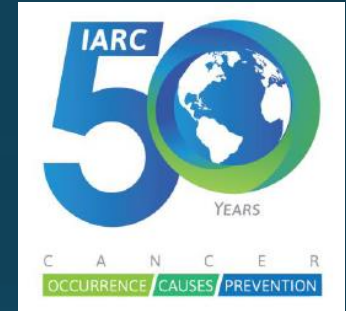


# Screening for Lung cancer should be implemented:

GLOBAL CANCER: OCCURRENCE, CAUSES,  
AND AVENUES TO PREVENTION



Professor John K Field PhD, FRCPath  
University of Liverpool Cancer Research Centre, UK.

J.K.Field@liv.ac.uk



World  
Cancer  
Research  
Fund International

Research we fund

Cancer facts & figures

Policy

Home – Cancer facts & figures – Data on specific cancers – Lung cancer statistics

Preventability estimates >

Link between lifestyle &  
cancer risk >

Data on specific cancers >

Worldwide data >

## Lung cancer statistics

Smoking is the principal cause of lung cancer; it is estimated to be responsible for 85 per cent of all types of this cancer.

**1.8 million new cases in 2012**

### Lung cancer statistics

#### Cases



New cases of lung cancer, 2013, UK

#### Deaths



Deaths from lung cancer, 2012, UK

#### Survival



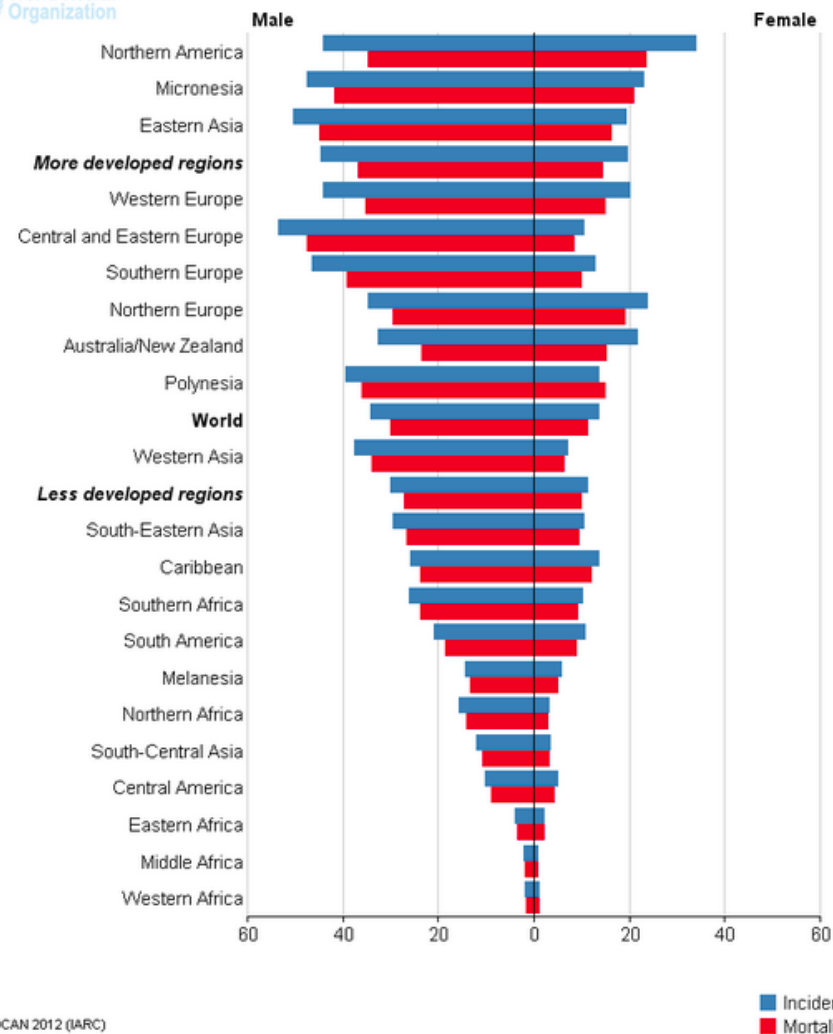
Survive lung cancer for 10 or more years, 2010-11, England and Wales

#### Prevention



Preventable cases of lung cancer, UK

International Agency for Research on Cancer



## A WORLD OF RISK

Annual incidence risks of lung cancer per 100,000 people in 2012. Tobacco is the main cause of the disease, but about one-tenth of lung-cancer patients have never smoked<sup>6</sup>.

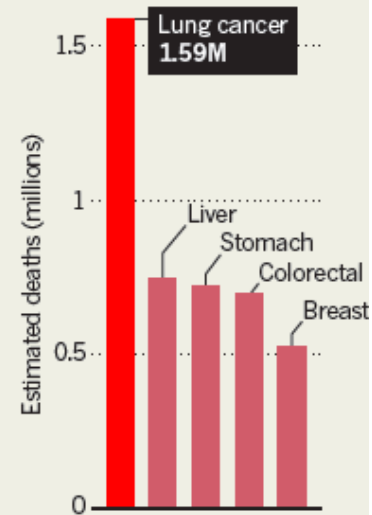
### United States

Aggressive tobacco-control programmes have caused a decline in smoking and the incidence rate is slowly falling.

### Hungary

The country has an ageing population and in the past many Hungarians smoked. Even though an estimated 33% of men and 23% women now smoke, according to 2009 World Health Organization data, it will take some years for any decrease in the number of people smoking to be reflected in fewer cases of lung cancer.

