Current role of radiological screening in lung cancer

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11/3/11

Introduction

- Lung cancer – leading cause of cancer death globally
- Accounts for 18% of cancer deaths & > 1 million deaths per year
- No of deaths/yr > no of deaths from Ca breast+colon+prostate/yr
- 85% lung cancer – “smoking”

PREVENTABLE

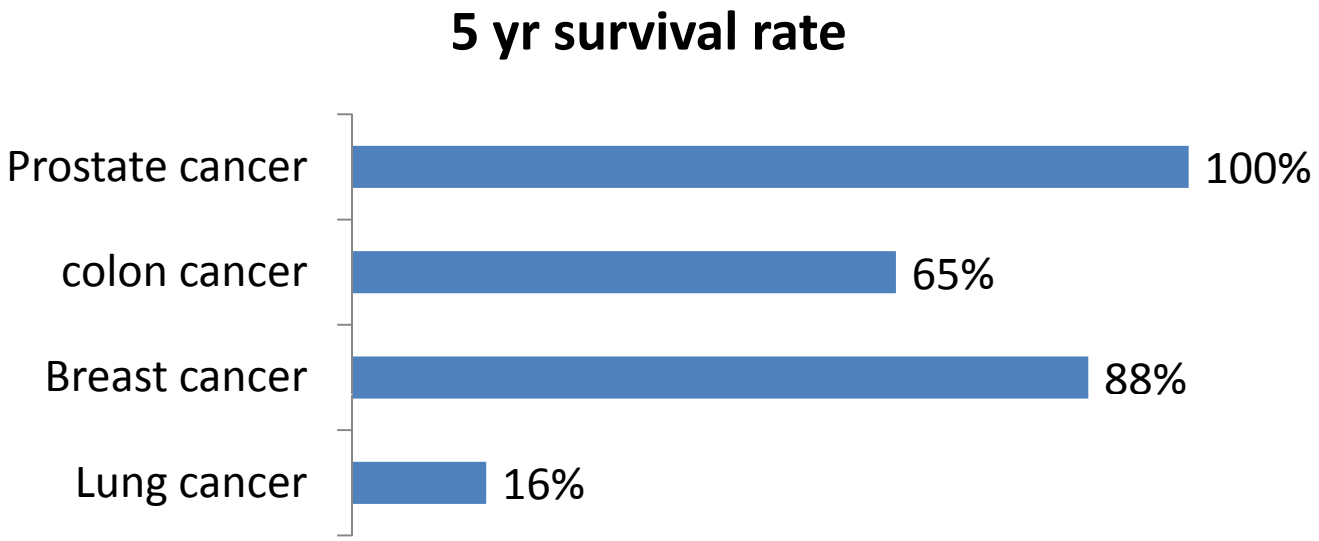
Rosen G.Johns Hopkins University Press; 1993

Survival

- 5 year survival rate combined for all stages is 16%
- 5 year survival rate is 6% for SCLC and 17% for NSCLC
- 5 year survival rate for localized disease is 53%
- 16% are diagnosed at localised stage
- Late diagnosis of extensive disease is the main reason of failure

