What is the target population for lung cancer screening ?

Antwerpen, oktober 2012

Rob van Klaveren

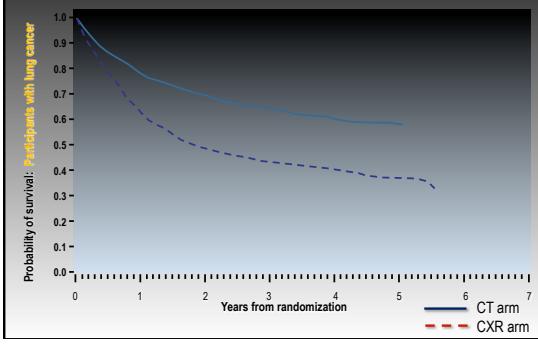
November 2010

Lung cancer trial results show mortality benefit with low-dose CT:
Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray

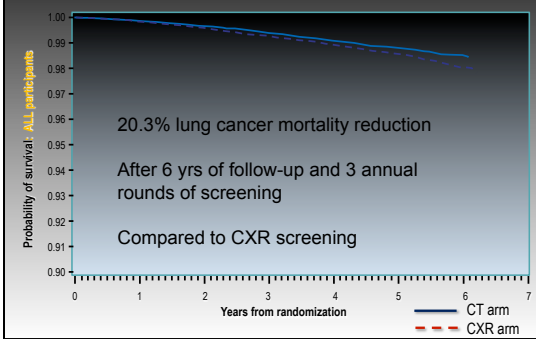
The National Cancer Institute (NCI) is today releasing initial results from a large-scale test of screening methods to reduce deaths from lung cancer by detecting cancers at relatively early stages…..

hhtp://www.cancer. gov/newscenter/pressrelease/NLSTresultRelease

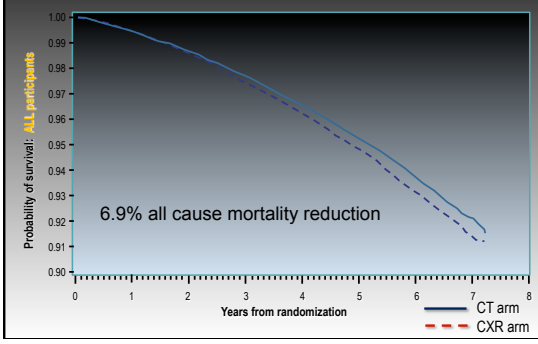
Lung cancer case survival Kaplan Meier curve



Kaplan-Meier curves for *lung cancer mortality*



Kaplan-Meier curves for *all-cause mortality*



ACCP and ASCO guidelines

- (former)-smokers age 55-74
- > 30 PY's
- Quit < 15 yrs
- 3 annual screening rounds

- Remark 4: quality metrics should be developed such as those in use for mammography screening which could enhance the benefits and minimize the harms

Gaps in our knowledge

- What will be the effect of CT screening as compared to an anti-smoking policy
- Concern about generizability of the NLST results (minorities)
- What is the optimal target populaton
- What is the optimal number of screening rounds and the length of the interval

Gaps in our knowledge

- Only data from a single US study (NLST):
  - DANTE no mortality reduction after 3-yrs of FU.
  - DLCST: no mortality reduction or stage shift, suggestion for overdiagnosis !
  - EU data (NELSON) awaited
  - PLCO data (n=154.901) CXR=Usual care !

Oken MW et al JAMA 2011

The effect of CT screening as compared to anti-smoking policy

- Lung Cancer Policy model: Tobacco control versus screening
- Age 30-84 yrs, 1975-2000, annual CT
  - Complete elimination: -28% mortality LC
  - Complete elimination + annual CT screening: -39% mortility LC
  - Conclusion: focus on smoking cessation !

McMahon P et al. Risk analysis vol 32 , 2012

Generalizability of the trial results

- Compared with similar US population, NLST cohort has similar gender distribution and smoking exposure
- However, NLST participants were
  - Younger
  - Better educated
  - Less likely to be current smokers
  - Less minorities

Comparing NLST with US census population

	NLST	US Census
Married	66.6	60.9
Education		
< HS	6.1	21.3
≥ College	31.5	14.4
Current smoker	48.2	57.1
Median pack yrs	48.0	47.0

Lynch DA et al. In press, J Natl Cancer Inst

Comparing NLST with eligible US census population

53,454 participants	NLST	US Census
Male (%)	59.0	58.5
Age		
55-59 (%)	42.8	35.2
60-64 (%)	30.6	29.3
65-69 (%)	17.8	20.8
70-74 (%)	8.8	14.7
Race | Ethnicity		
Black (%)	4.4	5.5
Hispanic (%)	1.7	2.4

Lynch DA et al. In press, J Natl Cancer Inst

Generizability of the NLST results

- Cultural factors: knowledge, beliefs, attitudes about the disease / screen process, fatalistic beliefs, mistrust healthcare system, financial burden of screening (lack of insurance), anxiety related to irradiation
- Especially in lower economic status / minorities underutilization of (CT) screening

Jonnalagadda et al. Lung Cancer 2012

"Predictions are risky - especially about the future…."