### Estimated worldwide cancer mortality, 2012



### Mexico

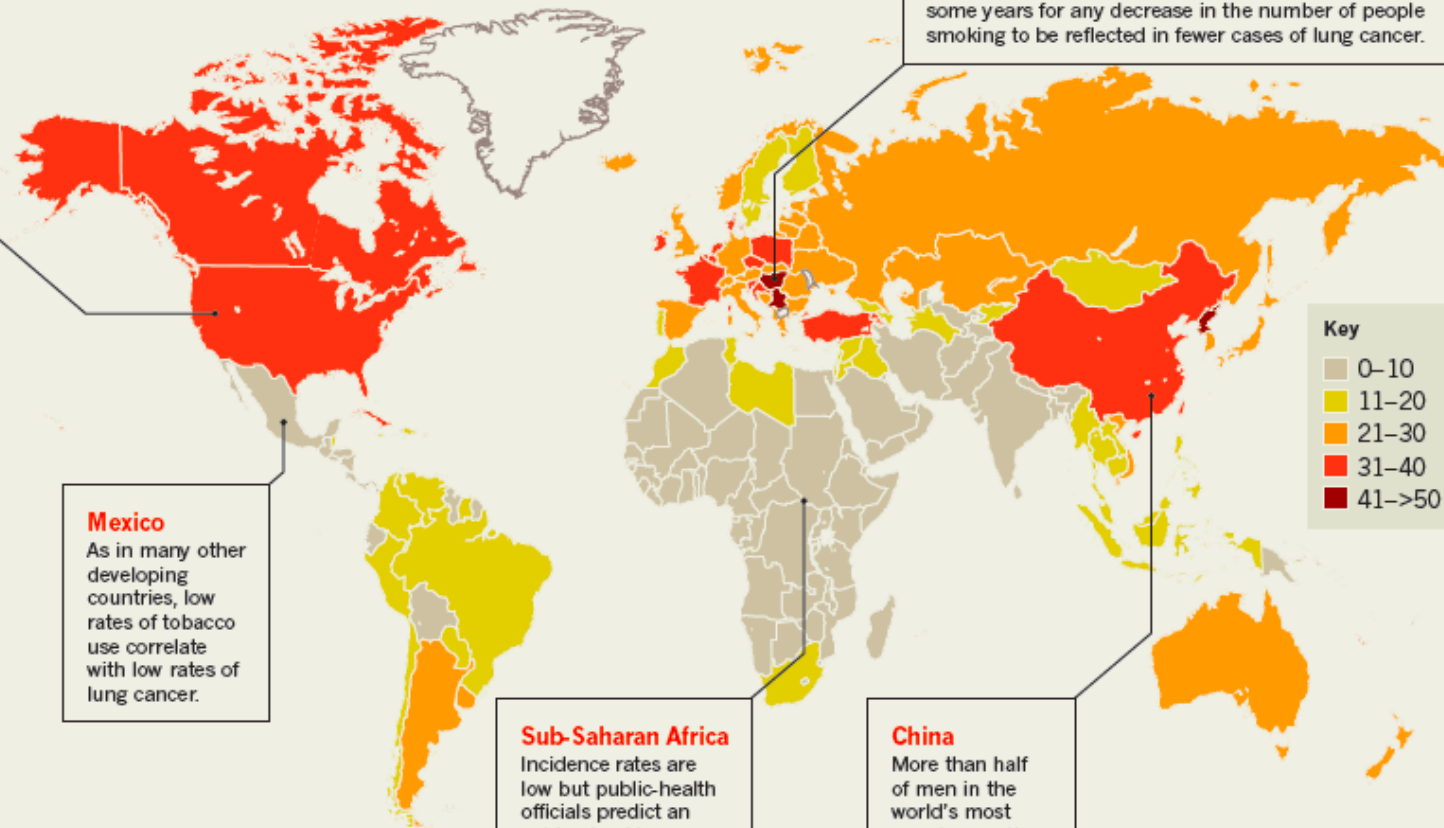
As in many other developing countries, low rates of tobacco use correlate with low rates of lung cancer.

### Sub-Saharan Africa

Incidence rates are low but public-health officials predict an epidemic of lung cancer because of tobacco advertising campaigns.

### China

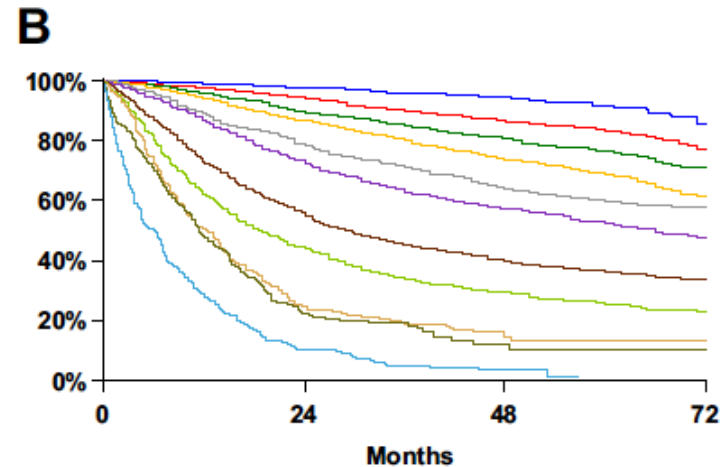
More than half of men in the world's most populous nation smoke, and lung cancer rates are soaring.



# GOOD NEWS: Early stage NSCLC

Excellent clinical outcome for Stage 1A and 1B

## IASLC Staging Project: Stage Grouping Proposals



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

ORIGINAL ARTICLE



The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

Peter Goldstraw, FRCS,<sup>a,\*</sup> Kari Chansky, MS,<sup>b</sup> John Crowley, PhD,<sup>b</sup> Ramon Rami-Porta, MD,<sup>c</sup> Hisao Asamura, MD,<sup>d</sup> Wilfried E. E. Eberhardt, MD,<sup>e</sup> Andrew G. Nicholson, FRCP,<sup>f</sup> Patti Groome, PhD,<sup>g</sup> Alan Mitchell, MS,<sup>h</sup> Vanessa Bolejack, MPH,<sup>i</sup> on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions

<sup>a</sup>Department of Thoracic Surgery, Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College, London, United Kingdom

<sup>b</sup>Cancer Research and Biostatistics, Seattle, WA, USA

<sup>c</sup>Department of Thoracic Surgery, Hospital Universitari Mutua Terrassa, University of Barcelona, and CIBERES

Lung Cancer Group, Terrassa, Barcelona, Spain

<sup>d</sup>Division of Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan

<sup>e</sup>West German Cancer Centre, University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany

<sup>f</sup>Department of Pathology, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, United Kingdom

