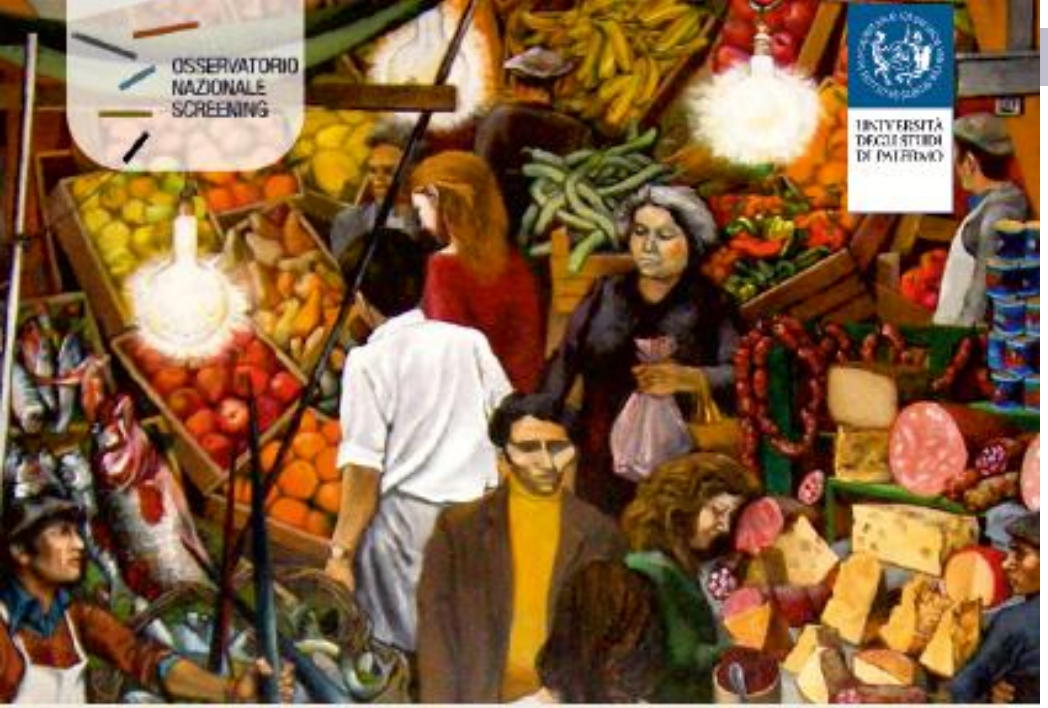


Documento di indirizzo Osservatorio Nazionale Screening

XI CONVEGNO OSSERVATORIO NAZIONALE SCREENING

STERI
PALERMO
12 e 13 Dicembre 2012

Screening per il tumore del polmone

ccm

REGIONE SICILIA

SST Servizio Sanitario della Toscana

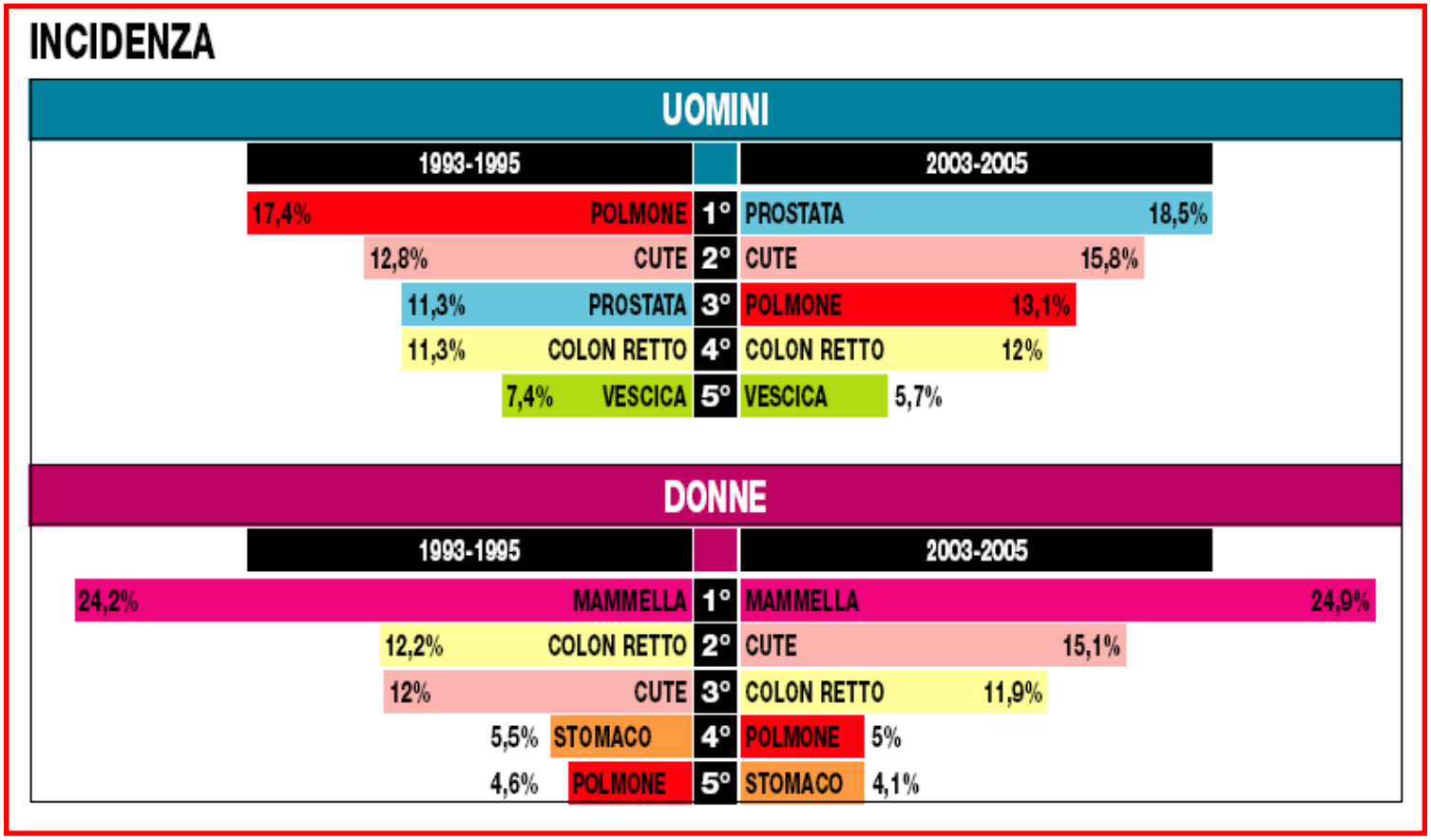
ispo ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA

ITT Istituto Toscano Tumori

Domande- documento indirizzo ONS

- **1) La mortalità per il tumore del polmone è un importante problema sanitario**
- **2) Lo screening mediante CT Scan è efficace nel ridurre la mortalità per Tumore del polmone? E la mortalità totale?**
- **Se sì, esistono prove che dimostrano la superiorità in termini di efficacia di un particolare protocollo?**

AIRTUM incidenza. I cinque tumori più frequenti e percentuale rispetto al totale dei tumori diagnosticati nel periodo 1993-1995 e 2003-2005, per sesso

