Eur Respir J 2007; 30: 843–847
DOI: 10.1183/09031936.00000607

Computed tomographic screening for lung cancer: individualising the benefit of the screening

International Early Lung Cancer Action Program Investigators

ABSTRACT: Individuals concerned about their risk of lung cancer are recommended to talk with their physicians about computed tomographic screening for lung cancer. To provide the necessary information, the survival benefit of the screening, specific to a particular person for a particular round of screening, is needed.

The probability of survival gain from the first, baseline, round of screening was addressed as the product of: 1) the screening resulting in a diagnosis of lung cancer; 2) not dying from some other cause for a sufficiently long period of time; and 3) cure resulting from pre-symptomatic treatment of lung cancer. These probabilities were estimated using the International Early Lung Cancer Action Program data on individuals aged 40–85 yrs with a cigarette smoking history of 0–150 pack-yrs.

The estimated probability of survival gain ranged from 0.4% for a 60-yr-old with a 10-pack-yr smoking history who quit smoking 20 yrs ago, to 3.1% for a 70-yr-old current smoker with a 100 pack-yr history and 2.0% for an 85-yr-old current smoker with a 150-pack-yr history.

When seeking counsel about initiation of screening for lung cancer, an estimate of the probability of survival gain from the first round of computed tomographic screening, specific to the person's age and history of smoking, can be provided.

KEYWORDS: International Early Lung Cancer Action Program, lung cancer, survival

AFFILIATIONS
All International Early Lung Cancer Action Programme investigators are listed in the acknowledgements.

CORRESPONDENCE
C.I. Henschke
Dept of Radiology
New York Presbyterian Hospital–Weill Cornell Medical Center
525 East 68th Street
New York
NY 10021
USA
Fax: 1 2127462811
E-mail: chensch@med.cornell.edu

Received:
January 02 2007
Accepted after revision:
July 12 2007

STATEMENT OF INTEREST
None declared.

In 2004, the US Preventive Services Task Force changed its recommendation for screening for lung cancer from D (against) to I (neither for nor against), and suggested that individuals talk with their physicians about whether they should be screened [1]. The American Cancer Society had previously made a similar recommendation [2], and others are now doing the same [3]. Indeed, the decision about screening for lung cancer does not lend itself to a general recommendation but rather requires consideration of its benefit specific to a particular person (survival benefit in the main) at a particular time. In the individual context, the decision to be made is about initiation or continuation of screening; it is thus about a single round of screening at a time.

The probability of survival benefit from a contemplated round of screening depends, for one, on the probability that this round would result in a diagnosis of lung cancer. This probability is naturally specific not only to the risk profile of the person at the time but also to the regimen of screening. Another consideration also specific to the person at the time is the probability of not dying from some other cause before the possible lung cancer death that could be averted by the early intervention that screening-based early diagnosis enables.

Estimates of profile-specific probabilities from data on computed tomographic (CT) screening for lung cancer, and also of the correspondingly individualised probabilities of survival benefit from a contemplated round of screening, focusing on baseline screening, are presented here.

METHODS

Data

The present report is based upon the data thus far accumulated by the International Early Lung Cancer Action Program (I-ELCAP). The focus was on baseline screening, and specifically on that conducted during the period 1993–2006, following the I-ELCAP protocol [4], on persons aged 40–85 yrs who had a cigarette smoking history of 0–150 pack-yrs and who had not undergone chest imaging in the previous 2 yrs. Out of the 33,925 persons identified, 5,588 had

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

never smoked, 15,754 were former smokers and 12,583 were current smokers. The protocol defined the baseline regimen of screening as the initial CT test, including positive and semi-positive results, both of which called for further diagnostic work-up. It also made recommendations for that further work-up. The work-up was documented in the web-based ELCAP Management System, as was death and its causes. All screenees gave informed consent under institutional review board-approved protocols. At baseline screening, the median age was 61 yrs, the median smoking history was 30 pack-yrs and 57% of subjects were males. As a result of baseline screening, 428 cases of lung cancer were diagnosed.

