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Computed tomography screening for lung cancer: Results of ten years of annual screening and validation of cosmos prediction model

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ABSTRACT

Introduction: It is unclear how long low-dose computed tomographic (LDCT) screening should continue in populations at high risk of lung cancer. We assessed outcomes and the predictive ability of the COSMOS prediction model in volunteers screened for 10 years.
Materials and methods: Smokers and former smokers (>20 pack-years), >50 years, were enrolled over one year (2000–2001), receiving annual LDCT for 10 years. The frequency of screening-detected lung cancers was compared with COSMOS and Bach risk model estimates.
Results: Among 1035 recruited volunteers (71% men, mean age 58 years) compliance was 65% at study end. Seventy-one (6.95%) lung cancers were diagnosed, 12 at baseline. Disease stage was: IA in 48 (66.6%); IB in 6; IIA in 5; IIB in 2; IIIA in 5; IIIB in 1; IV in 5; and limited small cell cancer in 3. Five- and ten-year survival were 64% and 57%, respectively, 84% and 65% for stage I. Ten (12.1%) received surgery for a benign lesion. The number of lung cancers detected during the first two screening rounds was close to that predicted by the COSMOS model, while the Bach model accurately predicted frequency from the third year on.
Conclusions: Neither cancer frequency nor proportion at stage I decreased over 10 years, indicating that screening should not be discontinued. Most cancers were early stage, and overall survival was high. Only a limited number of invasive procedures for benign disease were performed. The Bach model – designed to predict symptomatic cancers – accurately predicted cancer frequency from the third year, suggesting that overdiagnosis is a minor problem in lung cancer screening. The COSMOS model – designed to estimate screening-detected lung cancers – accurately predicted cancer frequency at baseline and second screening round.

1. Introduction

The US National Lung Screening Trial (NLST) [1] found that low-dose computed tomography (LDCT) screening reduced lung cancer mortality, however only three screening rounds were offered to high risk individuals and it is unclear how long screening should continue [2]. No long-term results of periodic screening are available, and most published trials screened for no longer than five consecutive years [3–8].

While ample data are available on the long-term survival of patients with screening-detected lung cancer [9,10], no information is available on long-term outcomes in entire populations of individuals undergoing protracted periodic screening. A risk model [11] based on a screened population has been published, but has not so far been validated on an independent population. In the present study we assessed long-term overall survival and cancer detection rate, and compared model-predicted with observed lung cancer detection frequencies over ten years, in an ongoing single-center pilot screening study of volunteers at high risk of developing lung cancer.

2. Methods

A total of 1035 high-risk asymptomatic volunteers (smokers and former smokers, >50 years, mean age 58 years, 71% men) were

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enrolled in 2000–2001 and followed for 10 years with annual LDCT (verification set). Study methods and protocol are described in detail elsewhere [6]. Briefly, to be eligible volunteers had to be over 50 years of age, have a smoking history of more than 20 pack-years and give written informed consent. At study entry, spirometry was performed, a self-reported questionnaire on smoking habits and other risk factors was compiled, and blood samples were collected for molecular analyses. A single detector CT scanner was used. In the subsequent COSMOS study (training set) a single detector CT scanner was used to 2003, for an 8- or 16-detector scanner was used subsequently. In both the verification set and training set, nodules ≤5 mm underwent repeat scan at 1 year; nodules 5.1–8 mm underwent CT 3 months later; lesions >8 mm received combined CT-positron emission tomography (CT-PET). The pre-COSMOS and COSMOS studies were approved by the ethical committee of the European Institute of Oncology. After five years, an Ethical Committee amendment allowed the pre-COSMOS study to continue for a further five years.

2.1. Statistical methods

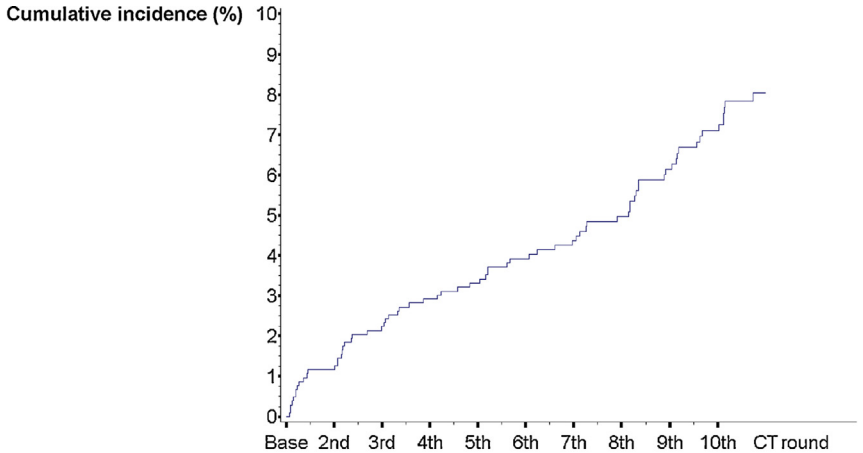
Lung cancer frequency and death rate were calculated dividing the number of events by the number of person-years of observation over the entire study period, from date of baseline screening to date of last follow-up or death. Overall survival and cumulative lung cancer incidence curves were constructed using, respectively, the Kaplan–Meier method and its compliment. The log-rank test was used to assess differences between curves. The expected numbers of lung cancers were calculated summing the risk of individual participants developing cancer as estimated by the Bach risk model [12] and the recalibrated model (COSMOS) proposed by Maisonneuve et al. [11]. Both models predict lung cancer based on age, sex, smoking history and exposure to asbestos. The COSMOS model used the number of screening-detected lung cancers at baseline among the 5203 asymptomatic participants of the COSMOS trial to recalibrate the original Bach model [11]. The numbers of cancers diagnosed in each of the 10 study years were compared with those predicted by the models, assuming that the observed cases followed a Poisson distribution. The analyses were performed with SAS version 8.2 (Cary, NC). All tests are two-sided. A P value <0.05 was considered statistically significant.