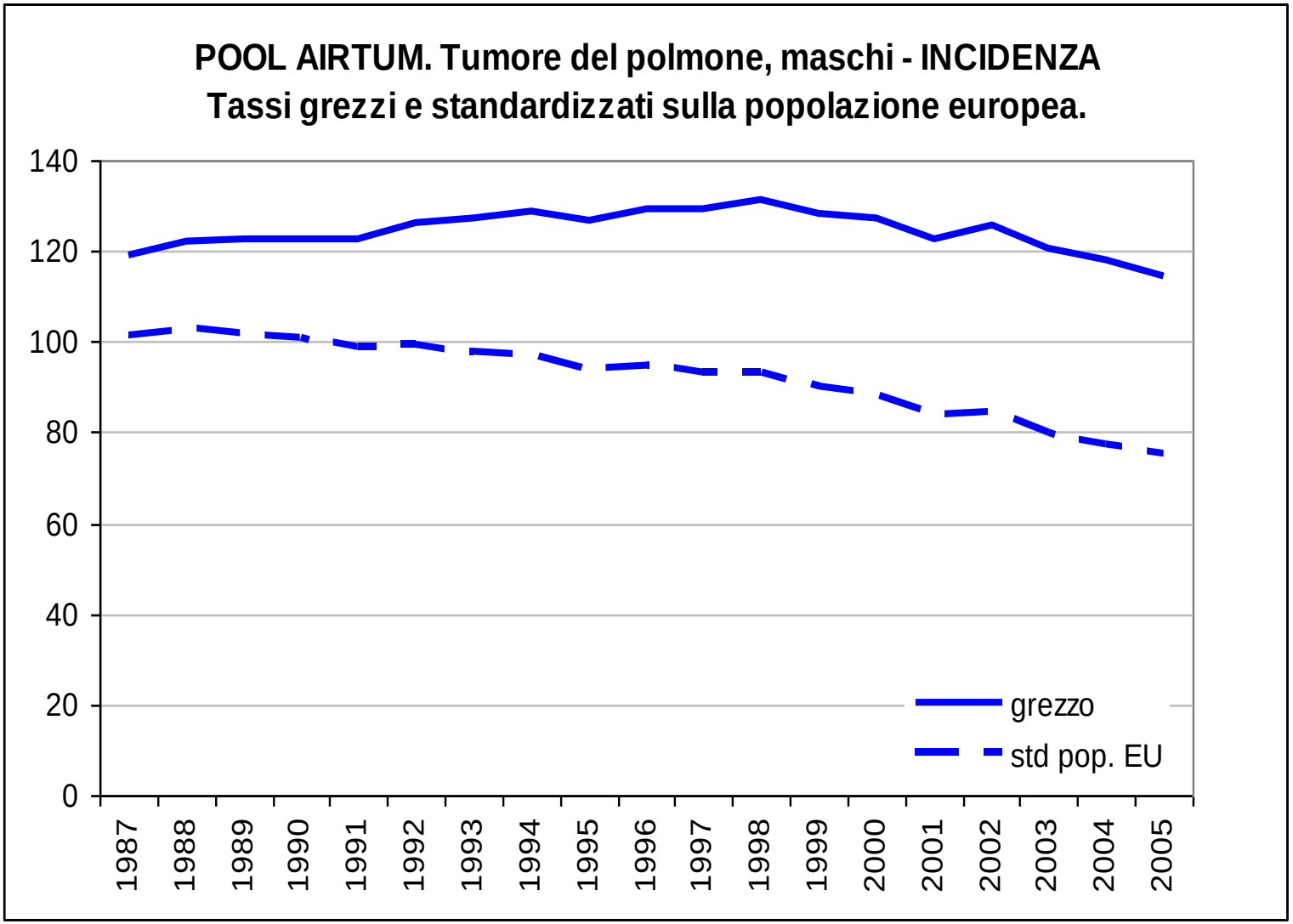


AIRTUM 2003-2005 mortalità. Prime cinque sedi tumorali in termini di peso percentuale sul totale della mortalità oncologica per sesso

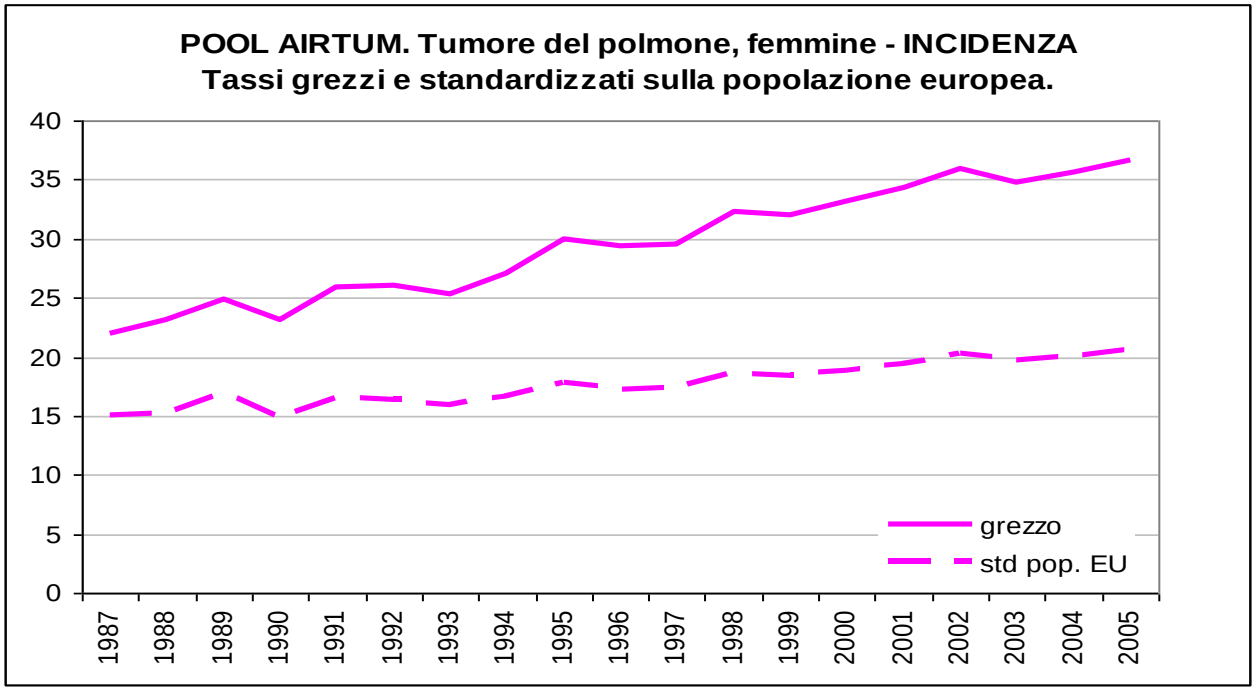
I 5 TUMORI CHE UCCIDONO DI PIÙ

	UOMINI	DONNE
1°	Polmone (27.6%)	Mammella (16.3%)
2°	Colonretto (10.7%)	Colonretto (11.9%)
3°	Prostata (8.5%)	Polmone (10.3%)
4°	Stomaco (7.3%)	Stomaco (7.2%)
5°	Fegato (6.1%)	Pancreas (6.5%)

La prevenzione primaria funziona ma il numero di malati (maschi) solo dal 2004 inizia a diminuire



Nelle donne il t.del polmone continua a crescere (tassi più bassi che nei maschi) , ma come numero di malati aumenta ancora di più