American Cancer Society. Cancer Facts & Figures 2010

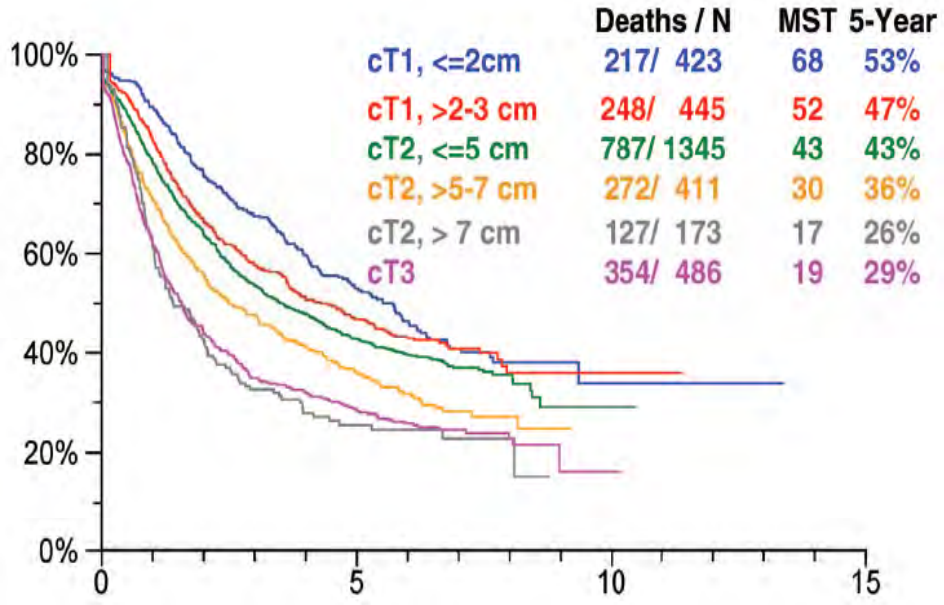
Rationale for early detection



American Cancer Society. Cancer Facts & Figures 2010

Lung cancer outcome

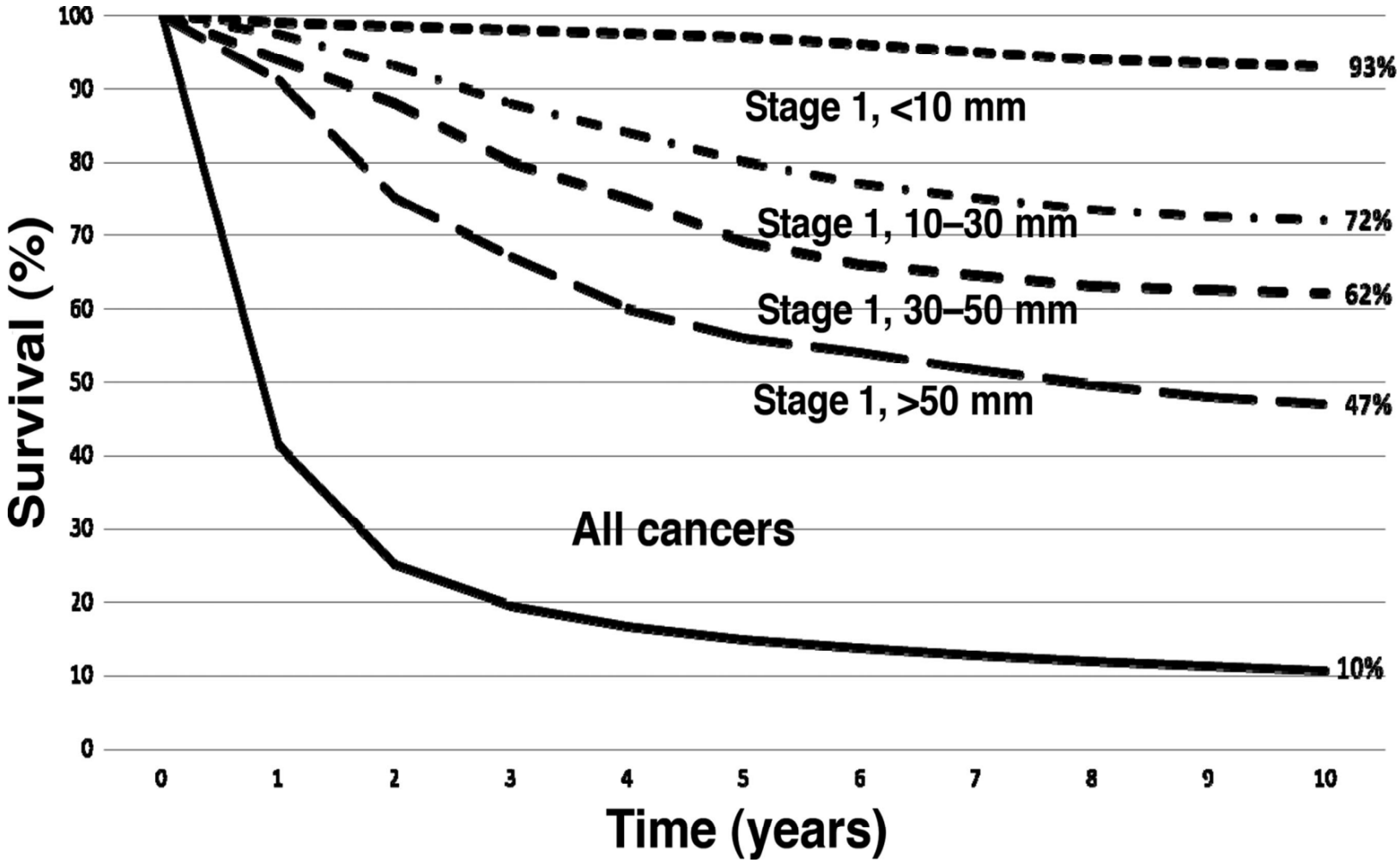
- Strongly related to size and stage: small tumors do better