<sup>g</sup>Queen's Cancer Research Institute, Kingston, ON, Canada

Received 5 August 2015; revised 31 August 2015; accepted 3 September 2015

# Evidence for Lung Ca Screening from the NLST:

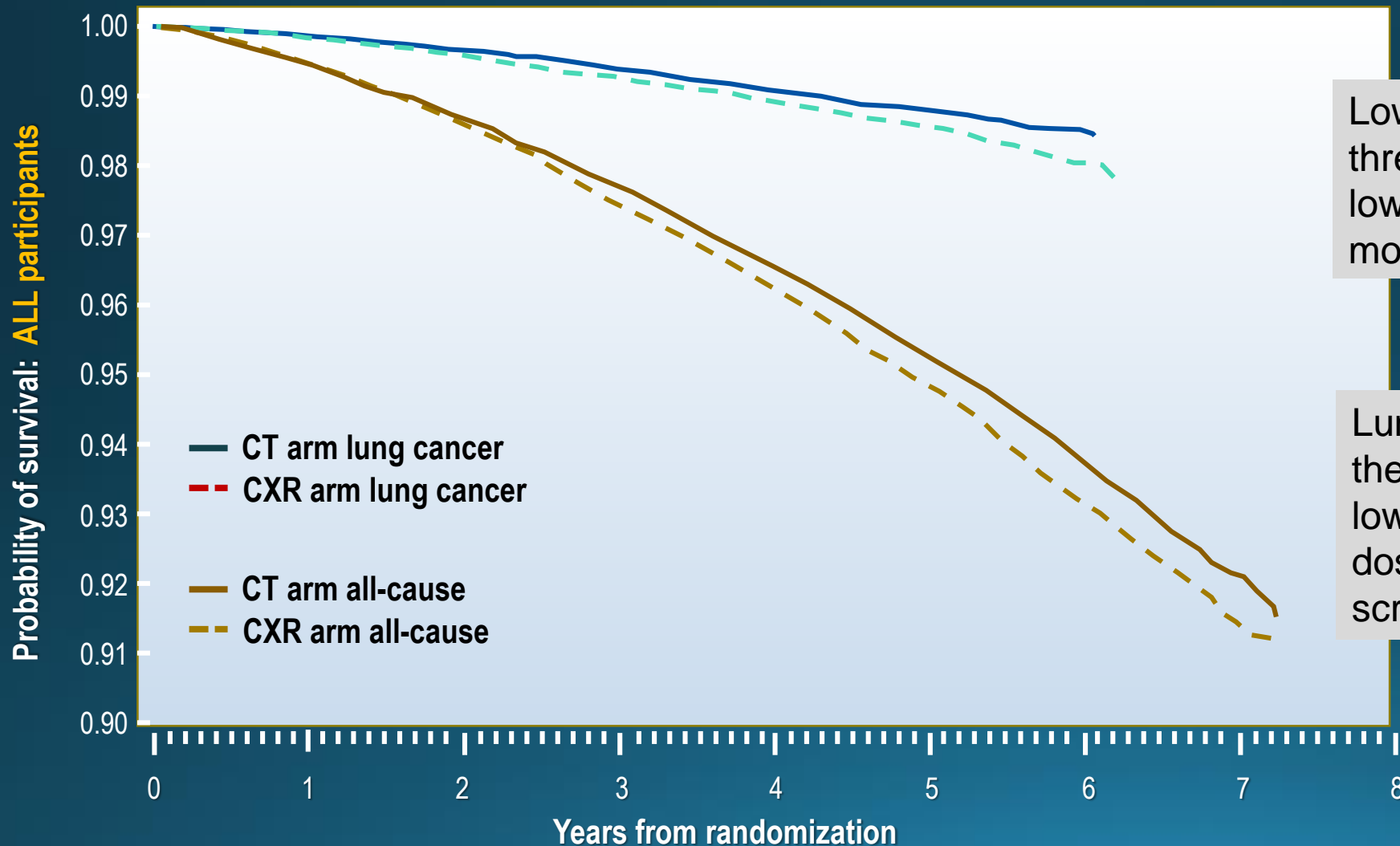
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Results of Initial Low-Dose Computed Tomographic Screening for Lung Cancer

The National Lung Screening Trial Research Team\*

## NLST - Kaplan-Meier curves for lung cancer & *all-cause mortality*



Low-dose helical CT annually for three screens in a high-risk group lowers lung cancer specific mortality by 20%

Lung cancer –related mortality and the all cause mortality was 6% lower in those screened with low dose CT, relative to those screened with chest radiographs

# RECOMMENDATIONS:

## International Assoc. Study Lung Cancer SSAC recommendations

Field JK, Smith RA, Aberle DR, et al. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report. J Thorac Oncol 2012;7:10-9.

## US Preventive Services Task Force recommendations on CT Screening :

1. Implementation based on the NLST entry criteria
2. Based on micro-simulation modelling 55-80 years of age.

Humphrey et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. Ann Intern Med 2013;159:411-20.

de Koning HJ et al.. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med 2014;160:311-20.

## Chinese recommendation for Screening:

Zhou QH, Fan YG, Bu H, et al. China national lung cancer screening guideline with low-dose computed tomography (2015 version). Thorac Cancer 2015;6:812-8.

