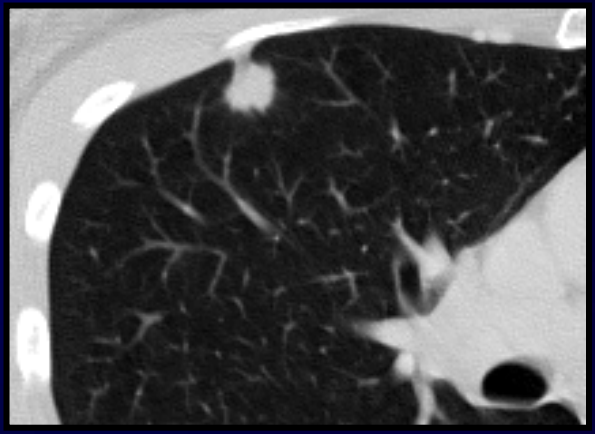
What do we see on CT? Definition of terms

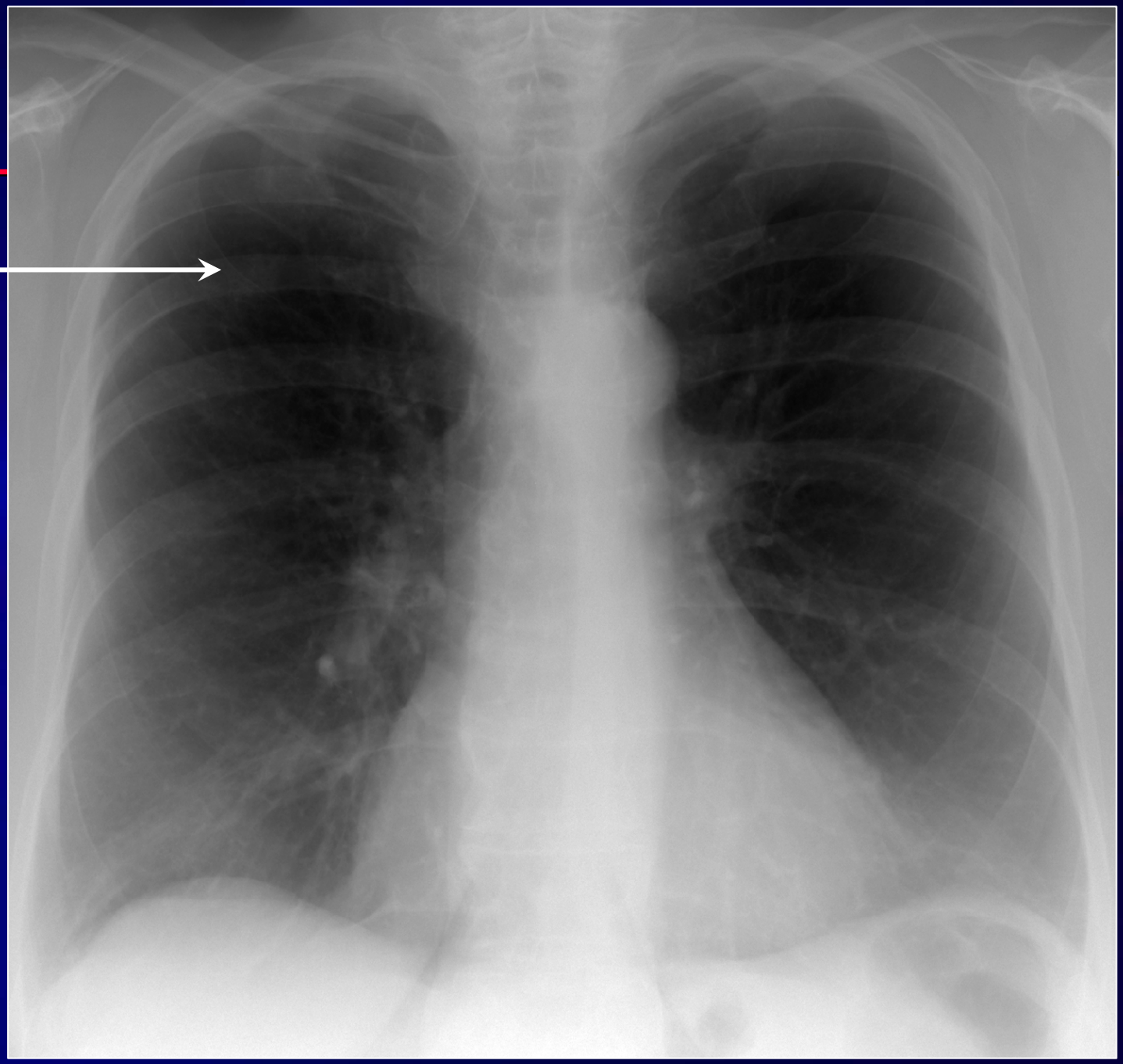
- GGO (non-solid): Nodule with hazy increased lung attenuation which does not obscure underlying bronchovascular markings.