Yogi Berra

Who could have predicted this outcome?

The Challenge for Lung Cancer…….

➢Lifetime probability of lung cancer in US

1 in 13 – men

1 in 17 - women

Smokers in the US
Current -21% - 45 million
Former -23% - 49 million

➢Lifetime probability of lung cancer in smokers

1 in 6.5 – men

1 in 10 - women

How to identify that fraction of smokers <u>most</u> likely to get lung cancer?

Commonly used definition of a high-risk smoker

- A Lung Cancer incidence > 300/100.000

Lung cancer incidence rates by age and amount smoked per day (rates per 100 000)

	Age at incidence (death—5 years)								
	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74
1–9				42	114	258	362	560	725
10–19				101	103	192	360	859	574
20			43	83	200	297	652	854	1372
21–39			25	114	218	442	510	1042	1326
40			57	159	254	507	836	1244	1525
40+		53	141	220	332	499	999	1469	4067
All	6	19	41	115	206	361	582	909	1118

CPS II data [22].

Int. J. Cancer: **120,** 868–874 (2006)
© 2006 Wiley-Liss, Inc.

Risk-based selection from the general population in a screening trial: Selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON)

Carola A. van Iersel[1,2*], Harry J. de Koning[1], Gerrit Draisma[1], Willem P.T.M. Mali[3], Ernst Th. Scholten[4], Kristiaan Nackaerts[5], Mathias Prokop[3], J.Dik.F. Habbema[1], Mathijs Oudkerk[6] and Rob J. van Klaveren[2]

Number of cigarettes smoked per day
Duration of smoking
Duration of cessation
Age 50-75

Other risk factors

Co-variates and lung cancer risk [9,10]

Relative risk factors for lung cancer	
Tobacco exposure	Variable
Environmental (radon)	3
Occupational exposure (asbestos)	5
Genetic factors	Uncertain
Gender	Variable
Diet	Variable
Chronic obstructive lung disease	4.5
Family history	2.5

Stratification of the high risk population

British Journal of Cancer (2007), 1 – 7

www.bjcancer.com

Full Paper

The LLP risk model: an individual risk prediction model for lung cancer

A Cassidy[1,3], JP Myles[2,3], M van Tongeren[3], RD Page[4], T Liloglou[1], SW Duffy[2] and JK Field*[,1]

[1]Roy Castle Lung Cancer Research Programme, University of Liverpool Cancer Research Centre, Liverpool, L3 9TA, UK; [2]Cancer Research UK Centre for Epidemiology, Mathematics and Statistics Wolfson Institute of Preventive Medicine, London, EC1M 6BQ, UK; [3]Institute of Occupational Medicine, Research Avenue North, Riccarton, Edinburgh, EH14 4AP, UK; [4]Department of Thoracic Surgery, The Cardiothoracic Centre, Liverpool, L14 3PE, UK

Using a model-based approach, we estimated the probability that an individual, with a specified combination of risk factors, would develop lung cancer within a 5-year period.

LLP Multivariate model

Variable		OR	95% CI	p-value
Cigarette smoker	1-19 years	2.07	1.17 – 3.64	0.01
	20-39 years	4.07	2.51 – 6.56	<0.001
	40-59 years	11.67	7.11 – 19.16	<0.001
	≥60 years	14.56	5.48 – 38.64	<0.001
Family history	≤60 years old	2.02	1.18 – 3.45	0.01
	≥60 years old	1.18	0.79 – 1.77	0.41
Pneumonia		1.83	1.26 – 2.64	<0.01
Previous malignancy		1.96	1.22 – 3.14	<0.01
Asbestos exposure		1.89	1.35 – 2.62	<0.001

† model adjusted for most important covariates

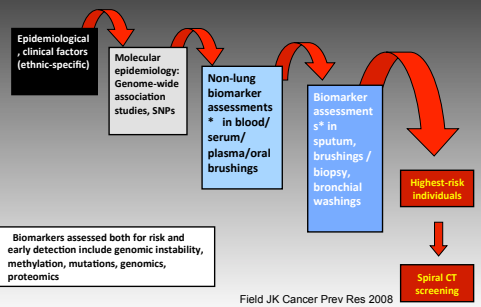
LLP-Risk Model Specific examples

- A man aged 64, 42 years smoking, history of other malignancy, relative with lung cancer aged over 60 at diagnosis,
- 5-year risk=9.5%- qualifies

- Woman aged 68, 26 years smoking, no other risk factors,
- 5-year risk = 1.5% - does not qualify

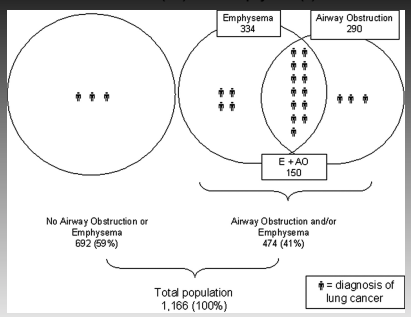
- Man aged 67, never-smoker, relative with lung cancer aged <60 at diagnosis, history of other malignancy and asbestos exposure,
- 5-year risk=3.2% - qualifies