Probability of diagnosis

The probability of the application of the regimen of baseline screening resulting in a diagnosis of lung cancer was addressed as a function of the person's age, smoking history and time since quitting smoking, in the framework of logistic regression analysis. With the dependent variate naturally defined as taking the value Y=1 if lung cancer was diagnosed and 0 otherwise, the independent variates were: 1) X_1=age (in yrs); 2) $X_2=X_1^2$; 3) X_3=1 for ever smokers, and 0 otherwise; 4) $X_4=X_3\times$cigarette smoking history (in pack-yrs); 5) $X_5=X_4^2$; and 6) $X_6=X_3\times$time since quitting smoking (in yrs).

With the fitting yielding the intercept a and coefficients b_1–b_6 for X_1–X_6, respectively, the corresponding estimate of the probability at issue here was taken to be:

$$p_1=1/\{1+\exp[-(a+b_1X_1+b_2X_2+b_3X_3+b_4X_4+b_5X_5+b_6X_6)]\} \quad (1)$$

The linearity of the continuous variates (age, cigarette smoking history and time since quitting) was confirmed using Box–Tidwell transformation in the logistic regression model.

Probability of otherwise surviving

The probability of surviving competing causes of death was addressed using the subcohort of those whose baseline screening took place during 1993–1999. During this time, initiation of screening was limited to persons aged $\geqslant$60 yrs with a cigarette smoking history of $\geqslant$10 pack-yrs. It thus focused on the 1,428 people who, at the time of enrolment, were aged 60–85 yrs, had a smoking history of 10–150 pack-yrs and had not died due to lung cancer by the end of 2006. The survival status at the end of 2006 was known for all of these 1,428 individuals. For logistic regression analysis, the dependent variate was defined as taking the value Y=1 if survival was $\geqslant$10 yrs after the initial CT test during the baseline screening, and 0 otherwise. The independent variates were, in principle, the same as those specified for the probability of diagnosis above; however, the fact that all were smokers meant that X_3 was uniformly 1 and thus needed to be omitted.

Probability of survival benefit

The individualised probability of survival benefit from such baseline screening for lung cancer, on the basis of the associated early intervention, was estimated as the product of the two person-specific probability estimates, derived as described above, multiplied by an estimate of the probability that a baseline-diagnosed case of lung cancer would be curable.

The probability that a baseline-diagnosed case would be curable was taken to be the product of two probabilities, both specific to the regimen of screening: 1) the probability that a baseline-diagnosed case would be stage I at the time of diagnosis; and 2) the probability that such a case would be curable by resection taking place within 1 month of diagnosis. In this calculation, lung cancer was assumed to be uniformly fatal in the absence of screening and death due to some other cause. For these two probabilities, I-ELCAP has produced estimates of 85% (95% confidence interval 82–88%) and 92% (88–95%), respectively [5], yielding 78% as the corresponding estimate of the probability that a baseline-diagnosed case of lung cancer would be curable.

Statistical analysis

Goodness-of-fit was tested using the Hosmer–Lemeshow test, and, if the resulting Chi-squared test result was not significant, the fitted model was not rejected.

RESULTS

For the probability of diagnosis of lung cancer resulting from baseline screening, the parameter estimates, together with their SEMs and p-values for the logistic regression function, are given in table 1. Table 2 addresses, and verifies, the goodness of fit of the fitted function. The values range from 0.07% for a 40-yr-old who never smoked, to 6.8% for an 80- or 85-yr-old with a smoking history of 100 pack-yrs who continues to smoke.