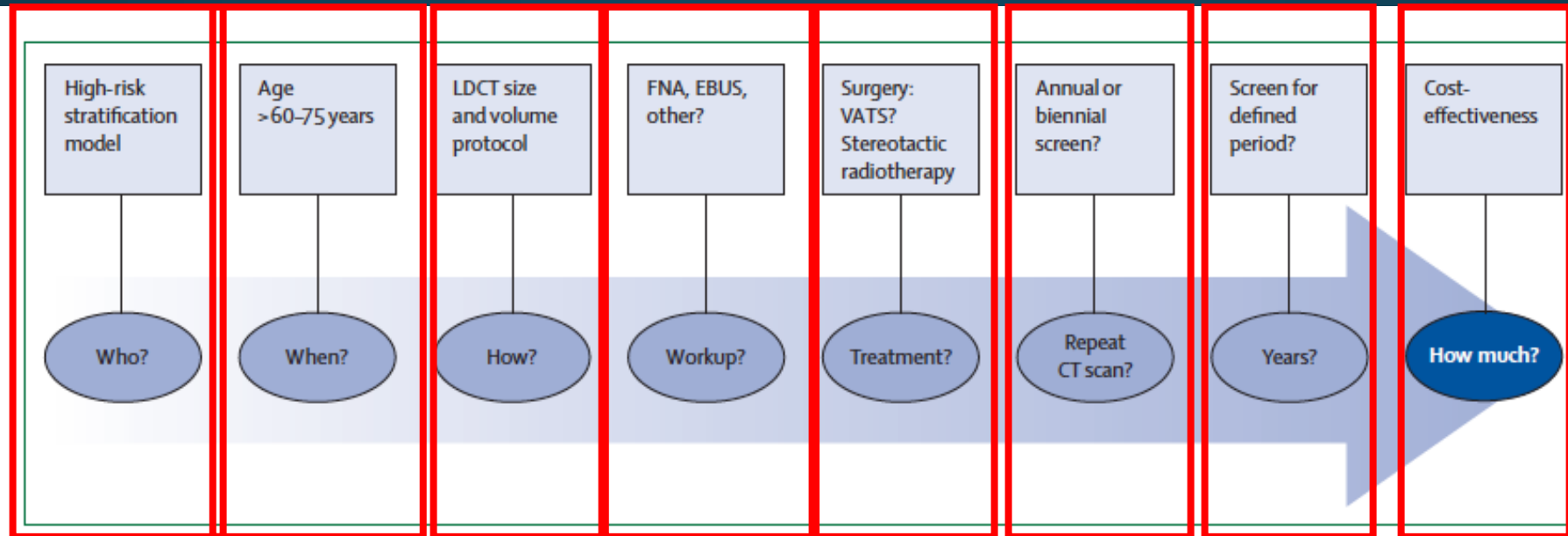
## Canadian Task Force on Preventive Health Recommendations on screening for lung cancer.

CMAJ 2016. DOI:10.1503/cmaj.151421

# The Evidence: Early Stage Disease

	Participants in screening arm	Screening Rounds	No. Published CT detected Lung Cancers	Stage IA & IB Lung Cancers	
Trial					
NLST	26,722	3	649	400 (61.6%)	
NELSON	7,915	4	209	148 (70.8%)	
DLST	2,052	5	69	47 (68.1%)	
ITALUNG	1,613	4	22	11 (50.0)	
DANTE	1,276	4	58	41 (70.7)	
MILD	1,190	10	20	18 (62.1%)	
	1,186	5	22	14 (70.0%)	
LUISI	2,029	4	22	18 (81.8%)	
UKLS	1,994	1	42	28 (67.8%)	
<b>TOTAL</b>	<b>54,977</b>	<b>1-10</b>	<b>1,120</b>	<b>725 (64%)</b>	

# Evidence : Implementation of the CT Lung cancer screening pathway



**Figure 1: Decisions for implementation of CT screening**

LDCT=low-dose CT. FNA=fine-needle aspiration. EBUS=endobronchial ultrasound. VATS=video-assisted thoracoscopic surgery.



**Lung Cancer 3**

**Prospects for population screening and diagnosis of lung cancer**


*John K Field, Matthijs Oudkerk, Jesper Holst Pedersen, Stephen W Duffy*

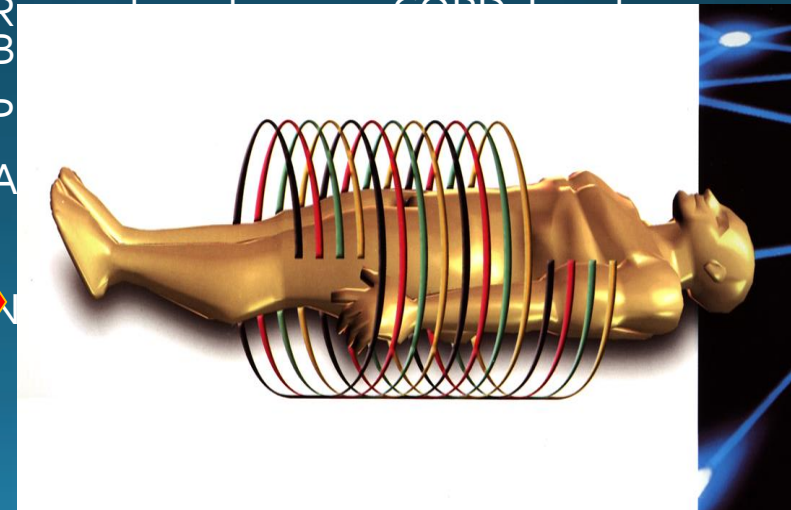
www.thelancet.com Vol 382 August 24, 2013



The diagram illustrates a two-step process for identifying high-risk individuals. It begins with a 'Population based invitation' stage, represented by a blue circle containing a group of diverse human figures. A large red arrow points from this circle to a funnel-shaped structure. Inside the funnel is a box labeled 'Targeted selection'. A smaller red arrow points from the bottom of the funnel to a group of three human figures, with a box labeled 'High risk' next to them.

## Factors to target (LLP<sub>v2</sub>)

- HEALTH TECHNOLOGY ASSESSMENT**
- VOLUME 20 ISSUE 4 MAY 2017  
ISSN 1366-5122
-  CrossMark  
click for updates
- The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer**
- John K Field, Stephen W Duffy, David R Baldwin, Kate E Brain, Anand Devaraj, Tim Eisen, Beverley A Green, John A Holemans, Terry Kanaganah, Keith M Kerr, Martin Lediard, Kate L Lifford, Fiona E McDonald, Arjun Nair, Richard D Page, Mahesh KB Parmar, Robert C Rintoul, Nicholas Sreeton, Nicholas J Wald, David Weir, David K Whynes, Paula R Williamson, Ghazem Yadegarfar and David M Hansell



# Evidence: Management of CT Screen detected nodules

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Management of Lung Nodules Detected by Volume CT Scanning

Rob J. van Klaveren, M.D., Ph.D., Matthijs Oudkerk, M.D., Ph.D.,  
Mathias Prokop, M.D., Ph.D., Ernst T. Scholten, M.D.,  
Kristiaan Nackaerts, M.D., Ph.D., Rene Vernhout, M.Sc., Carola A. van Iersel, M.Sc.,  
Karien A.M. van den Bergh, M.Sc., Susan van 't Westeinde, M.D.,  
Carlijn van der Aalst, M.Sc., Erik Thunnissen, M.D., Ph.D., Dong Ming Xu, M.D., Ph.D.,  
Ying Wang, M.D., Yingru Zhao, M.D., Hester A. Gietema, M.D., Ph.D.,  
Bart-Jan de Hoop, M.D., Harry J.M. Groen, M.D., Ph.D.,  
Geertruida H. de Bock, Ph.D., Peter van Ooijen, Ph.D., Carla Weenink, M.D.,  
Johnny Verschakelen, M.D., Ph.D., Jan-Willem J. Lammers, M.D., Ph.D.,  
Wim Timens, M.D., Ph.D., Dik Willebrand, M.D., Aryan Vink, M.D.,  
Willem Mali, M.D., Ph.D., and Harry J. de Koning, M.D., Ph.D.