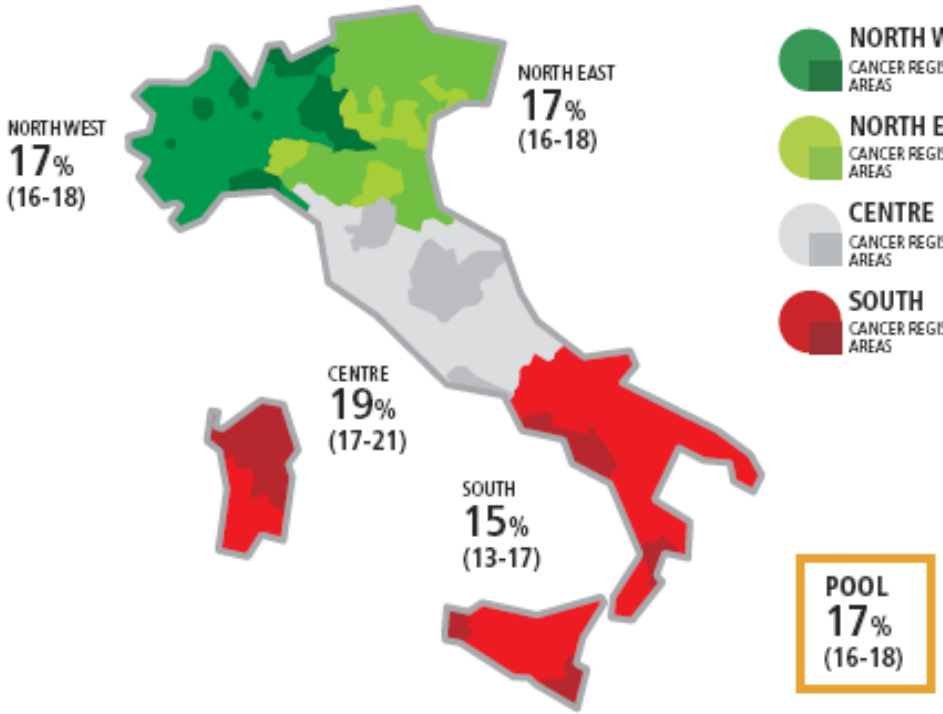


TUMORE DEL POLMONE
LUNG CANCER

LUNG CANCER — FEMALE

5-YEAR AGE-STANDARDIZED RELATIVE SURVIVAL (%) (CI 95%), BY GEOGRAPHICAL AREA, 2000-2004

POOL OF 31 CANCER REGISTRIES



Early Lung Cancer Action Project: overall design and findings from baseline screening

Claudia I Henschke, Dorothy I McCauley, David F Yankelevitz, David P Naidich, Georgeann McGuinness, Olli S Miettinen, Daniel M Libby, Mark W Pasmantier, June Koizumi, Nasser K Altorki, James P Smith

Lancet 1999; 354: 99–105

- Dal 1999 la proposta di screening per il tumore del polmone con CT Scan a bassa dose è stata oggetto di studi osservazionali (I-ELCAP)

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

The International Early Lung Cancer Action Program Investigators*

ABSTRACT

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.

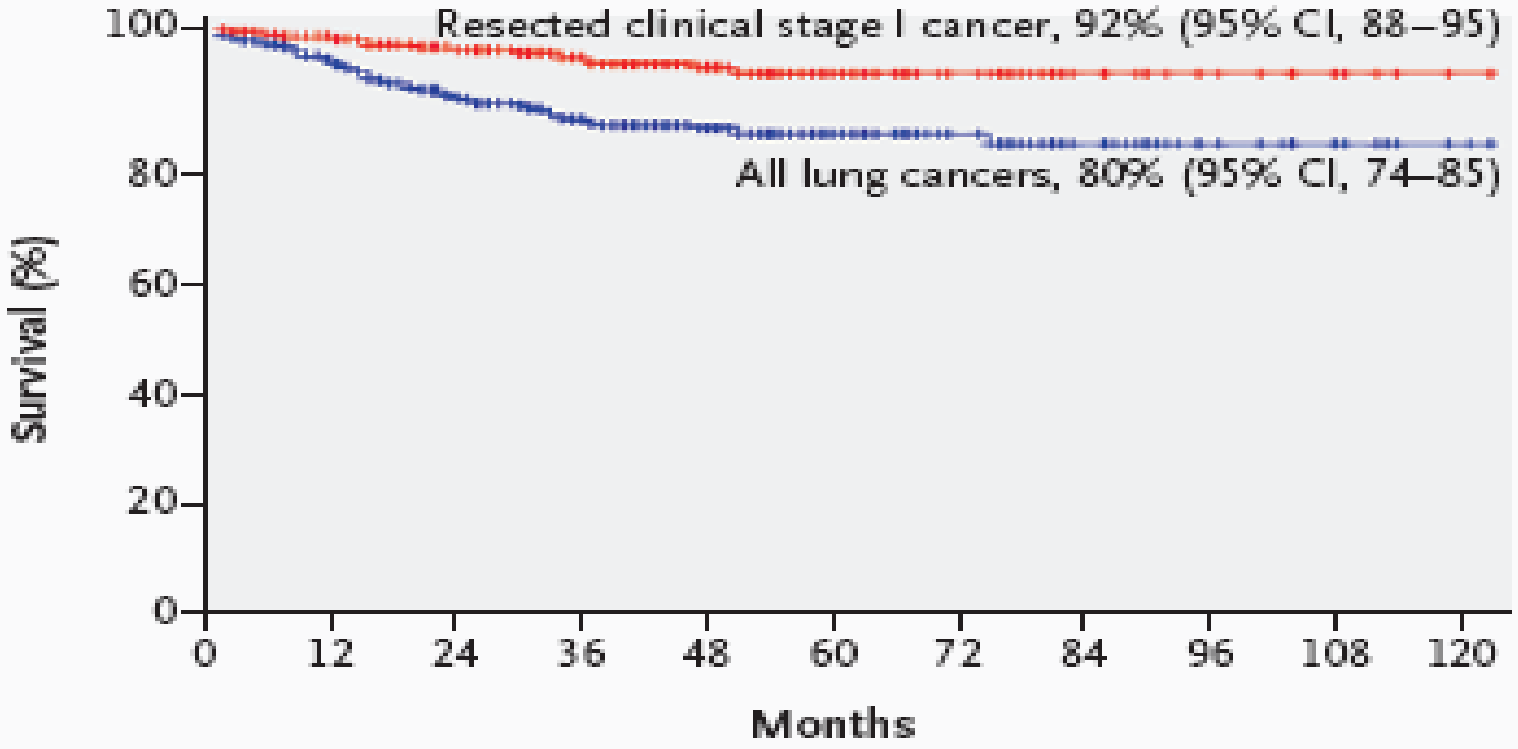
RESULTS
Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I 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.

The members of the Writing Committee (Claudia I. Henschke, M.D., Ph.D., David F. Yankelevitz, M.D., Daniel M. Libby, M.D., Mark W. Pasmantier, M.D., and James P. Smith, M.D., New York Presbyterian Hospital–Weill Medical College of Cornell University, New York; and Olli S. Miettinen, M.D., Ph.D., McGill University, Montreal) of the International Early Lung Cancer Action Program assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Henschke at New York Presbyterian Hospital–Weill Medical College of Cornell University, 525 E. 68th St., New York, NY 10021, or at chensch@med.cornell.edu.

*The International Early Lung Cancer Action Program investigators are listed in the Appendix.