- Mixed (part-solid): Nodules containing both ground glass and solid components



- Solid (soft tissue): Nodules with attenuation obscuring the bronchovascular structures





Nodules may be very subtle on screening CXR

Corresponding helical CT confirms nodule in RUL

Downstream Effects of CT Screening

- Radiation carcinogenesis
  - screening & consequent diagnostic tests: CT, PET
- Additional minimally invasive procedures
  - Percutaneous Lung FNA
  - Bronchoscopy
  - VATS
- Thoracotomy for benign disease
  - Is there an acceptable percentage?
  - Potential post-operative morbidity & mortality
- Evaluation for other observations: cardiac, renal, liver, adrenal disease

Summary of Selected Cohort Trials

Trial	Criteria	N	[+] Screens	Total Cancers	Stage I NSCLC	Survival
ELCAP 2001 CT + CXR	60+ Yr 10 Pk Yr	Yr 0: 1000 Yr 1: 841 Yr 2: 343	Baseline 233 (23.3%) Incidence 40 (3.4%)	Baseline: 31 (3.1%) Incidence: 07 Interval: 2	Baseline: 23 (74%) Incidence: 5 (55%)	All with cancer alive at 2.5 Yrs; 5 deaths other causes No mortality data
Swensen CT annual x 5 yrs	50+ Yr 20 PkYr Quit <10Yr	Yr 0 1520 Yr 1:1478 Yr 2:1438 Overall >95%	Baseline: 782 (51%) Incidence: 9.3-13.5%	Baseline: 31 (2%) Incidence: 32 Interval: 3	Baseline: 20 (65%) Incid: 17 (61%)	42 deaths overall: 09 lung ca (1.6) 33 all cause (6.0) [per 1000 person-Yr]
I-ELCAP	Site Specific	Yr 0: 31,567 Incid: 27,456	Baseline 4186 (13%) Incidence: 1460 (5%)	Baseline: 405 Incidence: 74 Interval: 5	Baseline: Incidence: Total: 347 (72%)	F/U = median 3.3 Yrs Estimates: -Overall 80% 10 Yr -Resected cStage 1 92%

Mayo Helical CT Study

- 1520 participants; baseline and 4 annual screens
- 1118 (74%) had 3356 uncalcified nodules
- 68 lung cancers in 66 participants
- Lung cancer mortality rates compared with MLP in similar age and sex subset
  - Incidence lung cancer mortality: 2.8 vs 2.0 per 1000 person-years

International Early Lung Cancer Action Project

- Prospective, international, multi-institutional study
- 31,567 patients at high risk for lung cancer screened
  - Azumi Health Care Program, Japan
    - 3,087 (10%) current or former smokers
    - 3,299 (10%) non-smokers
- Criteria for enrollment varied by institution
- 27,456 annual screens (second; what about later?)