Articles

## Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening

Nanda Harms\*, Joost van Rossum\*, Marjolijn A Heuvelmans, Carlijn M van der Aalst, Rozemarijn Vliegenhart, Ernst Th Scholten, Kristiaan Nackaerts, Jan-Willem J Lammers, Carla Weenink, Harry J Groen, Peter van Ooijen, Pin A de Jong, Geertruida H de Bock, Willem Mali, Harry J de Koning\*, Matthijs Oudkerk\*

Downloaded from [thorax.bmj.com](https://www.thorax.bmj.com) on February 16, 2011 - Published by [group.bmj.com](https://www.thorax.bmj.com)  
Thorax Online First, published on February 11, 2011 as 10.1136/thx.2010.152066

Lung cancer

## UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer

D R Baldwin,<sup>1</sup> S W Duffy,<sup>2</sup> N J Wald,<sup>3</sup> R Page,<sup>4</sup> D M Hansell,<sup>5</sup> J K Field<sup>6</sup>

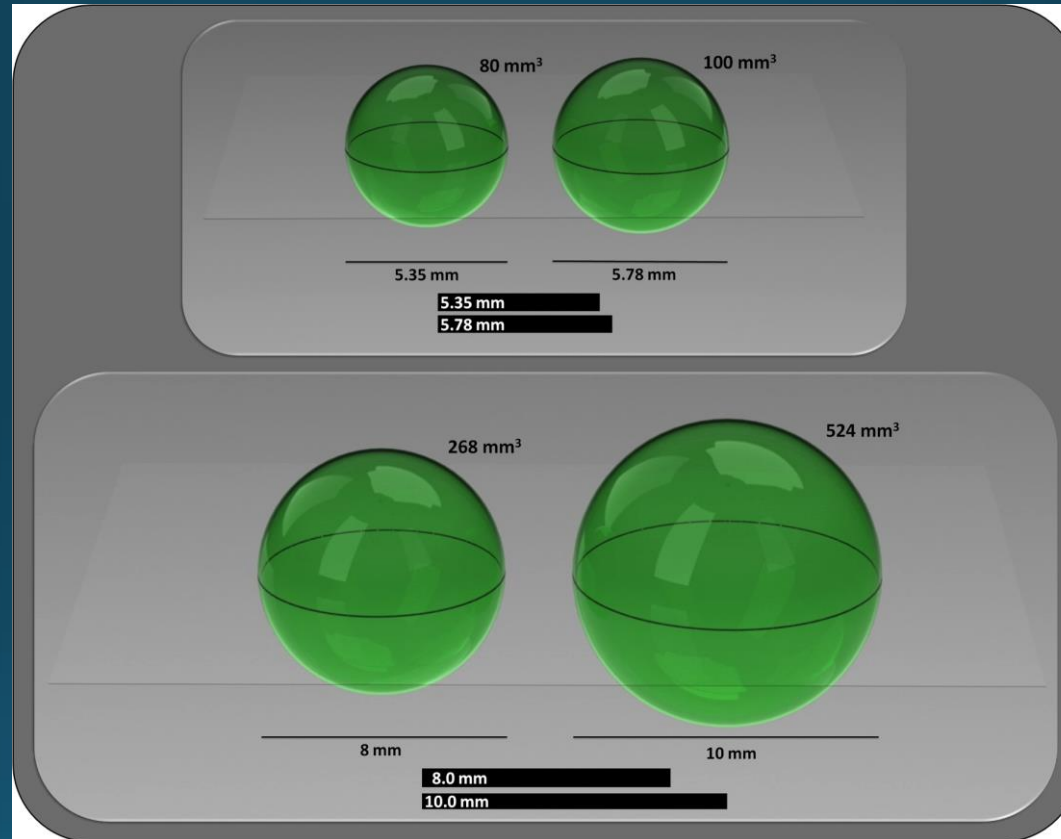
Lancet Oncol 2016

Published Online  
June 6, 2016

Articles

## Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial

Joan E Walter, Marjolijn A Heuvelmans, Pin A de Jong, Rozemarijn Vliegenhart, Peter M A van Ooijen, Robin B Peters, Kevin ten Haaf, Uroogh Yousef Khan, Carlijn M van der Aalst, Geertruida H de Bock, Willem Mali, Harry J M Groen, Harry J de Koning, Matthijs Oudkerk



Volume and diameter growth of pulmonary nodules

(A) volume increase of 26%, defined as growth by the NELSON / UKLS criteria, is hardly appreciable by diameter measurement (8% diameter increase, which is no growth according to existing criteria)

(B) 25% diameter increase—ie, the threshold for the current growth definition—represents almost a doubling in volume (95%).