N Engl J Med 2006;355:1763-71.



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.

No consensus (2007)

EDITORIALS

Computed tomography screening for lung cancer

Results of randomised trials are needed before recommending its adoption

NEWS

News | JNCI Vol. 99, Issue 3 | February 7, 2007

Lung Cancer Screening Debate Continues Despite International CT Study Results

By Renee Twombly

The Liverpool Statement 2005: Priorities for the European Union/United States Spiral Computed Tomography Collaborative Group

J.K. Field, PhD, BDS, FRCPath, R.A. Smith, PhD,† S.W. Duffy, MSc,‡ C.D. Berg, MD,§ R. van Klaveren, MD, PhD,‖ C.I. Henschke, PhD, MD,¶ D. Carbone, MD, PhD,** P.E. Postmus, MD, PhD,†† E. Paci, PhD,‡‡ F.R. Hirsch, MD, PhD,§§ and J.L. Mulshine, MD‖‖*

The Liverpool Statement 2005 was developed at the Fourth International Lung Cancer Molecular Biomarkers Workshop in Liverpool (October 27–29, 2005) and focused on the priorities for the European Union/United States (EU-US) Spiral Computed Tomography (CT) Collaborative Group. The application of spiral CT technology for early lung cancer screening has gained enormous momentum in the past 5 years. The EU-US Spiral CT Collaboration was initiated in 2001 in Liverpool, and subsequent meetings throughout Europe have resulted in the development of collaborative protocols and minimal data sets that provide a mechanism for the different trial groups to work together, with the ultimate aim to pool results. Considerable progress has been made with major national screening trials in the U.S. and Europe, which include IELCAP, NLST, and NELSON. The major objective of this international collaboration is the planned cross-analysis of the individual studies after they are reported. The EU-US researchers have agreed to a number of long-term objectives and to explore strategic areas for harmonization of complementary investigations.

Key Words: Lung cancer, Spiral CT, Early detection, Collaborative protocols, Radiology, Pathology, International screening trials.

(*J Thorac Oncol.* 2006;1: 497–498)

Lung cancer is a health problem of global proportions. Lung cancer is the most common cancer in the world, with a disproportionate number of cases occurring in the developed world. Despite intensive research over many years, the prognosis is still very poor, with less than 15% of the patients surviving 5 years after primary diagnosis in the U.S. and even fewer (5–10%) surviving in Europe and other countries. The poor survival is mainly attributable to the lack of effective treatment for systemic disease and the fact that more than two-thirds of patients present with regional or distant metastases. The best way to control the future incidence of lung cancer is to reduce cigarette smoking in the population, primarily through prevention and secondarily through smoking cessation. However, even after stopping smoking, long-term smokers remain at high risk of lung cancer.

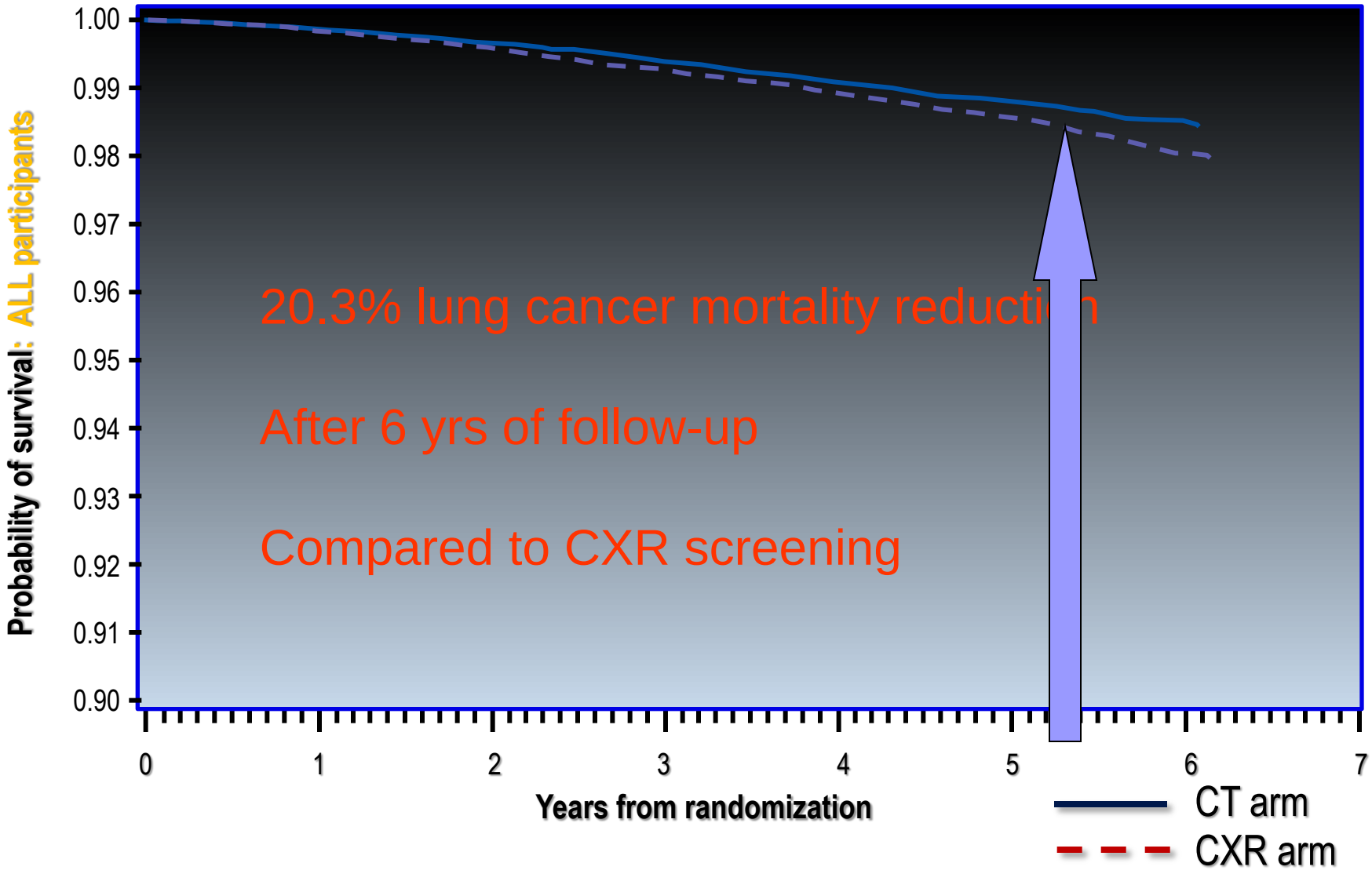
The application of spiral CT technology for early lung cancer screening has gained enormous momentum in the past 5 years,[1] and international approval for this approach is being sought through the gold standard scientific methodology, i.e., randomized controlled trials, before implementation by any national health care system will be considered. In 2001, it was our judgment that an international collaborative approach was required to achieve this objective.[2]