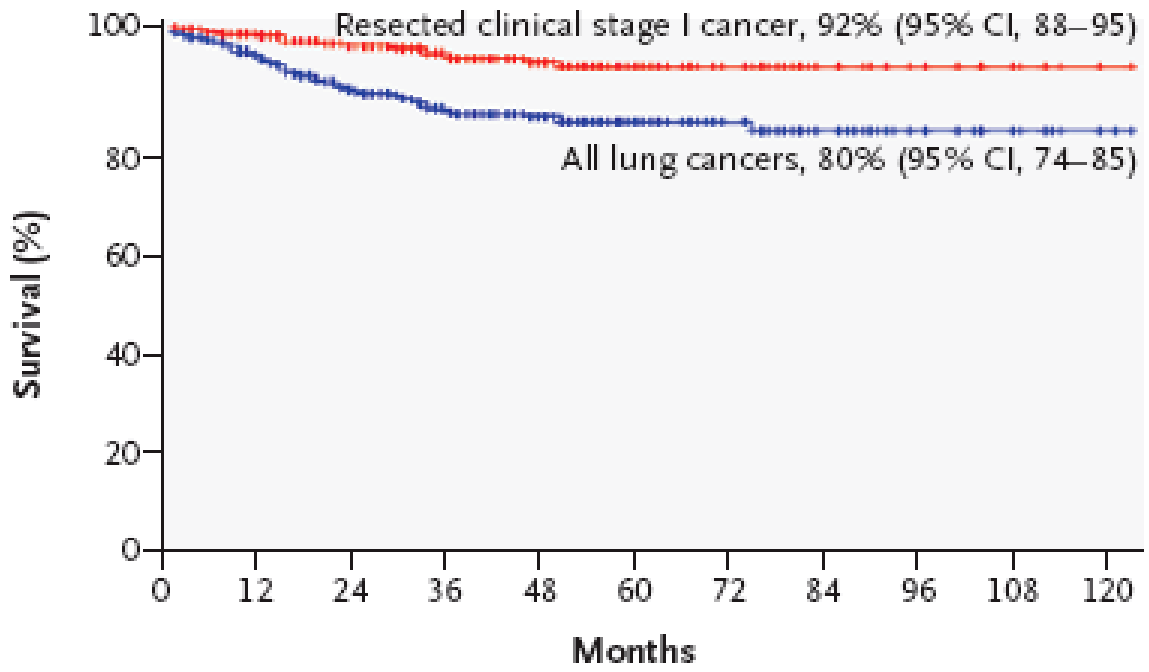
I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

I-ELCAP

- 31,567 baseline screens; 27,456 annual
- Low-dose CT per ELCAP protocol
  - Definition of a positive changed
    - Baseline 13% positive (original ELCAP)
    - Annual 5% positive
- Diagnostic work-up recommended but decision as to how to proceed left to individual and their physician
- 535 participants had biopsy as recommended in protocol; 2 deaths within 4 weeks in lung cancer patients after surgery
  - No comment as to how many biopsies done outside protocol

I-ELCAP

- Baseline: 31,567
  - 4186 nodules qualifying as positive result (13%)
  - 405 lung cancer
  - 5 interim diagnoses of lung cancer
- Annual repeat: 27,456
  - 1460 new nodule (5%)
  - 74 lung cancer; no interim
- Total lung cancers 484 out of 535 biopsies
  - 90.5% positivity rate
  - 412 (85%) Clinical Stage I



No. at Risk											
All participants	484	433	356	280	183	90	50	28	16	9	2
Participants undergoing resection	302	280	242	191	120	59	34	18	12	7	1

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

Lessons From CT Observational Trials

- Detected prevalence rate: 0.40 – 2.7%
  - Age is strong risk factor (> 60 years)
  - Pack year smoking history
- *Nodule* detection rate variable on CT: 5.1% - 51.4%
  - Function of [a] definition of “nodule” and [b] CT slice thickness
  - Benign nodules = majority of detected nodules: ~90%)
- CT results in *higher* lung cancer detection than CXR
  - ≥ 3-fold higher detection rate vs CXR; excess cancers early stage
  - 2-3 fold selective oversampling of adenocarcinoma
  - Stage shift *not* yet been shown

National Lung Screening Trial

- Determine effect on lung cancer mortality
  - 90% power, α of 5%, to detect a 20% difference
- Determine magnitude if any of stage shift
- Delineate adverse events
- Determine the ratio between risks and benefits
  - Thoracotomies for benign disease
  - Diagnostic radiation exposure in individuals without cancer; estimate radiation carcinogenesis