TABLE 1 Estimates of the logistic regression parameters for the probability of diagnosis of lung cancer resulting from baseline screening

Parameter estimated	Nature of coefficient	Estimate	p-value
$a^{\#}$		-16±2.6	
b_1	Age yrs	0.28±0.081	0.0006
b_2	b_1^2	-0.0017±0.00062	0.007
b_3	Ever smoking	-0.14±0.29	0.62
b_4	Smoking history pack-yrs	0.03±0.0069	<0.0001
b_5	b_4^2	-0.0001±0.000051	0.012
b_6	Time since quitting smoking yrs	-0.02±0.0055	0.0003

Data are presented as mean±SEM, unless otherwise stated. #: intercept.

TABLE 2 Frequency of lung cancer diagnosis by level of probability estimate from logistic regression[#,¶]

Regression estimate %	Measured frequency
0–1.0	82/17731 (0.5)
1.0–2.0	142/9457 (1.5)
2.0–3.0	104/3943 (2.6)
3.0–4.0	57/1759 (3.2)
4.0–5.0	31/751 (4.1)
5.0–6.0	11/228 (4.8)
⩾6.0%	1/56 (1.8)
Total	428/33925 (1.3)

Data are presented as n/N (%). #: from table 1; ¶: goodness of fit was not rejected using the Hosmer–Lemeshow test (Chi squared=5.09; p=0.75).

For the probability of not dying due to other causes within 10 yrs of the initial CT test at baseline, the corresponding results are given in tables 3 and 4. The probability estimates range from a high of 98% for a 60-yr-old with a smoking history of 10 pack-yrs who quit smoking 20 yrs ago, down to 37% for an 85-yr-old with a smoking history of 100 pack-yrs who continues to smoke.

Based on these probability functions, table 5 provides individualised estimates of the two probabilities. The table shows how, with increasing age and smoking history, the probability estimates for diagnosis of lung cancer increase and those for surviving competing causes of death decrease.

For current and former smokers aged 60–85 yrs with a smoking history of ⩾10 pack-yrs, table 6 gives probability estimates for survival gain. They range from 0.4% for a 60-yr-old with a 10-pack-yr smoking history who quit 20 yrs ago, to 3.1% for a 70-yr-old with a 100-pack-yr history who continues to smoke and 2.0% for an 85-yr-old with a 150-pack-yr history who continues to smoke.

DISCUSSION

Given that the decision about a person's possible screening for lung cancer is understood to be taken by the person themself in consultation with their doctor [1–3], the doctor's challenge is to be able to counsel the person meaningfully about the potential benefit that they might derive from the screening, and also about the potential harm.

The potential benefit is generally construed as prevention of lung cancer's fatal outcome by screening, meaning by the early intervention that screening-based early diagnosis provides for. That benefit would be realised if, and only if, each of the following were to be the case: the particular round of screening in question is carried out and results in the diagnosis of lung cancer; early treatment of that cancer is carried out and is curative, whereas late intervention, in the absence of screening, would not be; and the person avoids death from other causes until the cancer would have exhibited its fatal outcome in the absence of intervention.

The probability that a round of screening would result in a diagnosis of lung cancer is obviously dependent upon the person's age and smoking history, and also on the screening regimen, and differs between baseline and repeat rounds of screening. The results presented here indicate that, on baseline screening using the I-ELCAP regimen [4], the probability of lung cancer diagnosis ranges from 0.07%, for a 40-yr-old who has never smoked, to 6.8%, for an 80- or 85-yr-old continuing smoker with a smoking history of 100 pack-yrs, and 6.3%, for an 85-yr-old continuing smoker with a smoking history of 150 pack-yrs. Although the probability of diagnosis of cancer increases with age, the probability of dying due to other causes increases such that the overall benefit for a current smoker starts to decrease at age 81 yrs.