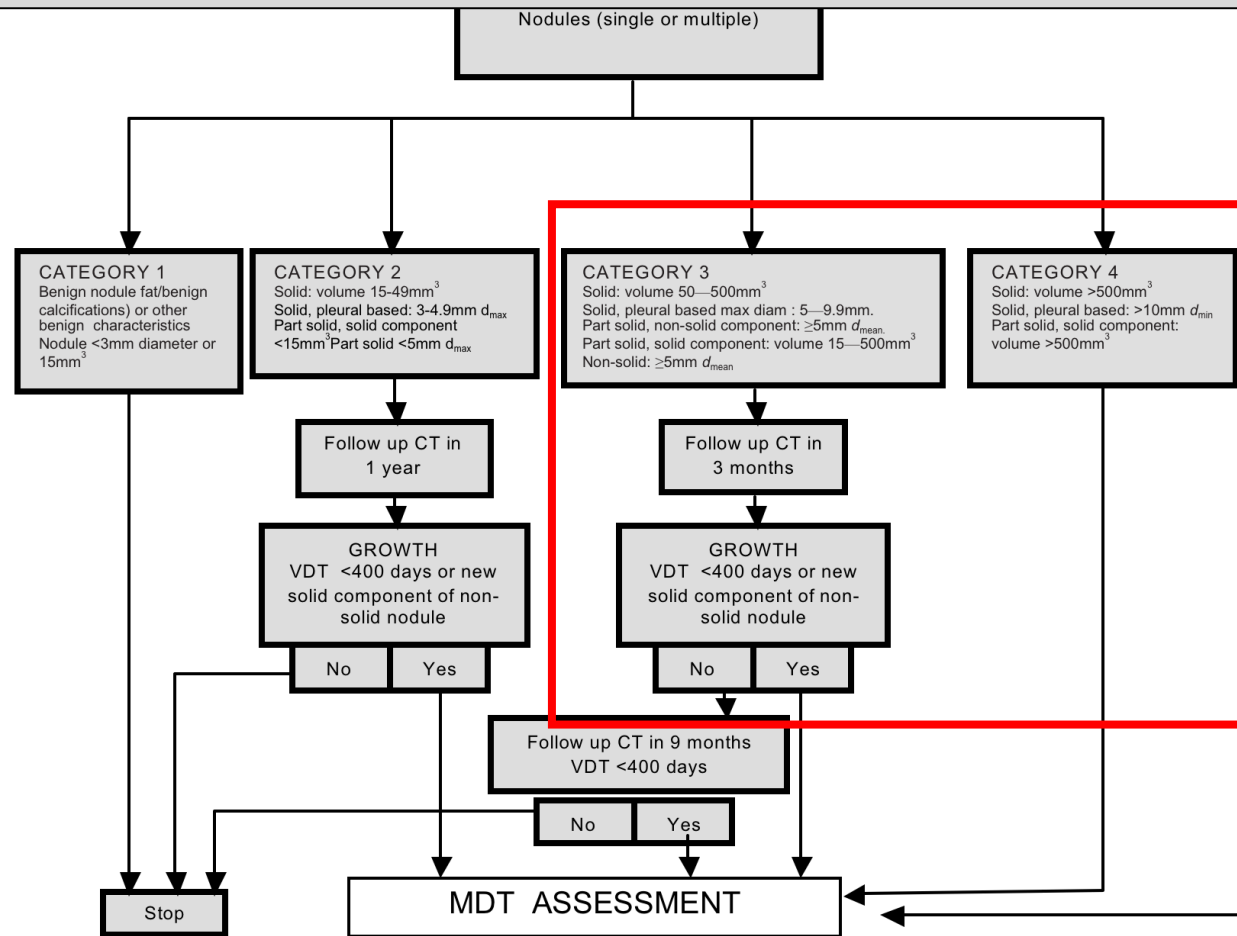


Lung Cancer 3

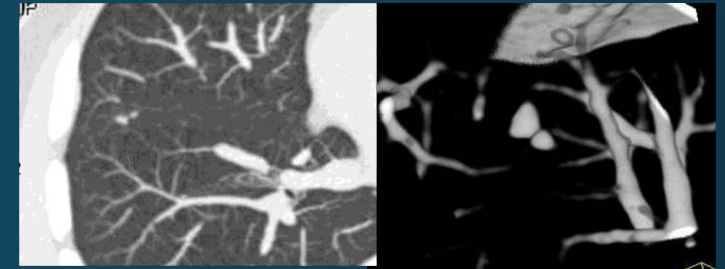
## Prospects for population screening and diagnosis of lung cancer

John K Field, Matthijs Oudkerk, Jesper Holst Pedersen, Stephen W Duffy

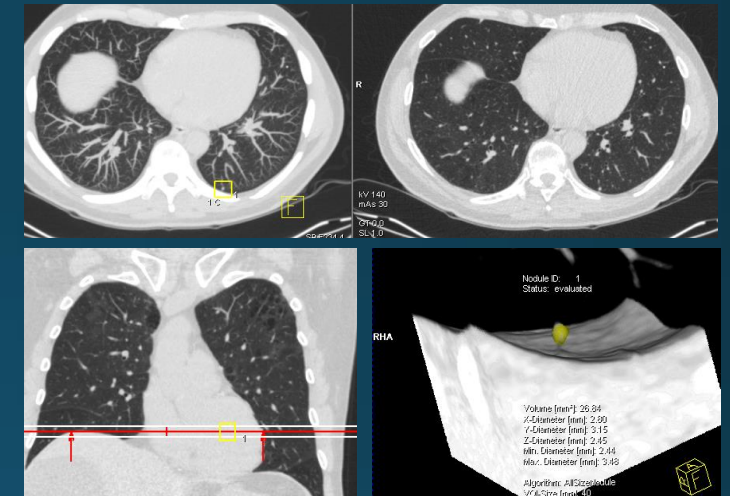
# Evidence :Nodule Care Pathway Management Protocol



Cat 1



Cat 2



Cat 4



**ELCAP & NELSON & UKLS – contributed to lung cancer screening:  
Indeterminate nodules >5mm -9.9mm diam; >50mm<sup>3</sup> 500mm<sup>3</sup>  
Growth VDT <400 days.**

Thorax Online First, published on February 11, 2011 as 10.1136/thx.2010.152066

UK Lung Screen (UKLS) nodule management protocol:  
modelling of a single screen randomised controlled  
trial of low-dose CT screening for lung cancer

D R Baldwin,<sup>1</sup> S W Duffy,<sup>2</sup> N J Wald,<sup>3</sup> R Page,<sup>4</sup> D M Hansell,<sup>5</sup> J K Field<sup>6</sup>

# False positives –major issue ?

In the UKLS, we defined false positives as those requiring further diagnostic investigation more immediately than a repeat annual screen, but who subsequently did not have lung cancer.