The EU-US Spiral CT Collaboration was initiated in

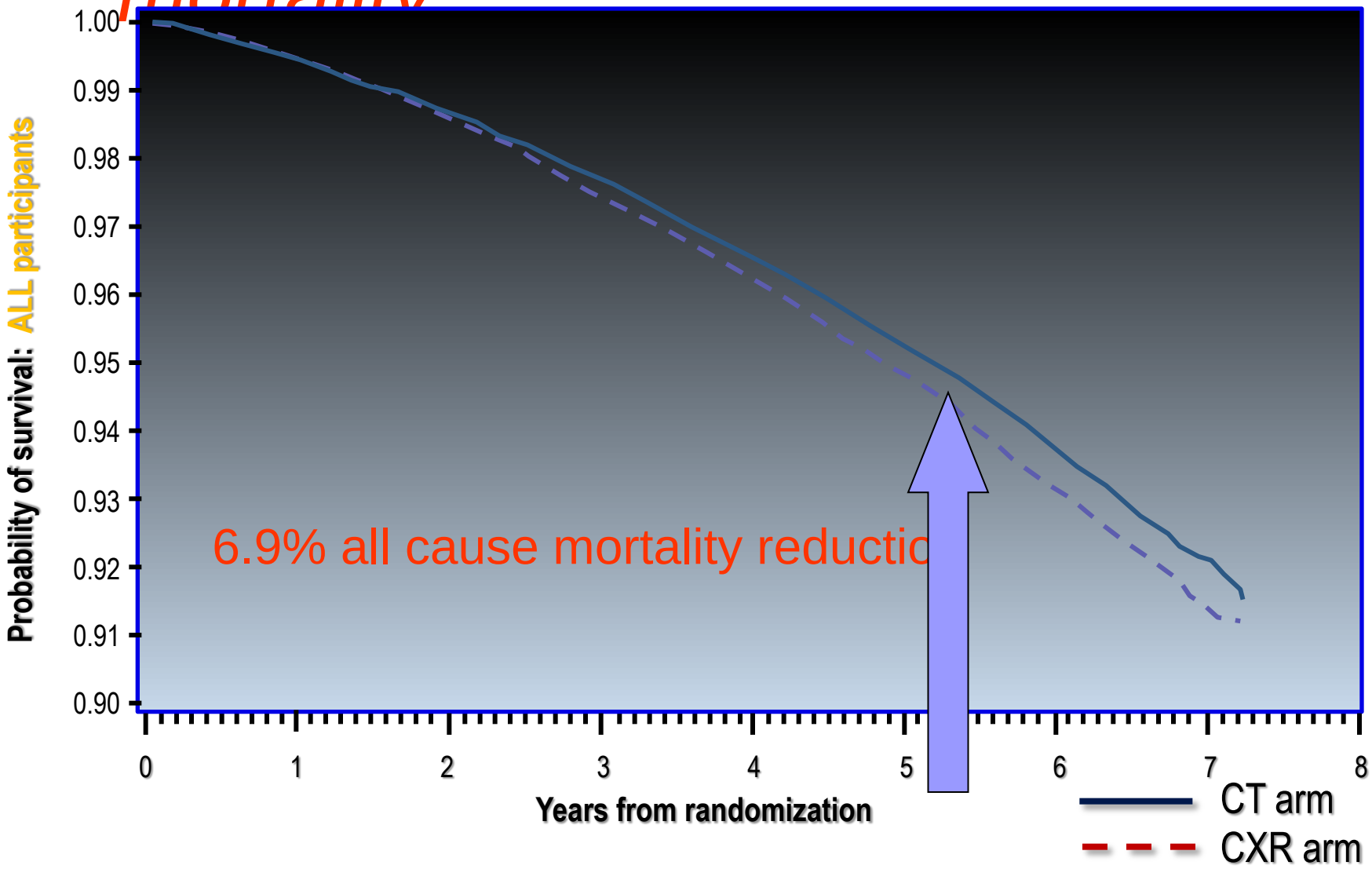
Denise R. Aberle, MD
Professor of Radiology and Bioengineering
David Geffen School of Medicine at UCLA
National PI, ACRIN-NLST

Christine D. Berg, MD
Chief, Early Detection Research Group
Division of Cancer Prevention, NCI
Project Officer, LSS-NLST

Kaplan-Meier curves for *lung cancer mortality*



Kaplan-Meier curves for *all-cause mortality*



Lung Cancer and All-Cause Mortality

Arm	Person years (py)	Deaths	All-cause mortality per 100,000 py	Reduction in all cause mortality, %	Value of test statistic	Value for significance
LDCT	167,394.9	1877	1121	6.7	–2.31	–1.96
CXR	166,332.2	2000	1202			

Lung cancer

- 25% of all deaths in NLST
- 56% of 123 excess deaths in CXR arm
- 20% reduction in disease deaths with screening
- 320 screenings needed to prevent 1 lung-cancer–related death

*P = .021

The National Lung Screening Trial Research Team. *N Engl J Med*. 2011;365:395-409.

RCTs

	NLST	Europe
LDCT arm	26722	16558
Control arm	26732	15820
Total enrolled	53454	36378

	NELSON	DLCST	LUSI	DANTE	ITALUNG	MILD	UKLS
LDCT	**7557**	**2052**	**1780**	**1276**	**1613**	**2280**	**2000**
Control arm	**7907**	**2052**	**1771**	**1196**	**1593**	**1301**	**2000**
Total	**15464**	**4104**	**3551**	**2472**	**3206**	**3581**	**4000**

Studi One-arm e dimostrativi italiani (parziale)

- **I-ELCAP Dr Giunta (IST Regina Elena)**
- Arruolamento chiuso, partecipa a follow-up I-ELCAP

- **COSMOS Dottssa Giulia Veronesi (IEO)**
- Chiuso primo studio (circa 5000 soggetti)
- In corso arruolamento studio dimstrativo multicentrico

PRINCIPALI DIFFERENZE TRA NLST E I TRIAL RANDOMIZZATI EUROPEI

- NLST : CXR nel gruppo di controllo
- EUCT: non screening nel controllo

- NLST: Intervallo tra screening, 1 anno, 3 rounds
- EUCT: differenti intervalli e passaggi (usualmente 1 anno)
- NLST: valutazione in 2D
- EUCT: valutazione in 2D e 3D

International workshop on
lung cancer screening randomized trials.
State of the art in Europe after
early conclusion of the US National Lung Screening Trial
The European Lung Cancer Trials (EULCT)
The PISA Position Statement
Pisa (Italy), March 4, 2011

- **The shared opinion of the trial investigators is that EULCT trials should continue and evaluate the full effect of screening with low-dose CT scan compared with non-screening (usual care) populations, in terms of mortality reduction as well as harmful side effects. The EULCT investigators decided to evaluate the feasibility of a combined interim analysis of the European randomized trials during 2012, while the trials will continue until the planned end.**

- **6) Esistono valutazioni con modelli di simulazione dell'impatto di politiche integrate di prevenzione primaria e diagnosi precoce?**

Research Article

Cancer Prevention Research

Can a National Lung Cancer Screening Program in Combination with Smoking Cessation Policies Cause an Early Decrease in Tobacco Deaths in Italy?

Giulia Carreras[1], Giuseppe Gorini[1], and Eugenio Paci[2]

ΓCP. *Cancer Prev Res; 1–9.* ©2012 AACR.

isp | CANCER PREVENTION AND RESEARCH INSTITUTE

Objective

to predict smoking attributable deaths for lung cancer and all causes in Italy, 2015-2040, assuming:

1. yet unimplemented tobacco control policies
2. a national, three-round annual lung cancer screening programme with low-dose CT for heavy and former heavy smokers

Scenarios of future predictions

- 1-Keeping the status quo
- 2-Raising cigarette taxes by 20%
- 3-Implementing cessation treatment policies:
  - funding treatment, setting-up an active quit-line, promoting counselling among health professionals
- 4-Introducing a three-round annual lung cancer screening programme with low-dose CT
  - for current and former heavy smokers aged 55-74 years, with a 70% compliance, and a 20% lung cancer mortality reduction
- 5-Combining 2,3,4.