Persons seeking counsel about screening for lung cancer are generally in good health relative to that typical of people of their age with the same history of smoking. The prospects for surviving competing causes of death naturally vary, even when dependent upon age and smoking history, and thus also need to be assessed with a view to the particular person's general health at the time screening for lung cancer being considered. In the I-ELCAP experience reported in the present study, the 10-yr survival rate, when excluding deaths due to lung cancer, ranged from 98%, for a 60-yr-old with a 10-pack-yr smoking history who quit 20 yrs ago, to 37%, for an 85-yr-old continuing smoker with a 100-pack-yr smoking history.

TABLE 3 Estimates of the logistic regression parameters[#] for the probability of not dying from some other cause 10 yrs after baseline screening[¶]

	Estimate	p-value
a	1±11	
b_1	0.15±0.32	0.63
b_2	-0.0017±0.0023	0.45
b_4	-0.038±0.014	0.007
b_5	0.00017±0.000099	0.09
b_6	0.017±0.0095	0.08

Data are presented as mean±SEM, unless otherwise stated. #: nature of coefficients detailed in table 1; ¶: in 60–85-yr-olds with a smoking history of ⩾10 pack-yrs.

TABLE 4 Frequency of dying from some other cause by level of probability estimate from logistic regression[#,¶]

Regression estimate %	Measured frequency
49–90	504/611 (82)
90–92	168/181 (93)
92–94	197/211 (93)
94–96	218/232 (94)
96–98	178/182 (98)
98–100	10/11 (91)
Total	1275/1428 (89)

Data are presented as n/N (%). #: from table 3; ¶: goodness of fit was not rejected using the Hosmer–Lemeshow test (Chi squared=13.12; p=0.11).

TABLE 5 Estimates of the probability of diagnosis of cancer and of not succumbing to illness other than lung cancer within 10 yrs by age and smoking history[#]

Age yrs	Smoking history pack-yrs	Continued smoking		Quit 20 yrs ago	
		p_1 %	p_2 %	p_1 %	p_2 %
60	10	0.7	97	0.5	98
	30	1.1	95	0.8	97
	60	2.0	91	1.4	94
	100	2.9	87	2.0	90
	150	2.7	89	1.8	92
70	10	1.3	95	0.9	96
	30	2.1	91	1.4	93
	60	3.6	83	2.5	88
	100	5.2	77	3.6	82
	150	4.8	80	3.3	85
80	10	1.6	86	1.1	90
	30	2.7	77	1.8	83
	60	4.7	63	3.2	71
	100	6.8	53	4.7	61
	150	6.2	58	4.2	66
85	10	1.7	76	1.1	82
	30	2.7	64	1.9	71
	60	4.7	47	3.2	55
	100	6.8	37	4.7	45
	150	6.3	42	4.3	50

p_1: probability of diagnosis of lung cancer; p_2: probability of surviving competing causes of death for $\geqslant$10 yrs. [#]: resulting from application of the International Early Lung Cancer Action Program regimen of screening at baseline.

TABLE 6 Estimates of the probability of survival gain[#] by selected ages and smoking histories[¶]

Age yrs	Smoking history pack-yrs	Probability of survival gain	
		Continued smoking	Quit 20 yrs ago
60	10	0.5	0.4
	30	0.9	0.6
	60	1.4	1.0
	100	2.0	1.4
	150	1.9	1.3
70	10	0.9	0.6
	30	1.5	1.0
	60	2.4	1.7
	100	3.1	2.3
	150	3.0	2.2
80	10	1.1	0.8
	30	1.6	1.2
	60	2.3	1.8
	100	2.8	2.2
	150	2.8	2.2
85	10	1.0	0.7
	30	1.4	1.0
	60	1.7	1.4
	100	2.0	1.6
	150	2.0	1.7

[#]: product of p_1 and p_2 (from table 5) multiplied by estimated stage I cancer curability rate (78%); [¶]: resulting from application of the International Early Lung Cancer Action Program regimen of screening at baseline.