Definition of High Risk Participants

- Males and females
- 55-74 Yrs
- Asymptomatic current or *former* smokers ≥ 30 pack yrs
- Former smokers must have quit within ≤ 15 yrs
- No prior Hx lung cancer
- No Hx *any* cancer within past 5 years
- No chest CT w/in prior 18 months

NLST Trial Design

53,464
High-Risk
Subjects

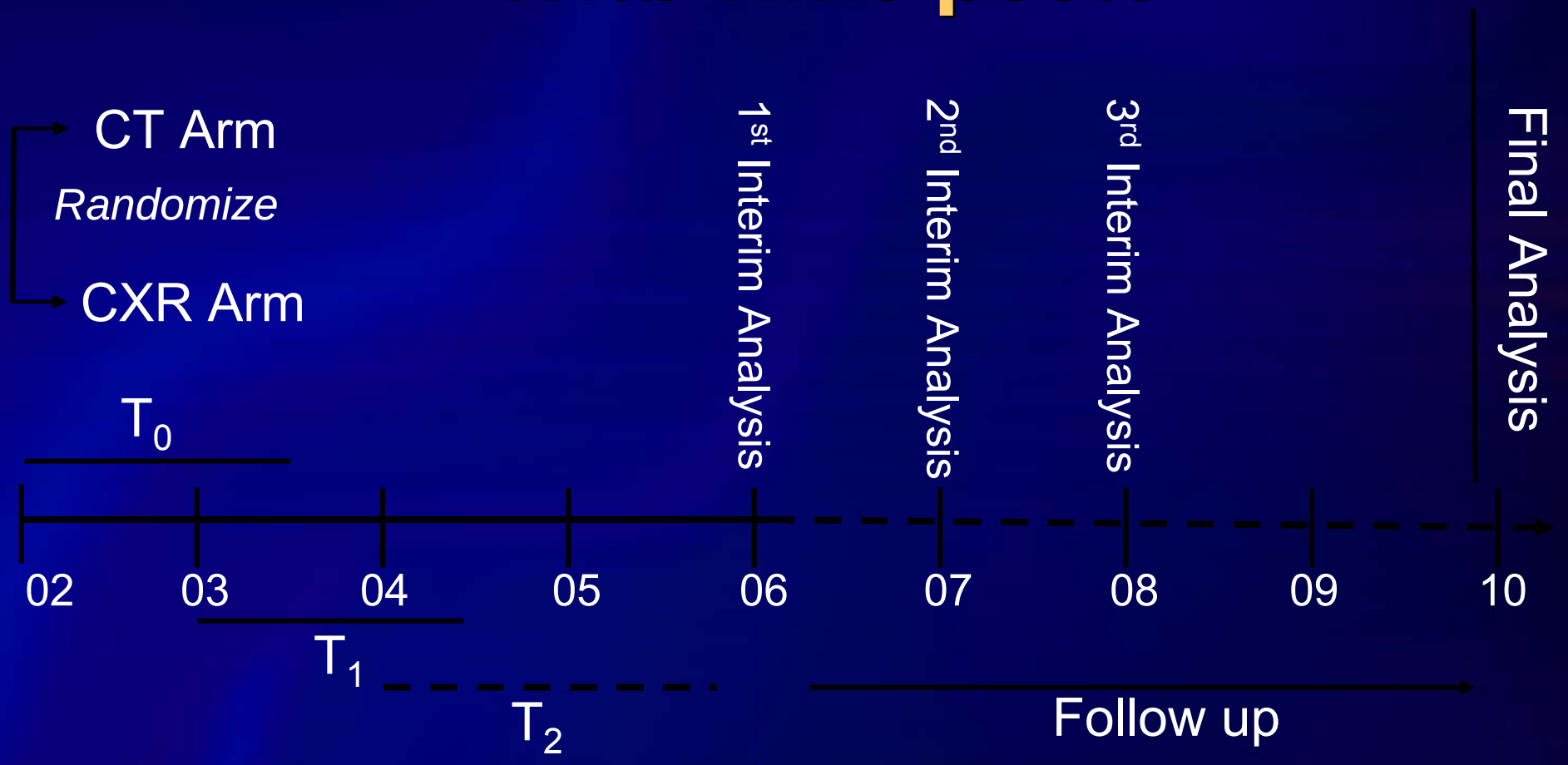
CT Arm

Randomize

CXR Arm

3 annual screens: T0, T1, T2

Trial Time posts



Trial-Wide Participant Demographics

N = 53,464

Category	CT #	CT %	CXR #	CXR %	Total #	Total %
GENDER						
Male	15776	59.0%	15769	59.0%	31545	59.0%
Female	10951	41.0%	10968	41.0%	21919	41.0%
EDUCATION						
HS or Less	7913	29.7%	8047	30.2%	15960	29.9%
More than HS	18212	68.2%	18053	67.5%	36265	67.8%
SMOKING						
Current	12884	48.2%	12921	48.3%	25805	48.3%
Former	13837	51.8%	13805	51.6%	27642	51.7%

Minority Accrual

Category		LSS-NLST % Ppts	ACRIN-NLST % Ppts	ALL % Ppts	Population of eligible persons %
RACE	White	89.9	92.3	90.8	91.7
	African American	3.7	5.8	4.4	6.3
	Asian	2.9	0.6	2.1	1.0
	American	0.4	0.4	0.4	1.0
	Indian/Alaskan	0.5	< 0.1	0.4	-
	Pacific Islander	1.7	0.5	1.3	-
	More than one race	1.0	0.4	0.7	
ETHNICITY	Hispanic	2.0	1.3	1.8	3.4
	Non-Hispanic	96.9	98.5	97.5	96.6
	Unknown	1.1	0.3	0.8	-

* Estimates derived from the Tobacco Use Supplement of the Current Population Survey (Census Department) for 1998 & 1999. Eligibility defined as: age 55-74; ≥ 30 pack yr smoking history; and current or former smoker of ≤ 15 yrs.

Screening Exam Compliance
(as of June 30, 2006)