Results - 2

The lung cancer screening programme brought:

1. a 3.0% constant annual reduction in smoking attributable deaths for lung cancer, relative to the status quo scenario
2. decreased or postponed smoking attributable deaths for all causes by 1.7% annually (a half due to respiratory diseases), relative to the status quo scenario
3. The effect was noticeable after few years from its introduction.

Smoking attributable deaths **for lung cancer**, status quo scenario, number of lives saved in the 4 preventive scenarios (% decline with respect to the status quo), **men**

Scenario / year	2015	2020	2030	2040
1. Status Quo	20,337	18,923	17,169	17,410
2. Tax policy	0	0	339 (2.0)	481 (2.8)
3. Cessation treatment Policies	0	0	1,463 (9.3)	2,871 (19.7)
4. Low-dose CT scan screening, 70% compliance	0	567 (3.1)	513 (3.1)	564 (3.4)
5. 2+3+4	0	567 (3.1)	2,211 (14.8)	3,687 (26.9)

Conclusions

tobacco control policies + lung cancer screening programme:

1. an early decrease in lung cancer and respiratory disease mortality due to the screening programme
2. followed by a more substantial drop in mortality for all causes in subsequent decades due to the implementation of tobacco control policies

- **3) Quali sono gli effetti collaterali negativi che si evidenziano nei trial e negli studi one-arm (eccesso di incidenza, sovra diagnosi, richiami, richiami invasivi, esposizione a Rx)? Si possono quantizzare?**

- **Nessuna società o gruppo Europeo ha per ora proceduto a revisione delle Linee Guida, che al momento scoraggiano l'utilizzo di una politica di diagnosi precoce per il tumore del polmone.**
- **Diverse nuove linee guida negli USA**

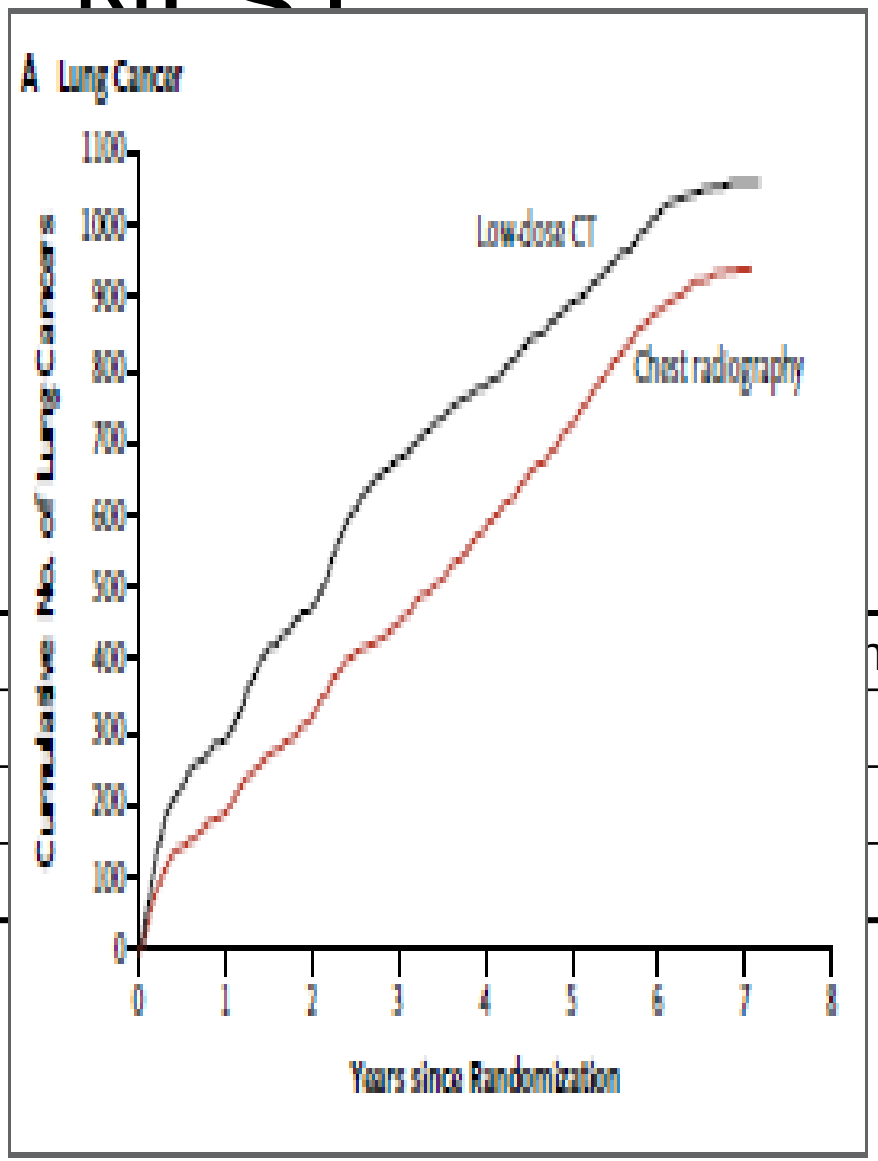
LUNG CANCER SCREENING
CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

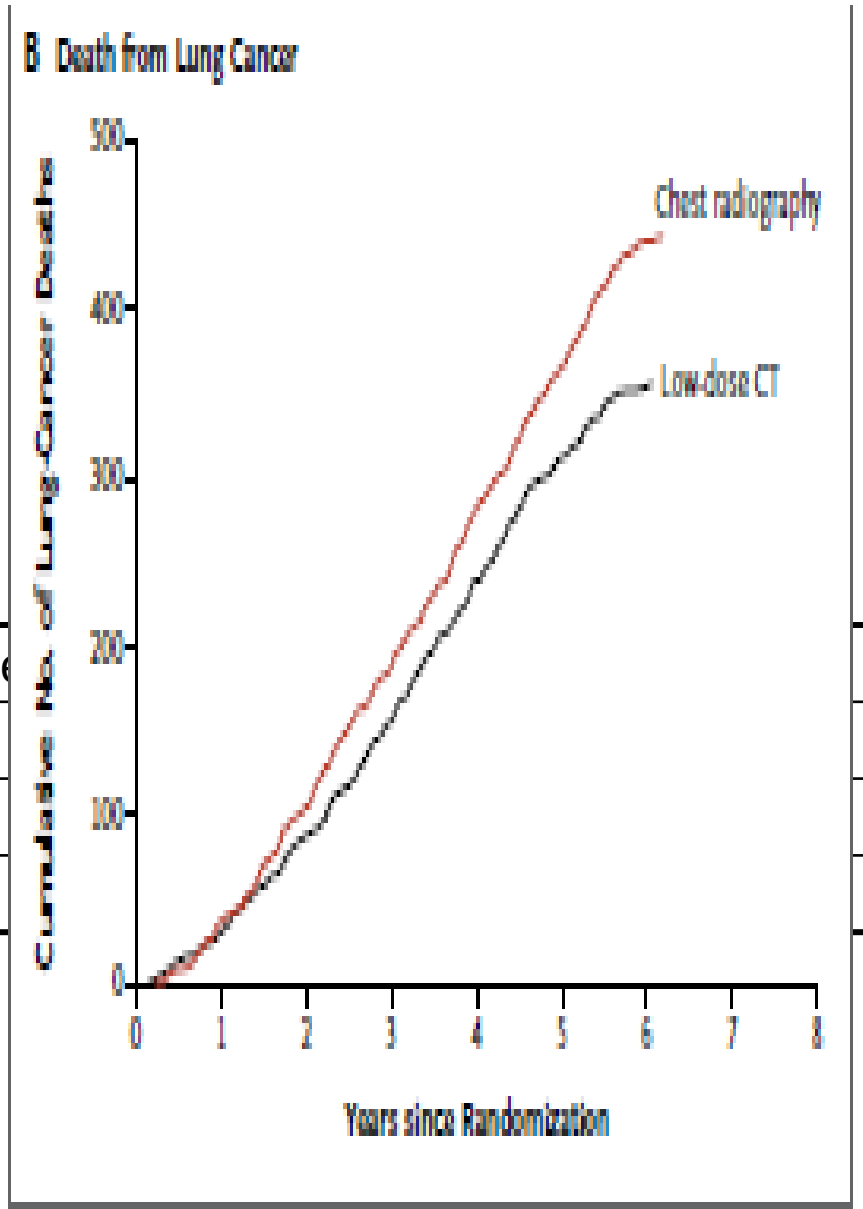
NCCN - National Comprehensive Cancer Network
***J Natl Compr Canc Netw* 2012;10:240-265**