After surgery

Rami-Porta R et al. J Thorac Oncol. 2007;2:593-602

Curability of lung cancer within stage I disease by tumor diameter and for all stages combined as estimated by 10-year survival rates.



The Oncologist 2008;13:65–78

How to improve the outcome of lung cancer?

- Improve therapy
  - may take decades
- Detect tumors at a curable stage
  - screen the high risk group

Rationale for Early Detection

- Early Stage disease
  - Radically treatable
  - Better survival

- Clear Risk Factors
  - Smoking –length & dose
  - Asbestos exposure
  - COPD

Screening

- Systematic testing of asymptomatic individuals with respect to some target disease

- Purpose – to prevent, interrupt, or delay the development of advanced disease

Hillman et al. JACR 2004;1(11):861-864

Principles of screening

- Detect a cancer in its preclinical stage
- Accessibility, cost and morbidity associated with a screening test should be reasonable
- Early intervention in the preclinical stage should change the course of the disease and decrease mortality

- Effective screening
- Ineffective screening
- Unnecessary screening
- Screening Biases
  - Lead time bias
  - Length Bias
  - Overdiagnosis Bias
  - Biological Bias

Biological Bias

- BACs have greater transradiancy
- GGO - far less contrast with the surrounding lung
- Less detectable with CXR than are adeno- and squamous carcinomas(solid density)
- BACs are overrepresented in CT screenings, relative to both their proportion in CXR screenings and reflecting their slow growth, to the proportion of LC that become clinically evident.

Why don’t we screen lung cancer

Screening tools

- Radiological→Mainly lung parenchyma; adenoca, large cell
  - CXR
  - Low dose CT

- Sputum→ Mainly larger airways; squamous, SCLC
  - Cytology

- Autofluorescence bronchoscopy-Only larger airways; squamous, SCLC

The value of lung cancer detection by six-monthly chest radiographs

G. Z. BRETT

From the Mass Radiography Service, N.W. Metropolitan Region, 285 Harrow Road, London W.9

Results are reported of a prospective study, carried out by the Mass Radiography Service of the North-West Metropolitan Region for the purpose of evaluating early lung cancer detection by six-monthly chest radiographs. The lung cancer experience of a test group of 29,723 men aged 40 and over who were offered six-monthly chest radiographs over a period of three years is compared with a similarly constituted control group of 25,311 men who were radiographed only at the beginning and the end of the study. In the test group 29,416 men (98·9%) and in the control group 25,044 men (99%) were followed up. The methods employed to achieve this result are analysed. The six-monthly surveys of the test group yielded 65 cases of lung cancer, giving an annual incidence and detection rate of 0·9 per thousand examined. Of these cases 65% were resected. Of all cases of lung cancer in the test group, irrespective of their source of detection, 43·6% were operable, compared with 29% in the control group. The difference ($P=0·03$) is statistically significant. The annual mortality rate from lung cancer based on 62 deaths in the test group and 59 deaths in the control was 0·7 and 0·8 per thousand respectively. The conclusions are reached that since early detection by six-monthly chest radiographs has not significantly reduced the mortality from lung cancer in a population at risk, a policy of such large-scale surveys of men in the cancer age would not seem justified, but that the increased discovery of resectable lung cancer by this method forms a reasonable basis for encouraging individuals in high-risk groups to make regular use of existing mass radiography facilities.