- **The UKLS False positive rate was 3.6%** and the interval imaging rate was 23.2%.
- In NLST, a CT was regarded as positive if it showed any non-calcified nodule at least 4mm in diameter (i).
- The overall false positive rate for the CT screening arm in **NLST was 23.3%**.
- In the NELSON trial lung nodules with a volume  $>500 \text{ mm}^3$  or those with a volume-doubling time  $<400$  days, were regarded as positive tests.
- **3.6% of all NELSON participants** (273 out of 7,582) had a false–positive screening result (ii).

(i) N Engl J Med .2011; 365: 395-409.  
(ii) Eur Respir J. 2013; 42: 1659-1667.

# Evidence: The Impact of CT screening

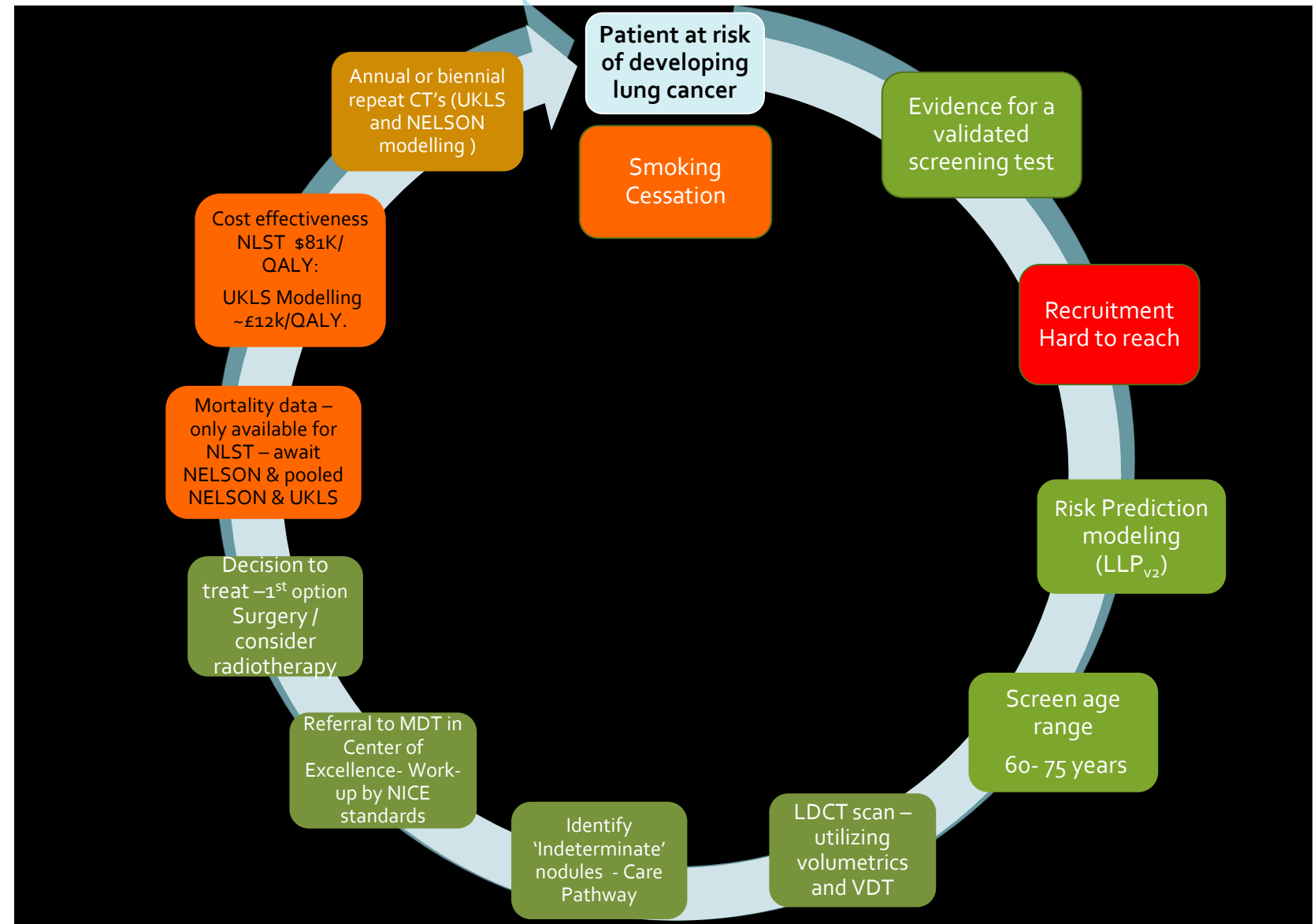
	<b>NELSON</b>	<b>UKLS</b>	<b>NLST</b>
False positives	273/7582 (3%) <sup>i</sup>	72/1994 (3%) <sup>ii</sup>	23.3% <sup>iii</sup>
Interval Imaging		463/1994 (23%)	
Stage I disease	64%: 72%	67%	63%
Benign Disease surgical interventions	25/92 (27%) 12/62 (19%)	4/ 39 (10.3%)	Not available
Psychosocial Harms	Transient (NS.)	Transient (NS.)	Not available

(i) Eur Respir J. 2013; 42: 1659-1667

(ii) Thorax 2016;71:161-70.

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

# What remains to be done?



**Fig. 1.** Levels of evidence for the implementation of lung cancer CT screening in Europe.

The colour codes refer to the current status in 2015, where green indicates we have sufficient evidence, amber is borderline evidence and red requires further evidence.





## natureOUTLOOK



Field JK. Perspective: The screening imperative.

Nature. 2014 Sep 10;513(7517):S7

### PERSPECTIVE



#### The screening imperative

Lung cancer kills more people than any other malignancy. Let's not delay in implementing a screening programme, says John K. Field.

Roughly every two minutes during 2012, someone in the European Union (EU) died of lung cancer. Those 208,000 lung cancer fatalities represented more than one fifth of all EU cancer deaths. The good news is that screening for lung cancer using low-dose computed tomography (CT) could reduce this enormous burden of mortality through early detection and treatment that improves survival<sup>1</sup>. Nearly 75% of lung cancer patients present with late-stage disease, when effective treatment is unlikely to succeed. However, if the disease is treated at an early stage, more than 70% of patients survive another five years. Lung cancer CT screening makes early detection possible, and so could add many years to many lives.