Health Technology Assessment
I problemi aperti

- **Selezione dei soggetti ad alto rischio per tumore del polmone (MMG, Biomarkers)**
- **Proporzione di richiami per accertamenti sia di diagnostica per immagini che invasivi (learning, CAD, Biomarkers)**
- **Sovradiagnosi e sovratrattamento (indicatori di aggressività)**
- **Costi-benefici**
- **Impatto delle politiche antifumo-sussidiarietà dello screening**

NLST


A Lung Cancer
Cumulative No. of Lung Cancers
1100
1000
900
800
700
600
500
400
300
200
100
0
Low-dose CT
Chest radiography
0
1
2
3
4
5
6
7
8
Years since Randomization


B Death from Lung Cancer
Cumulative No. of Lung-Cancer Deaths
500
400
300
200
100
0
Chest radiography
Low-dose CT
0
1
2
3
4
5
6
7
8
Years since Randomization

Criticità gestione clinica

- Elevata qualità nella lettura, anche con sviluppo di lettura assistita CAD e volumetria
- Elevata qualità e stretta osservanza dei protocolli nella gestione dei noduli non calcifici
- Valutazione di protocolli di Follow up dei soggetti postivi , verifica dell'intervallo annuale.

How to select subjects expected to receive benefit from Lung Cancer Screening

British Journal of Cancer (2010) 103, 423 – 429
© 2010 Cancer Research UK All rights reserved 0007 – 0920/10
www.bjcancer.com

Comparison of discriminatory power and accuracy of three lung cancer risk models

AM D'Amelio Jr[1], A Cassidy[1,2], K Asomaning[3], OY Raji[2], SW Duffy[4], JK Field[2], MR Spitz[1], D Christiani[3] and CJ Etzel[*,1]

[1]*Department of Epidemiology, UT MD Anderson Cancer Center, 1155 Pressler Street – Unit 1340, Houston, Texas 77030-4009, USA;* [2]*Roy Castle Lung Cancer Research Programme, School of Cancer Studies, The University of Liverpool Cancer Research Centre, Liverpool L3 9TA, UK;* [3]*Departments of Environmental Health and Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA;* [4]*Cancer Research UK Centre for EMS, Queen Mary University of London, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK*

BACKGROUND: Three lung cancer (LC) models have recently been constructed to predict an individual's absolute risk of LC within a defined period. Given their potential application in prevention strategies, a comparison of their accuracy in an independent population is important.

METHODS: We used data for 3197 patients with LC and 1703 cancer-free controls recruited to an ongoing case–control study at the Harvard School of Public Health and Massachusetts General Hospital. We estimated the 5-year LC risk for each risk model and compared the discriminatory power, accuracy, and clinical utility of these models.

RESULTS: Overall, the Liverpool Lung Project (LLP) and Spitz models had comparable discriminatory power (0.69), whereas the Bach model had significantly lower power (0.66; $P = 0.02$). Positive predictive values were highest with the Spitz models, whereas negative predictive values were highest with the LLP model. The Spitz and Bach models had lower sensitivity but better specificity than did the LLP model.

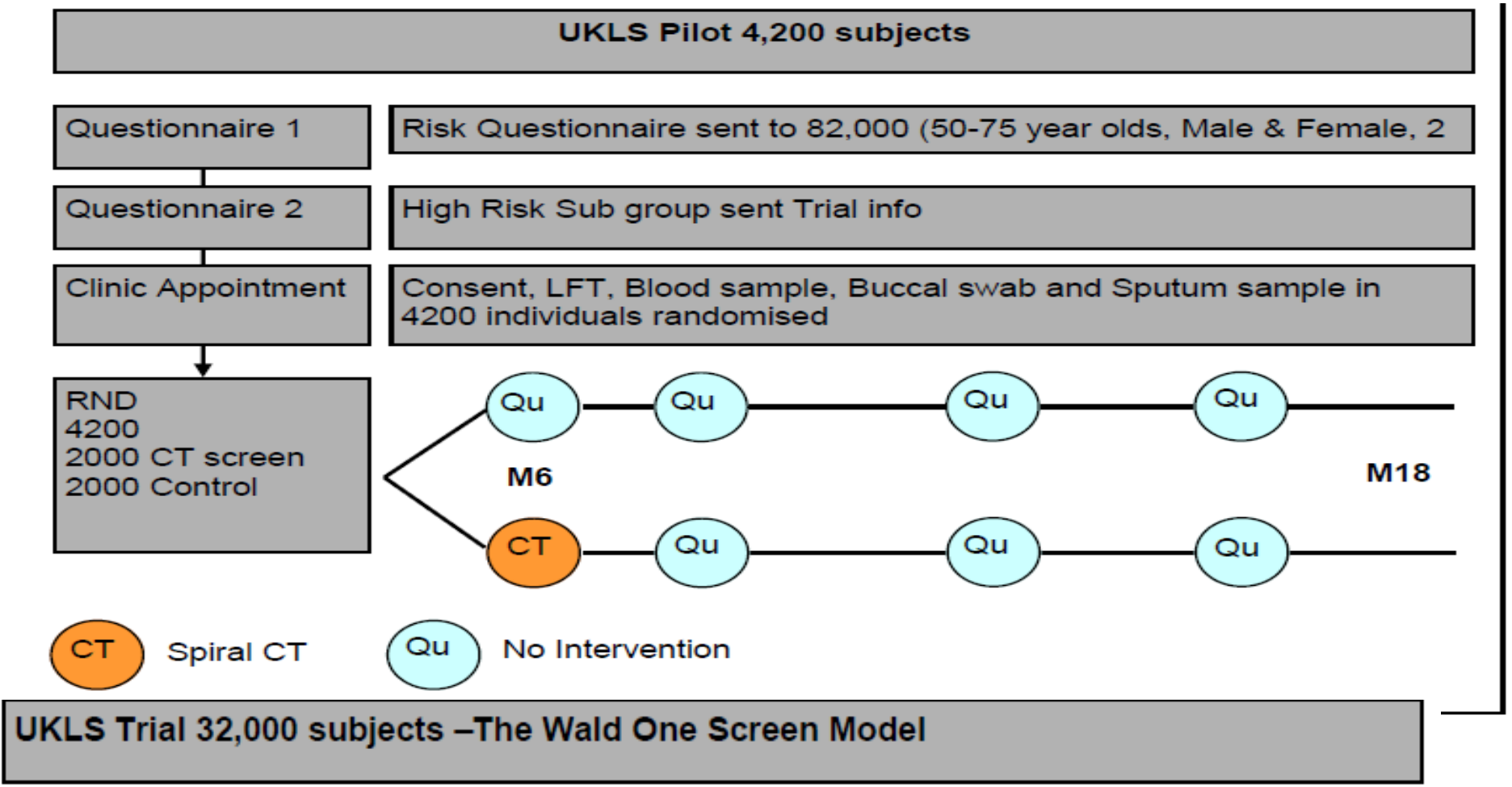
CONCLUSION: We observed modest differences in discriminatory power among the three LC risk models, but discriminatory powers were moderate at best, highlighting the difficulty in developing effective risk models.