Brett G. Thorax 1968:23;414

Study	Intervention	No. of Participants	No. of Lung Cancers Detected at First Screening (Prevalence)	No. of Lung Cancers Detected After First Screening	No. of Stage III and IV Cancers*	Lung Cancer Mortality†‡	5-year Survival (%)†
Memorial Sloan-Kettering (11,12)					173	NA	35
Experimental arm	Annual chest radiography, sputum cytology every 4 mo	4968	30	146	…	…	…
Control arm	Annual chest radiography	5072	23	155	…	…	…
Johns Hopkins (13,14)					NA		NA
Experimental arm	Annual chest radiography, sputum cytology every 4 mo	5226	39	194	…	3.4/1000 PY	…
Control arm	Annual chest radiography	5161	40	202	…	3.8/1000 PY	…
Mayo Lung Project (15–17)			91 in all§				
Experimental arm	Chest radiography, sputum cytology every 4 mo	4618	…	206	123‖	4.4/1000 PY	35
Control arm	Recommended annual chest radiography, sputum cytology	4593	…	160	119‖	3.9/1000 PY	19
Czechoslovakian RCT (18,19)			19 in all§				NA
Experimental arm	Chest radiography and sputum cytology every 6 mo × 3 years, annually after year 3	3171	…	108	53	7.8%	…
Control arm	Chest radiography and sputum cytology annually after year 3	3174	…	82	46	6.8%	…

Radiology.258: 1Jan 2011

Outcome of CXR Screening

- More cancers detected in screened groups
- Most early stage
- No mortality reduction
- No “ no screening” arm
- Era of squamous Ca
- Inadequate sample size
- Male predominant

Chest 2003; 123:72S-82S
Am Rev Respir Dis 1984; 130:561-565.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

- Largest RCT-(1993 to 2001)
- Participants of 154942
- Age 55-74
- CXR at baseline and annually thrice (if smoker) or twice (non-smoker)

Stage I 44 %

Result	Baseline screening chest radiograph		
	All	Women	Men
No. screened	67 038	32 899	34 139
No. positive screens	5991	2700	3291
% positive of total screened	8.9	8.2	9.6
No. patients examined by biopsy	206	100	106
% of positive screens examined by biopsy	3.4	3.7	3.2
No. lung cancers diagnosed	126	59	67
PPV of screening test, % (95% CI for PPV)*	2.1 (1.7 to 2.5)	2.2 (1.6 to 2.7)	2.0 (1.6 to 2.5)
% of biopsy examinations positive	61.2	59.0	63.2
No. lung cancers per 1000 screens	1.9	1.8	2.0

J Natl Cancer Inst 2005;97:1832 – 9

Loopholes

- Underrepresentation of blacks & hispanic
- No exposure history
- Data from higher S.E. strata

Moratlity benefit ?? 2015

Advantages of CT

- Cross-sectional data acquisition and display, which reduces the problem of overlying structures obscuring the detection of lung nodules

- Visualization of more subtle abnormalities

LDCT

- Average effective dose - 1.5 mSv
- Conventional chest CT- 8 mSv

Screening for Ca lung with LDCT

Purpose: Because efficacy of lung cancer screening using chest x-ray is controversial and insufficient, other screening modalities need to be developed. To provide data on screening performance of low-dose helical computed tomography (CT) scanning and its efficacy in terms of survival, a one-arm longitudinal screening project was conducted.

Patients and Methods: A total of 1,611 asymptomatic patients aged 40 to 79 years, 86% with smoking history, were screened by low-dose helical CT scan, chest x-ray, and 3-day pooled sputum cytology with a 6-month interval.

Results: At initial screening, the proportions of positive tests were 11.5%, 3.4%, and 0.8% with low-dose helical CT scan, chest x-ray, and sputum cytology, respectively. In 1,611 participants, 14 (0.87%) cases of lung cancer were detected, with 71% being stage IA disease and a mean tumor diameter of 19.8 mm. At repeated screening, the proportions of positive tests were 9.1%, 2.6%, and 0.7% with low-dose helical CT, chest x-ray, and sputum cytology, respectively. In 7,891 examinations, 22 (0.28%) cases of lung cancer were detected, with 82% being stage IA disease and a mean tumor diameter of 14.6 mm. The 5-year survival rate for screen-detected lung cancer was 76.2% and 64.9% for initial and repeated screening, respectively.

Conclusion: Screening with low-dose helical CT has potential to improve screening efficacy in terms of reducing lung cancer mortality. An evaluation of efficacy using appropriate methods is urgently required.

Brett et al .J Clin Oncol 1999 20:911-20.