The "upfront risk stratification" approach



Field JK Cancer Prev Res 2008

Distribution of participants with lung cancer according to the presence or absence of airway obstruction (AO) and/or emphysema (E).



de Torres J P et al. Chest 2007;132:1932-1938

CHEST

Improvements of LC risk models

Vol 452|3 April 2008|doi:10.1038/nature06885 nature

LETTERS

A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25

Please cite this article in press as: Landi et al., A Genome-wide Association Study of Lung Cancer Identifies a Region of Chromosome 5p15 Associated with Risk for Adenocarcinoma, The American Journal of Human Genetics (2009), doi:10.1016/j.ajhg.2009.09.012

REPORT

A Genome-wide Association Study of Lung Cancer Identifies a Region of Chromosome 5p15 Associated with Risk for Adenocarcinoma

- Adding DNA repair capacity no improvement in
- 5p15.33 locus 2 genes , telomerase reverse transcriptase gene

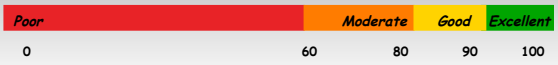
Multivariable Risk Models for Lung Cancer

Never smokers (330 cases/379 controls)	Odds Ratio
• Family History of cancer	2.00
• Environmental tobacco smoke (ETS)	1.80
Former smokers (784 cases/884 controls)	
• Emphysema	2.65
• Family History of cancer	1.59
• Dust Exposures	1.59
• Age at smoking cessation –3rd tertile	1.50
• No Hay fever	1.45
Current smokers (737 cases/738 controls)	
• Emphysema	2.13
• Pack- years – 4th quartile	1.85
• Asbestos Exposure	1.51
• No Hay fever	1.49
• Family history (smoking-related cancers)	1.47
• Dust Exposures	1.36

Discriminatory Power of Extended Genetic Model
(n = 1016 cases, 1111 controls)

Model	AUC	95% CI	P-value*
Baseline	0.661	0.64-0.68	–
*+ SNP's	0.673	0.65-0.70	0.023

* baseline + chr 15 and 5 SNP's



H. Pass, Biomarkers Where are we ?

- Technologies are approaching 90% specificity and sensitivity for early detection markers in *training sets*
- Technologies vary in complexity, expense and comprehensiveness
- > 2,000 papers on biomarkers
- >99.9% not validated !
- Only biomarkers which can be validated in large cohorts in blinded investigations at designated centers deserve to move towards clinical decision making in high risk cohorts or patients with lung cancer

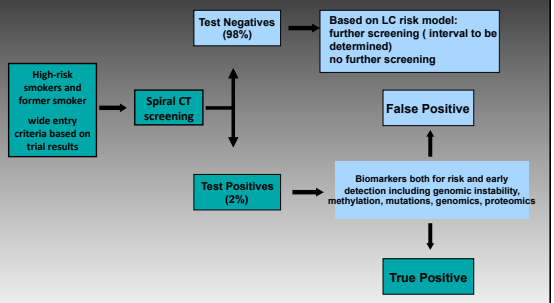
The Pro´s of upfront stratification

- Provides better cancer risk-estimates than on smoking history alone
- Helps smokers to understand the true nature of their risk and put it into a proper perspective
- Could help to assist counseling smokers to participate in LC screening program
- Will limit LC screening to certain high-risk subgroups
- Cost-effective way to use public health resources

The Con´s

- In general, screening is controversial
- Screening of certain high risk subgroups is even more controversial
  - Gail model for breast cancer screening has been developed for women who underwent 1 screening round and considered to participate in additional rounds
  - License to continue smoking for those at lower risk for lung cancer
  - Participation claims based on RCT results
  - Biomarker(s) with a very high sensitivity required
- Not for the near future
  - Not yet validated
  - Public education required

The "wide entry" approach



The Pro's

- all high risk smokers and former smoker invited to undergo at least 1 CT screening round
- Those who are test negative have a very high NPV of 99.7% (95%CI: 99.6-99.8%) and need no rescanning for at least 2-years
- Work-ups limited to test-positives (2%) which is manageable
- Is more "acceptable"' than upfront stratification
- Information from 1st screening round can be incorporated into LC risk model

Lung Cancer Risk Prediction to select smokers for screening CT – a model based on the Italian Cosmos Trial

Massonneuve P et al. Cancer Prev Res Nov 2011

Based on 1st CT scan

- Presence of emphysema on CT
- Nodule type (NS>PS>S)
- Size of the largest NCN

- Strongest predictors of subsequent lung cancer risk
- AUC = 0.744 (moderate)

Results

- 40% of population heavy smokers had < 0.3% annual risk of lung cancer
- During 3-yrs of FU only 10% of LC's diagnosed
- This population screen interval 3 yrs ?
- Saved 4000 CT scans, avoided surgery for benign nodules in 7, delayed surgery for lung cancer in 10