Study Year	Spiral CT		Chest X-ray		Total	
	Expected	Screened	Expected	Screened	Expected	Screened
T0	26,715	98.5%	26,728	97.5%	53,443	98.0%
T1	26,334	93.9%	26,429	91.2%	52,763	92.5%
T2	26,014	91.3%	26,160	87.9%	52,174	89.6%

- By sex: Female CXR slightly lower than male CXR
- By age group: consistent
- By race/ethnicity: AA, Hispanic is lower than White at T1,T2

NLST Image Standardization and QC

Image Interpretation & Diagnostic Pathways

ACRIN/NLST CT Technique
Parameter
kV
Gantry Rotation Time
mA (Regular patient-Large patient values)
mAs (Reg-Lg) [1]
Scanner effective mAs[2] (Reg-Lg)
Detector Collimation (mm) - T
Number of active channels - N
Detector Configuration - N x T
Collimation (on operator console)
Table incrementation (mm/rotation) - I
Pitch ([mm/rotation] /beam collimation) - I/NT
Table Speed (mm/second)
Scan Time (40 cm thorax)
Nominal Reconstructed Slice Width
Reconstruction Interval [3]
Reconstruction Algorithm[3]
Images/Data set (40 cm thorax)
$CTDI_{vol}$ (Dose in mGy) [4]

NLST-ACRIN Physics Committee

- CT Technique Chart
  - Standardized 18 parameters
  - 14 different CT scanners
  - 4 manufacturers: 4-64 channel
- Equipment certification annually
- Bi-monthly CT phantom calibration
- CXR techniques from CRFs reviewed

Interpretation Results

- [-] Screen

  No significant findings –or – minimal findings not significant for lung cancer

- [-] Screen

  Significant findings unrelated to lung cancer
  [Some form of diagnostic recommendation required; e.g., echocardiogram for suspected pulmonary hypertension)