I-Elcap results

- Large multicenter, multinational, nonrandomized trial
- 31,567 baseline and 27,456 repeat scans 7-18 months after baseline
- 484 cancer cases detected
- All cases: 10-yr survival 80%
- Stage I resected cases (85%): 10-yr survival 92%
- Stage I untreated cases (n=8): dead within 5-yrs

N Engl J Med 2006; 355:1763-1771

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2006 VOL. 355 NO. 17

Survival of Patients with Stage I Lung Cancer Detected on CT Screening

BACKGROUND

The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.

METHODS

In a large collaborative study, we screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005, 27,456 repeated screenings were performed 7 to 18 months after the previous screening. We estimated the 10-year lung-cancer–specific survival rate among participants with clinical stage I lung cancer that was detected on CT screening and diagnosed by biopsy, regardless of the type of treatment received, and among those who underwent surgical resection of clinical stage I cancer within 1 month. A pathology panel reviewed the surgical specimens obtained from participants who underwent resection.

RESULTS

Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92% (95% CI, 88 to 95). The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis.

CONCLUSIONS

Annual spiral CT screening can detect lung cancer that is curable.

I-Elcap: controversies

- No control arm
- Cannot rule out lead-time, length-time and overdiagnosis biases
- Does not account for potential harm

N Engl J Med 2006; 355:1763-1771

LDCT v/s usual care RCT's

Trials		F/U	No screened (Male)	Control arm	Volumetry	Expected
NELSON	2004-11	6 yr	15750(85%)	Usual care	Y	2015
DLCST	2002-04	5 yr	4104(55%)	Usual care	Y	-
ITALUNG-CT	2004-06	6 yr	1019	Usual care	N	2012
UKLS	2011-12	-	3551 Target 28000	Usual care	N	2015

LDCT v/s CXR RCT's

	Period	expected	number	Control
LSS	2000-02	Done	3318	CXR
NLST	2002-04	2015	53456(59% male)	CXR
DEPISCAN	2002-04	Done	765	CXR
DANTE	2002-04	Done	2500	CXR

Dante trial

	LDCT (*n* = *1,276*)(%)	Control (*n* = *1,196*)(%)	*P* Value
Patients with lung cancer	60 (4.7)	34 (2.8)	0.02
Stage*	61 (4.8)	35 (2.9)	
IA	20 (1.6)	4 (0.3)	
IB	13 (1.0)	8 (0.7)	
All Stage I	33 (2.6)	12 (1.0)	0.004
II	4 (0.3)	2 (0.2)	
IIIA	7 (0.6)	4 (0.3)	
IIIB	6 (0.5)	3 (0.3)	
IV	11 (0.9)	14 (1.2)	
Stage IIIB-IV	17 (1.3)	17 (1.4)	0.86
Histology*	63 (4.9)	36 (3.0)	
Adenocarcinoma	19 (1.5)	12 (1.0)	
BAC	8 (0.6)	1 (0.1)	0.04
Squamous cell	19 (1.5)	11 (0.9)	
Small cell	6 (0.5)	2 (0.2)	
NSCLC, NOS	5 (0.4)	3 (0.3)	
Other†	4 (0.3)	2 (0.2)	
NA	2 (0.2)	5 (0.4)	

Infante et al. Am J Respir Crit Care Med 2009(180)445–53.

Dante trial

	LDCT (*n* = 1,276)(%)	Control (*n* = 1,196)(%)	Total	*P* Value
Cause of death				
Lung cancer	20 (1.6)	20 (1.7)	40	0.84
Other causes	26 (2.0)	25 (2.1)	51	0.93
Total deaths	46 (3.6)	45 (3.8)	91	0.83

Infante et al. Am J Respir Crit Care Med 2009(180)445–53.