A separate analysis of the I-ELCAP data has indicated that, when baseline screening with the regimen resulted in the diagnosis of lung cancer, it was stage I in 85% of cases, and also that, given resection within 1 month of diagnosis of a stage I cancer, the 10-yr survival rate, when excluding deaths due to other causes, was 92% [5]. The product of these two proportions, 78%, is an estimate of the curability rate for lung cancer diagnosed using the I-ELCAP regimen for baseline screening.

For example, then, if a 60-yr-old current smoker with a 60-pack-yr smoking history consults a doctor about the justifiability of initiating screening for lung cancer as a means of averting death due to this dreaded disease, the doctor might think about screening using the I-ELCAP regimen and its results and advise the person along the following lines. For this person, the probability of survival gain resulting from the contemplated baseline screening is the product of three probabilities, that of the round of screening resulting in the diagnosis of lung cancer, that of the diagnosed cancer being curable by early treatment and that of the person escaping death due to other causes long enough to benefit from the lung cancer death that was thus prevented. For these probabilities, the estimates from the I-ELCAP experience are 2.0 (table 5), 78 (see above) and 91% (table 5), respectively; thus the corresponding estimate for the probability product is $0.020 \times 0.78 \times 0.91$, or 1.4% (table 6).

The probability estimates presented here are based upon the largest currently available experience, but require further supplementation as additional screening and longer term follow-up data become available. The probability of diagnosing a stage I lung cancer was based on the full cohort, whereas the probability of otherwise surviving was based on a more limited cohort for whom $\geqslant$8 yrs of follow-up for all causes of death was available. Thus future updating of the estimates is needed. In addition, these probability estimates address only the benefit of the first, baseline, round of screening, during which four to five times as many cancers are identified as in the absence of screening. If the baseline round does not result in the diagnosis of lung cancer, the benefit of each repeat screening needs to be addressed separately.

The doctor should, however, be able to convey with great assurance the qualitative point that the screening does have the potential of serving to prevent death due to lung cancer. For this not to be the case, at least one of the relevant probabilities would have to be zero, and the present authors believe that it would be very difficult plausibly to argue that this might be the case. If, on this basis, the person decides to undergo the baseline screening, they would later face a similar decision about the first round of possible repeat screening. The survival

benefit from this would need to be addressed in a similar way, based on experience with repeat screening.

ACKNOWLEDGEMENTS

The writing committee consisted of C.I. Henschke, N. Altorki, A. Farooqi, J. Hess, D. Libby, D.I. McCauley, M.W. Pasmantier, A.P. Reeves, J.P. Smith, M. Vazquez, D.F. Yankelevitz, R. Yip, L. Zhang, K. Agnello (all Joan & Sanford I. Weill Medical College of Cornell University, New York, NY, USA); J. Ostroff (Memorial Sloan-Kettering Cancer Center, New York, NY, USA); and O.S. Miettinen (McGill University, Montreal, Canada).

The pathology review panel consisted of D. Carter (Dept of Pathology, Yale University School of Medicine, New Haven, CT, USA) E. Brambilla (University of Grenoble, Grenoble, France); A. Gazdar (Univesity of Texas Southwestern Medical Center, Dallas, TX, USA); M. Noguchi (University of Tsukuba, Tsukuba, Japan); and W.D. Travis (Memorial Sloan-Kettering Cancer Center, New York, NY, USA).