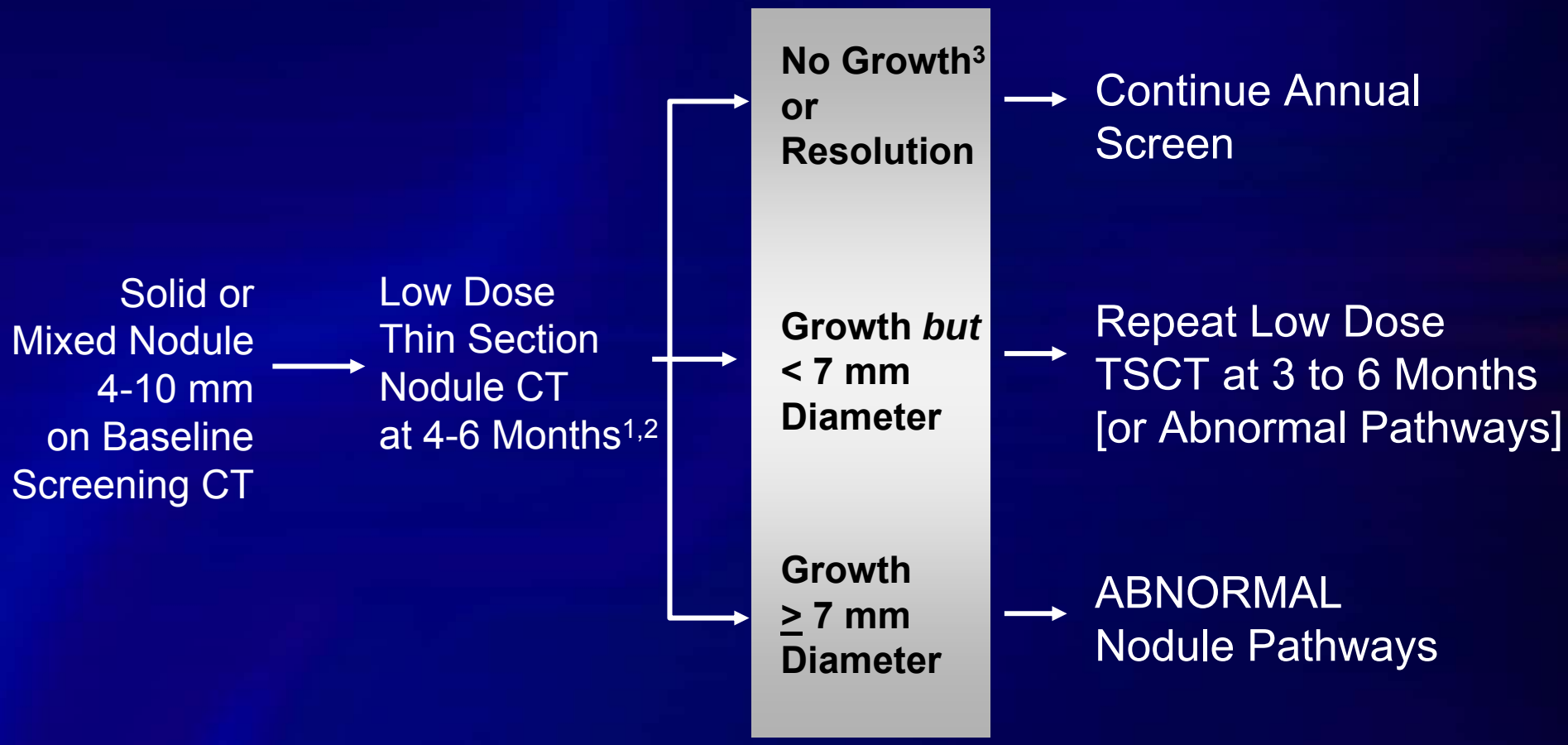
- [+] Screen

  Findings potentially related to *lung cancer*
  [diagnostic recommendation of some form required]