British Journal of Cancer (2010) **103,** 423 – 429. doi:10.1038/sj.bjc.6605759 www.bjcancer.com
Published online 29 June 2010

Keywords: lung cancer; risk model; 5-year lung cancer risk; relative risks; discriminatory power

LLP
Bach
Spitz
Prediction of the absolute risk of lung cancer

Selezione dei soggetti ad alto rischio per tumore del polmone



DOCUMENTO DI INDIRIZZO OSSERVATORIO NAZIONALE SCREENING

- Allo stato delle conoscenze lo screening per il tumore del polmone con CT Scan a bassa dose deve essere scoraggiato al di fuori di progetti dimostrativi che siano avviati da centri di eccellenza in diagnostica polmonare e con protocolli di ricerca adeguati.

- **4) Esistono modelli di rischio individuale o altre modalità - inclusi biomarker - per identificare gruppi di individui a maggior rischio e per criteri di screening selettivo? Quali sono le indicazioni per gruppi ad alto rischio (per es. esposti ad amianto)?**

How to manage an integrated screening for lung cancer

- **Integrated screening approach combining Individual risk assessment,biomarkers and CT Scan**

- **Biomarkers as support in decision making at assessment?**

Lung Cancer. 2010 May;68(2):216-21

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Molecular profile in body fluids in subjects enrolled in a randomised trial for lung cancer screening: Perspectives of integrated strategies for early diagnosis

Francesca Maria Carozzi[a,*], Simonetta Bisanzi[a], Patrizia Falini[b], Cristina Sani[a], Giulia Venturini[a], Andrea Lopes Pegna[c], Roberto Bianchi[c], Cristina Ronchi[c], Giulia Picozzi[d], Mario Mascalchi[d], Laura Carrozzi[e], Filomena Baliva[e], Francesco Pistelli[e], Laura Tavanti[e], Fabio Falaschi[f], Michela Grazzini[g], Florio Innocenti[g], Eugenio Paci[b], for the ITALUNG Study Research group[1]

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Molecular markers
Computed tomography (CT)
Cancer diagnosis
Screening
Randomised clinical trial

ABSTRACT

The aim of this study was to evaluate the diagnostic value of a grid of molecular genetic markers detectable in sputum and plasma samples of individuals enrolled in a lung cancer screening program with low-dose CT. Subjects enrolled in the baseline screening round of the ITALUNG (randomised) screening trial were invited to provide biological specimens for molecular analysis (1356 subjects out of 1406). We included 98 subjects in this analysis. There was a highly statistically significant difference between proportion of subjects with a negative baseline CT screening test who were positive to allelic imbalance, and those with a non-calcified nodule (NCN greater than or equal to 5 mm), the reason of recall for all suspects at CT Scan (χ^2: 22.9; P < 0.0001). Allelic imbalance showed good performance for screening of NCN ≥5 mm. In subjects recalled for NCN ≥5 mm, LOH, K-ras mutations and high levels of free plasma DNA (>5 ng/ml plasma) might be important to support clinical decision making for further follow-up and repeated screening. This study, embedded in an early diagnosis randomised trial, suggests that a multi-screening approach integrating imaging technique and a biomolecular marker panel is worth of further investigation.

Preclinical Exploratory	*PHASE 1*	*Promising directions identified*
Clinical Assay and Validation	*PHASE 2*	*Clinical assay detects established disease*
Retrospective Longitudinal	*PHASE 3*	*Biomarker detects preclinical disease and a "screen positive" rule defined*
Prospective Screening	*PHASE 4*	*Extent and characteristics of disease detected by the test and the false referral rate are identified*
Cancer Control	*PHASE 5*	*Impact of screening on reducing burden of disease on population is quantified*

Selection of High-Risk Individuals for Screening - Annual screening is recommended for:

- A
  - Age 55-74 y and
  - 30 pack-year history of smoking and
  - Smoking cessation < 15 y (category 1)
- B
  - Age 50 y and
  - 20 pack-year history of smoking and
  - One additional risk factor (other than secondhand smoke) (category 2B)
    - cancer history
    - lung disease history
    - family history of lung cancer
    - radon exposure
    - occupational exposure

Criticità

- Necessità di selezionare gruppi ad alto rischio
- Elevati tassi di richiamo per accertamenti
- Evidenze di identificazione di lesioni a bassa probabilità di progressione (sovradiagnosi e sovratrattamento)

- **8) Quali sono le questioni aperte per l’avvio di un programma di sanità pubblica di popolazione?**

IASLC CT Screening Workshop 2011 Report July 2011

- The Position Statement stated, that to inform the process of implementation of lung cancer screening at a national level, the IASLC will assemble and disseminate information about the relevant evidence regarding the range of specific issues with implementing and optimizing lung cancer screening care:
- (i) define optimal risk populations who will benefit from screening;
- (ii) what is the cost effectiveness of CT screening;
- (iii) harmonisation of the CT screening protocols to an acceptable level of consistent performance, utilising volumetric analysis;
- (iv) define the value of the individual work-up techniques, standardisation of performance and defining appropriate sequence;
- (v) define the optimal surgical management of patients with screen-detected nodules.

Conclusioni

Gli studi Italiani sono in fase di follow up e contribuiranno a una valutazione europea dell'efficacia

- **E' necessario avviare un progetto di Health Technology Assessment nazionale e dare Raccomandazioni regionali di appropriatezza e qualità**
- **Devono essere proposti studi dimostrativi regionali basato sulla selezione di soggetti ad alto rischio**
- **E' importante che si sviluppino studi di screening di popolazione di soggetti ad alto rischio**

Proposta per il programma regionale : un progetto dimostrativo di e-screening

- Selezione dei soggetti da parte dei Medici di medicina generale e servizi di medicina del lavoro, eligibilità dei soggetti ad alto rischio e informativa via web
- Invito degli elegibili presso un Centro di screening di area vasta , esame funzionalità respiratoria e prelievo sangue e sputo.

Il test e la rete delle immagini digitali

- **Esecuzione del test presso i centri di Screening regionali (AOU Careggi e Pisa), sperimentazione CAD**

- **Doppia lettura distribuita con network di immagini digitali**
- **Gestione approfondimenti e chiusura dell'episodio di screening**
- **Referto al centro di screening e gestione cessazione del fumo e altri interventi**

Galleria degli Uffizi