Additional procedures after screening

	LDCT	%	Controls	%	*p*-Value
Imaging					
High-resolution CT	128	10.0	20	1.7	<0.05
PET	35	2.7	2	0.2	<0.05
Invasive procedures					
Bronchoscopy	15	1.2	6	0.5	
Fine-needle aspiration biopsy	17	1.3	4	0.3	<0.05
Mediastinoscopy	4	0.3	0	0.0	
VATS biopsy	8	0.6	5	0.4	
Thoracotomy	32	2.5	6	0.5	<0.05
Lung cancer	22	1.7	6	0.5	<0.05
Other disease[a]	4	0.3	0		
Benign pulmonary nodule[b]	6	0.5	0		
Any invasive procedure	53	4.2	12	1.0	<0.05

Infante M et al. Lung Cancer (2008) 59, 355—363

National lung screening trial

- Multicenter, RCT
- LDCT vs CxR in screening current & former heavy smoker (≥ 30 pack-year)
- 53,456 participants (sept 02- april 04)
- randomized to undergo a baseline and two annual screenings by using either low-dose CT or chest radiography.

Posted 4/11/10 www.cancer.gov

National lung screening trial

- Primary end point – lung ca mortality
- 20% Ca lung mortality reduction
- 7 % all cause mortality reduction

Posted 4/11/10 www.cancer.gov

Meta-analysis

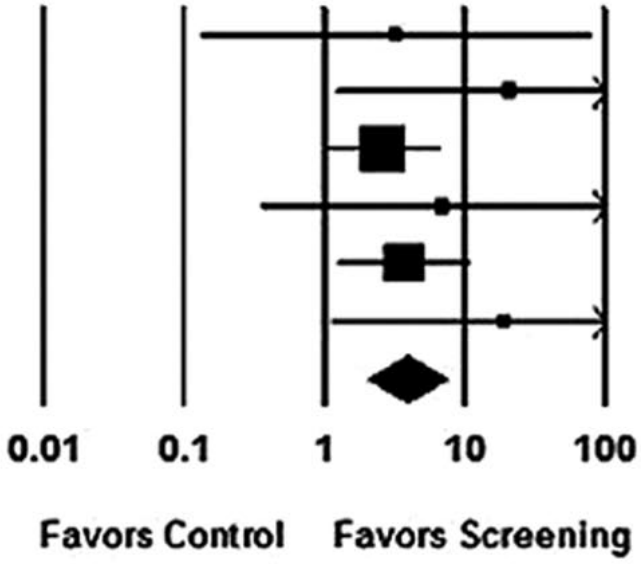
Name of Study	Screening Duration	Sample Size	Trial Randomization	Age (yr)	Sex	Smoking History (yr)/ Ex-Smokers Quit (yr)	Collimation of LDCT Scan (mm^3)	Year Final Results Expected
Garg/Colorado University[16]	2001 (1 yr)	92 LDCT, 98 control (190)	LDCT vs. usual care	50–80	97.4% male, 2.6% female	>30	5	n/a
ITALUNG[32]	2004–2006	1613 LDCT, 1593 controls (3206)	LDCT vs. usual care	55–69	64.7% male, 35.3% female	>20/<10	1–3	2012
LSS[33,35,45]	2000–2004	1660 LDCT, 1658 CXR (3318)	LDCT vs. CXR	55–77	59% male, 41% female	>30/<15 (NLST), <10 (LSS)	0.6–2 (NLST)/ 5 (LSS)	2011
DEPISCAN[31]	2002–2004	385 LDCT, 380 controls (765)	LDCT vs. CXR	50–75	71% male, 29% female	>15/<15	1–1.5	n/a
DANTE[30]	2001–2006	1276 LDCT, 1196 controls (2472)	LDCT vs. usual care	60–74	Male only	>20/<10	5	n/a
DANISH[54]	2004–2006	2052 LDCT, 2052 controls (4104)	LDCT vs. usual care	49–74	55.2% male, 44.8% female	>20	3	2011

Gopal et al . J Thorac Oncol: Vol 5(8), Aug2010

Meta-analysis

Forest Plot of Odds Ratio of Stage I NSCLC in LDCT Arm Compared to Control Arı

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Garg et al	3.230	0.130	80.283	0.715	0.475
ITALUNG	20.869	1.222	356.434	2.098	0.036
NLS/LSS	2.680	1.046	6.865	2.054	0.040
DEPISCAN	6.963	0.358	135.267	1.282	0.200
DANTE	3.784	1.262	11.351	2.374	0.018
Danish	19.084	1.110	328.096	2.032	0.042
	3.905	2.052	7.430	4.151	0.000