Image Interpretation

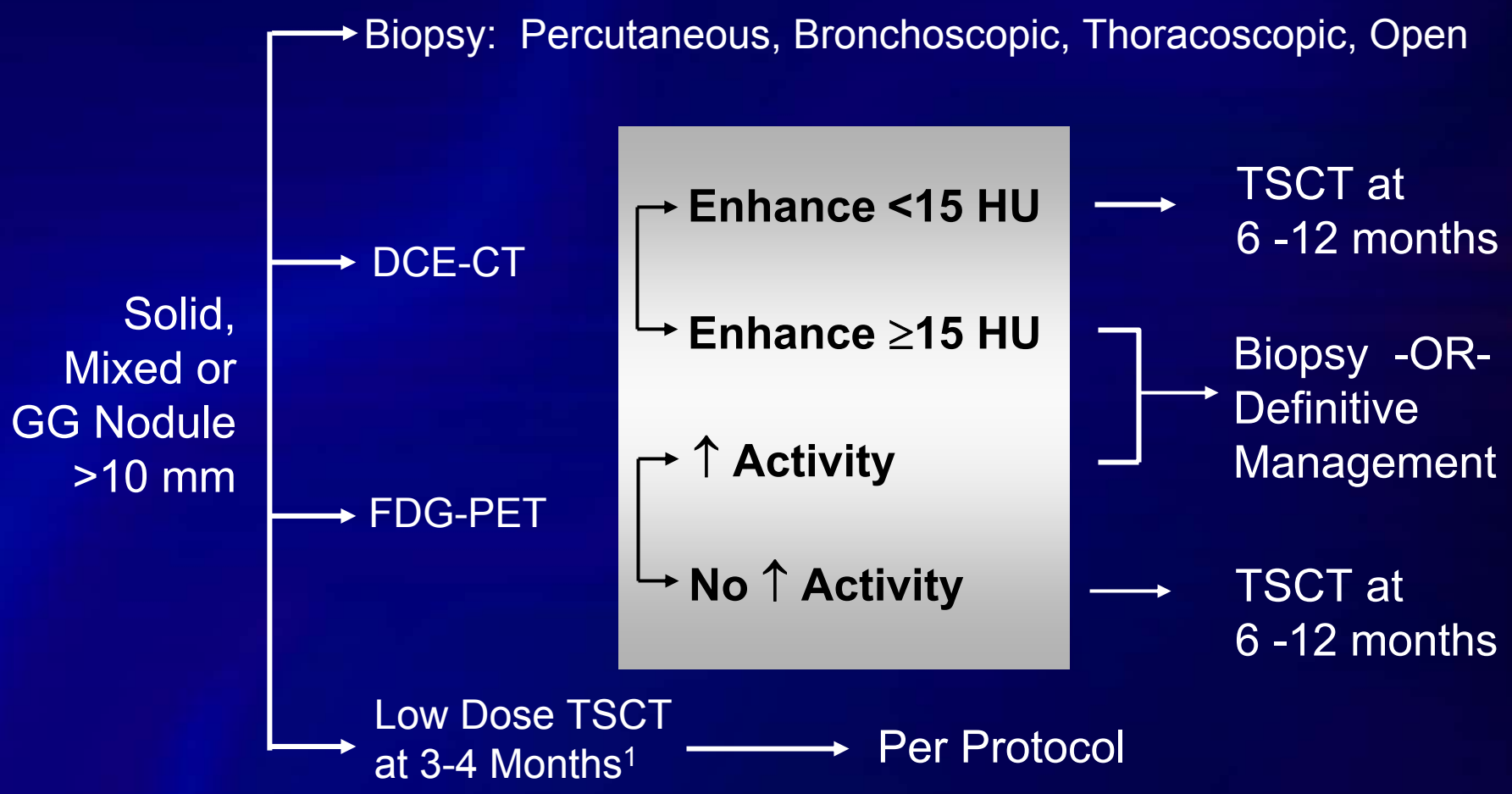
- 51 Non-calcified nodule(s)
  Record slice #; lobe, diameters; margins, attenuation
- 52 Micronodules < 4 mm
- 53 Benign or calcified nodules
- Other major findings:
  - 54 Atelectasis, segmental or greater
  - 55 Pleural thickening | effusion
  - 56 Hilar | mediastinal adenopathy
  - 60 Significant cardiovascular abnormality (CM, CAD, AV Ca++)
  - 61 Interstitial fibrosis
  - 63 Significant other findings above diaphragm
  - 64 Significant findings below diaphragm