The International Early Lung Cancer Action Program investigators (including coordinating centre and pathology panel investigators) are as follows. C.I. Henschke (principal investigator), D.F. Yankelevitz, D.I. McCauley (Joan & Sanford I. Weill Medical College of Cornell University); S. Sone, T. Hanaoka (Azumi General Hospital, Nagano, Japan); S. Markowitz, A. Miller (Center for the Biology of Natural Systems, City University of New York at Queens College, New York, NY, USA); K. Klingler, T. Scherer, R. Inderbitzi (LungenZentrum Hirslanden, Zurich, Switzerland); J. Zulueta, L. Montuenga, G. Bastarrika (Clinica Universitaria de Navarra, Pamplona, Spain); S. Giunta, M. Crecco, P. Pugliese (Regina Elena National Cancer Institute, Rome, Italy); M. Tockman (H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA); D. Shaham (Hadassah Medical Organization, Jerusalem, Israel); K. Rice, R. Aye (Swedish Medical Center, Seattle, WA, USA); H. Roberts, D. Patsios (University of Toronto, Princess Margaret Hospital, Toronto, ON, Canada); T. Bauer, J. Lally (Christiana Care, Helen F. Graham Cancer Center, Newark, DE, USA); J.H.M. Austin, G.D.N. Pearson (Columbia University Medical Center, New York, NY, USA); D. Naidich, G. McGuinness (New York University Medical Center, New York, NY, USA); M. Rifkin, E. Fiore (State University of New York at Stony Brook, Stony Brook, NY, USA); S. Kopel (Maimonides Medical Center, New York, NY, USA); D. Klippenstein, A. Litwin, P.A. Loud (Roswell Park Cancer Institute, Buffalo, NY, USA); L.J. Kohman, E.M. Scalzetti (State University of New York, Upstate Medical Center, Syracuse, NY, USA); A. Khan, R. Shah (North Shore–Long Island Jewish Health System, New Hyde Park, NY, USA); M.V. Smith, H.T. Williams, L. Lovett (Georgia Institute for Lung Cancer Research, Atlanta, GA, USA); D.S. Mendelson (Mount Sinai School of Medicine, New York, NY, USA); R. Thurer (Jackson Memorial Hospital, University of Miami, Miami, FL, USA); R.T. Heelan, M.S. Ginsberg (Memorial Sloan–Kettering Cancer Center, New York, NY, USA); F. Sullivan, M. Ottinger (Holy Cross Hospital Cancer Institute, Silver Spring, MD, USA); D. Vafai (Eisenhower Lucy Curci Cancer Center, Rancho Mirage, CA, USA); T.A.S. Matalon (New York Medical College, Valhalla, NY, USA); S-L. Odzer (Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, USA); X. Liu (Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China); B. Sheppard (Dorothy E. Schneider Cancer Center, Mills–Peninsula Health Services, San Mateo, CA, USA); E. Cole (St. Agnes Cancer Center, Baltimore, MD, USA); P.H. Wiernik (Our Lady of Mercy Medical Center, New York, NY, USA); D. Ray (Evanston Northwestern Healthcare Medical Group, Evanston, IL, USA); H. Pass, C. Endress (Karmanos Cancer Institute, Detroit, MI, USA); D. Mullen (Greenwich Hospital, Greenwich, CT, USA); M. Kalafer (Sharp Memorial Hospital, San Diego, CA, USA); F. Grannis, A. Rotter (City of Hope National Medical Center, Duarte, CA, USA); M.K. Thorsen, R. Hansen (ProHealth Care Regional Cancer Center, Waukesha & Oconomowoc Memorial Hospitals, Oconomowoc, WI, USA); E. Camacho (Comprehensive Cancer Center, Desert Regional Medical Center, Palm Springs, CA, USA); and D. Luedke (St. Joseph Health Center, St Charles, MO, USA).

REFERENCES

1 Humphrey LL, Teutsch S, Johnson M. Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004; 140: 740–753.

2 Smith RA, von Eschenbach AD, Wender R, *et al.* American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancer. Also: update 2001 – testing for early lung cancer detection. *CA Cancer J Clin* 2001; 51: 38–75.

3 Strauss GM, Dominioni L, Jett JR, Freedman M, Grannis FW. Como international conference position statement: lung cancer screening for early diagnosis 5 years after the 1998 Varese conference. *Chest* 2005; 127: 1146–1151.

4 International Early Lung Cancer Action Program protocol. www.IELCAP.org/professionals/protocols.htm Date last updated: May 30, 2007. Date last accessed: September 10, 2007.

5 The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006; 355: 1763–1771.