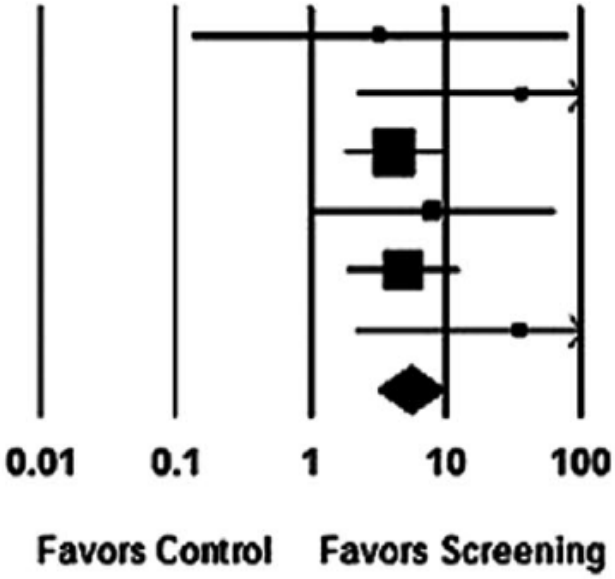


Gopal et al . J Thorac Oncol: Vol 5(8), Aug2010

Meta-analysis

Forest Plot of Odds Ratio of Total NSCLC in LDCT Arm Compared to Control Arm

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Garg et al	3.230	0.130	80.283	0.715	0.475
ITALUNG	36.954	2.225	613.718	2.518	0.012
NLS/LSS	4.194	1.832	9.600	3.393	0.001
DEPISCAN	8.042	1.001	64.617	1.961	0.050
DANTE	4.955	1.896	12.945	3.266	0.001
Danish	35.292	2.121	587.255	2.484	0.013
	5.507	3.127	9.698	5.908	0.000

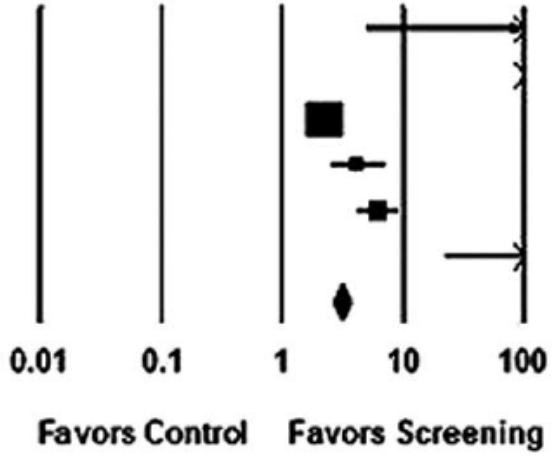


Gopal et al. J Thorac Oncol: Vol 5(8),

Meta-analysis

Forest Plot of Odds Ratio of False Positive Nodules in LDCT Arm Compared to Control Arm

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Garg et al	82.710	4.958	1379.718	3.075	0.002
ITALUNG	1980.070	123.573	31727.701	5.363	0.000
NLS/LSS	2.255	1.825	2.787	7.524	0.000
DEPISCAN	4.212	2.510	7.065	5.447	0.000
DANTE	6.227	4.166	9.310	8.915	0.000
Danish	352.850	21.961	5669.261	4.141	0.000
	3.122	2.621	3.720	12.740	0.000



Gopal et al . J Thorac Oncol: Vol 5(8), Aua2010

Untoward effects of screening

- Unnecessary procedures
- Anxiety
- Radiation exposure

Screening and smoking cessation

- 16.6% of the trial participants quit smoking(3-7% in general population.)
- Screening - lower prolonged abstinence rate (14.5%) compared with no screening (19.1%) →after ITT analysis this difference was no longer observed
- Screening is a teachable moment to improve smoking behaviour

van der Aalst et al.Thorax. 2010 Jul;65(7):600-

LUNG Cancer: recommendations

- Chest X-rays cannot be recommended for screening of lung cancer.
  - Recommendation IA

- Low-dose CT scan cannot yet be used for screening of lung cancer unless in a clinical trial.
  - Recommendation IIC

Annals of Oncology 21 (Supplement 5): v103–v115, 2010

TAKE HOME MESSAGE

- Screening – mortality benefit??
- No definitive evidence that screening with LDCT is ineffective
- Too early to say→ wait till 2015
- Can anything help???

Prevention is cure

STOP SMOKING