Diagnostic Pathways for CT Nodules 4-10 mm



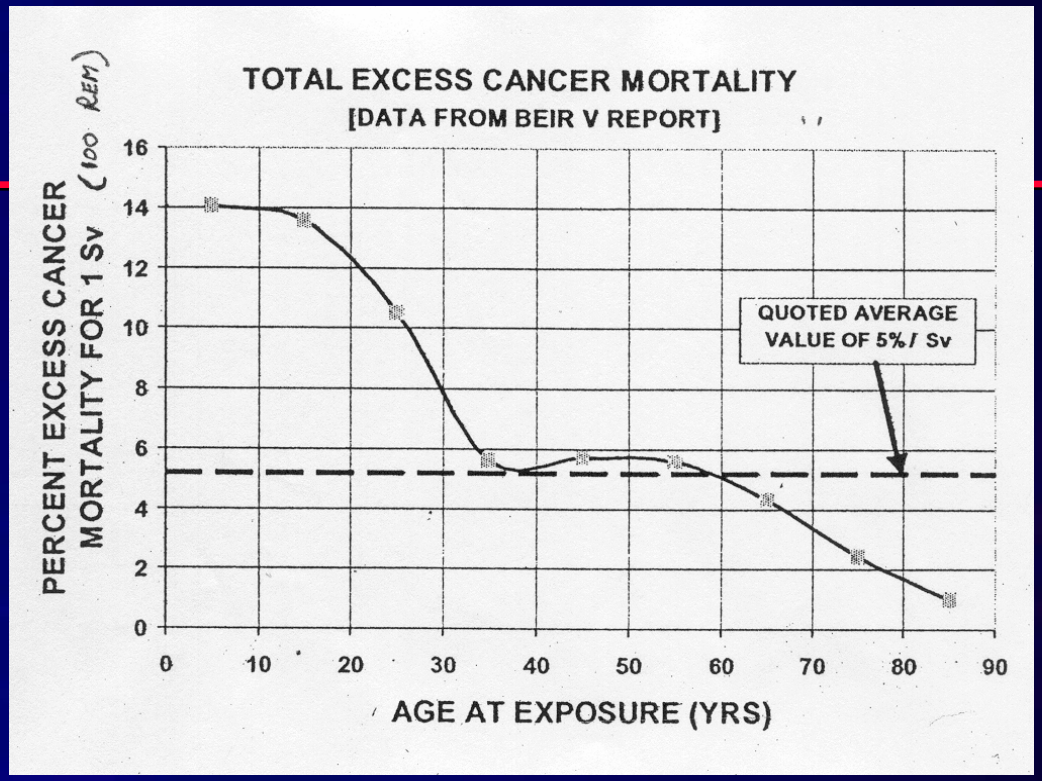
[1] Pure ground glass nodules can be followed-up at 6-12 months if < 10 mm.
[2] Some nodules 4-10 mm may go directly to biopsy or other tests in ABNORMAL pathways.
[3] No growth is defined as < 15% increase in overall diameter OR no ↑ in solid component.

ABNORMAL Pathways: Nodules >10 mm



[1] Reserved for nodules considered highly likely to be BENIGN [polygonal shape, 3D shape ratio > 1.78]

WHAT'S THE RISK?



ASSUMING AN INCREMENTAL CANCER MORTALITY RISK OF 5% / Sv, AND A LINEAR, NO THRESHOLD, DOSE RELATIONSHIP, YIELDS

CXR @ 0.033 mSv = INCREMENTAL RISK OF 0.00017% (1/600,000)

CT @ 2.2 mSv = INCREMENTAL RISK OF 0.011% (1/9,000; 67/600,000)

Society of Thoracic Radiology Physician Responsibility

- Discuss benefits and risks of spiral CT screening
- Warn the subject that a negative screen does not preclude development of lung cancer
- Ensure that the subject knows that some lung cancers may not be amenable to detection by CT screening
- Ensure that the subject is contacted with results of the CT screening
- Ensure that appropriate physicians are available to council and treat the patient with a positive result
- Ensure that patients understand the problem of the number of small lung nodules that are benign and the implications thereof.