Unfortunately, there are major barriers obstructing the implementation of life-saving screening. The lung cancer community has evidence for a mortality benefit from CT screening from a massive study in the United States: the National Lung Screening Trial (NLST). This randomized trial of more than 55,000 individuals — current and former smokers aged 55–74 — was stopped early when it became clear that low-dose CT screening resulted in a 20% decrease in lung cancer mortality over screening with standard chest X-rays<sup>2</sup>. Based on these results, five clinical professional groups in the US support the implementation of CT screening, as does the US Preventive Services Task Force<sup>3</sup> — although Medicare, the federal agency that insures Americans aged over 65, has not yet approved coverage.

Despite the clear findings of the NLST, European health authorities have decided not to go ahead with lung cancer screening. Instead, officials are awaiting the outcome of the NELSON trial<sup>4</sup> in the Netherlands and Belgium and the pooling of data from smaller EU trials, due in the next two years, which will provide European mortality and cost-effectiveness data<sup>5</sup>.

This delay is a mistake. Now is the time to start planning to implement lung cancer screening in Europe. The major stumbling block is uncertainty over screening's cost-effectiveness. In the US, lung cancer screening is estimated to cost anywhere from US\$19,000 to \$140,000 per quality-adjusted life year (a standard method used to assess medical treatments by taking into account a person's quality of life after a medical intervention). But these figures are based on a health-care system that is very different from those that exist in Europe. Modelling in Britain, before the UK Lung Cancer Screening (UKLS) trial, provided an estimate of only £14,000 (£21,000 per quality-adjusted life year) — a figure much more likely to be acceptable to a cost-conscious health-care system.

Clearing the cost hurdle is necessary but not sufficient for low-dose CT to be ready for widespread lung cancer screening. Another issue relates to the criteria for interpreting the image produced by the scan. There are two schools of thought. One is to judge the nodule by its diameter, as measured by callipers on the radiograph. This is the approach used by the NLST. But diameter is not always accurate or

consistent: nodules tend to be highly irregular. Thus a small nodule might show up as large if it is measured along its greatest dimension, creating a false-positive result, and vice versa for a large nodule measured along its shortest axis. That is why it's better to use the volume of a nodule to judge the risk it poses, which was what both the NELSON and UKLS trials did. This radiological approach has gained acceptance in Europe and is highly likely to reduce the number of false positives.

The next question to ask is: 'Who should be screened?' The US Preventive Services Task Force recommends that CT screening should be undertaken in past or present smokers aged 55–80 who meet the NLST entry criteria<sup>3</sup>. Evidence from the UKLS trial<sup>6</sup> — using the Liverpool Lung Project risk prediction model (people with a 5% risk of developing lung cancer in the next five years) however, shows that a screening programme will be more cost-effective if it is limited to the highest-risk segment of that population, which is those aged 60–75. Drawing a line like this will, of course, have life-and-death consequences: withholding screening from 55–59 year olds will result in a small number of lung cancers being missed. Such are the decisions that any preventative health programme must confront.

Likewise, there is no consensus on how often to screen. The largest evidence base is from the US trial, which involved annual scans. But modelling that uses the UKLS selection criteria and the NLST mortality data has shown that after an initial scan, the most cost-effective programme would involve not annual but biennial screening. According to this model, biennial scans would save 20% fewer lives than annual ones, but the predictions suggest that mortality benefits would still be substantial and cost effective<sup>7</sup>.

The existence of unanswered questions about lung cancer screening does not argue for inaction. The additional data that will flow out of the NELSON and pooled EU trials is necessary, but there is no need to wait before taking concrete steps towards planning to implement a widespread lung cancer screening programme among the highest-risk populations. Every year we delay could needlessly sacrifice tens of thousands of lives to the world's biggest cancer killer. ■

John K. Field is a clinical professor at the University of Liverpool Cancer Research Center, UK, and is the chief investigator for the UK Lung Cancer Screening trial.  
e-mail: J.K.Field@liverpool.ac.uk

1. Field, J. K. et al. *Lancet* 382, 732–741 (2013).
2. National Lung Screening Trial Research Team. *N. Engl. J. Med.* 365, 395–409 (2011).
3. van Kesteren, R. J. et al. *N. Engl. J. Med.* 363, 2221–2229 (2010).
4. van Kesteren, R. J. et al. *Lancet Oncol.* 14, 603–609 (2013).
5. Himpson, L. L. et al. *Am. J. Respir. Med.* 178, 411–420 (2013).
6. McDonald, L. L. et al. *Cancer Prev. Epidemiol. Biomarkers* 22, 371–375 (2013).
7. Duffy, S. W. et al. *Br. J. Cancer* 110, 1834–1840 (2014).

### Mortality from smoking worldwide<sup>a</sup>

Richard Peto\*, Alan D Lopez†, Jillian Boreham\*, Michael Thun§, Clarke Heath Jr§ and Richard Doll\*

\*ICRF/MRC/BHF Clinical Trial Service Unit & Epidemiological Studies Unit, Harkness Building, Radcliffe Infirmary, Oxford, UK, †Tobacco or Health, World Health Organization, Geneva, Switzerland, §Epidemiology Unit, American Cancer Society, Atlanta, Georgia, USA

<sup>a</sup>Adapted from Peto *et al.* (1994)<sup>1</sup>

Estimates are made of the numbers and proportions of deaths attributable to smoking in 44 developed countries in 1990. In developed countries as a whole, tobacco was responsible for 24% of all male deaths and 7% of all female deaths, rising to over 40% in men in some former socialist economies and 17% in women in the USA. The average loss of life for all cigarette smokers was about 8 years and for those whose deaths were attributable to tobacco about 16 years. Trends in mortality attributable to tobacco differed between countries. In some the mortality in middle age (35–69 years) had decreased by half in men since 1965; in others it was continuing to increase. In women, the proportion was mostly increasing, almost universally in old age. Mortality not attributable to smoking decreased since 1955 in all OECD (Organization for European Collaboration and Development) countries, by up to 60% in men and more in women. No precise estimate can be made of the number of deaths attributable to smoking in undeveloped countries, but the prevalence of smoking suggests that it will be large. In the world as a whole, some 3 million deaths a year are estimated to be attributable to smoking, rising to 10 million a year in 30–40 years' time.

10 million  
per year  
in 2026–36