3. Results

Table 1 shows baseline characteristics of participants, together with outcomes. Eighty-four percent were current smokers at baseline. After 10 annual screening rounds and a median follow-up of 9.6 years, 71 lung cancers (6.9%) were diagnosed by screening (detection rate = 0.83 per 100 person-years) and 60 had died (mortality rate = 0.67 per 100 person-years). Compliance was good, with 671/1035 (65%) participants presenting for the tenth screening round. Death was attributed to lung cancer in 23 cases, other cancer in 12 cases, cardiovascular disease in 10 cases, and other causes in 15 cases. Twelve of the 71 lung cancers were detected at baseline and 59 subsequently; 78% were stage I. Histology was: squamous cell carcinoma, 14 (19.4%); adenocarcinoma or bronchioloalveolar carcinoma, 44 (61.1%); large cell carcinoma, 1 (1.4%); other non-small cell carcinoma, 1 (1.4%); small cell carcinoma, 7 (9.7%); and carcinoid, 5 (6.94%). The mean size of CT-detected non-small cell cancers was 12.5 mm. Stage breakdown was: IA, 48 (66.6%); IB, 6; IIA, 5; IIB, 2; IIIA, 5; IIIB, 1; IV, 5; limited small cell cancer, 3. Forty-three (70.5%) of the 61 non-small cell cancers were stage IA at diagnosis. Postoperative (30-day) morbidity was 31% (including 8% serious complications and 23% minor complications); there were no postoperative deaths.

Fig. 1 shows the cumulative incidence of screening-detected lung cancers over the ten-year period. The lung cancer detection rate was 1.1 per 100 person-years at the two first screening rounds and stable at around 0.7% per 100 person-years at following rounds.

The number of lung cancers detected during the first two screening rounds (n = 23) was higher (P < 0.001) than expected (n = 9.9) based on the risk prediction model of Bach et al. [12] to estimate incident lung cancers in high risk smokers, but close to that predicted (n = 25.9) by the COSMOS model [11] to estimate



	Base	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Total
N receiving CT	1035	996	974	938	889	848	792	760	716	671	9,230
Lung cancers											
Detected	12	11	6	6	5	4	6	8	8	5	71
Expected (Bach model)†	4.8	5.1	5.4	5.7	5.8	6.1	6.2	6.3	6.4	6.5	58.3
Expected (Recalibrated model)‡	12.5	13.4	14.4	15.2	15.7	16.4	16.8	17.0	17.3	17.5	156.2
Deaths	-	4	4	7	7	14	5	8	8	3	60
Cumulative drop-outs (%)	-	35 (3.4)	53 (5.1)	82 (7.9)	124 (12.0)	151 (14.6)	202 (19.5)	226 (21.8)	262 (25.3)	304 (29.4)	304 (29.4)

Fig. 1. Cumulative incidence of lung cancer detected by annual CT. †Number of lung cancers expected calculated using the prediction model proposed by Bach et al. [12]. ‡Number of lung cancer expected calculated using the recalibrated prediction model proposed by Maisonneuve et al. [11] screening.

Table 1
Baseline characteristics and cancer outcomes in a lung cancer screening trial after a median follow-up of 9.6 years (range 0–10.6).

Baseline characteristics	Participants *N* (%)	Lung cancer cases	Deaths				
			All causes	Lung cancer	Other cancer[a]	Vascular[b]	Other, unknown
		N (rate/100 person-years)	*N* (rate/100 person-years)	*N* (rate/100 person-years)	*N* (rate/100 person-years)	*N* (rate/100 person-years)	*N* (rate/100 person-years)
Totals	1035 (100.0)	71 (0.83)	60 (0.67)	23 (0.26)	12 (0.13)	10 (0.11)	15 (0.17)
Sex							
Men	738 (71.3)	51 (0.84)	52 (0.82)	20 (0.32)	11 (0.17)	8 (0.13)	13 (0.21)
Women	297 (28.7)	20 (0.80)	8 (0.31)	3 (0.12)	1 (0.04)	2 (0.08)	2 (0.08)
Age (years)							
50–54	295 (28.5)	15 (0.60)	12 (0.47)	5 (0.20)	3 (0.12)	1 (0.04)	3 (0.12)
55–59	320 (30.9)	25 (0.92)	18 (0.64)	9 (0.32)	3 (0.11)	4 (0.14)	2 (0.07)
60–64	273 (26.4)	20 (0.88)	17 (0.72)	5 (0.21)	3 (0.13)	3 (0.13)	6 (0.25)
65 or more	147 (14.2)	11 (1.00)	13 (1.12)	4 (0.34)	3 (0.26)	2 (0.17)	4 (0.34)
Smoking status							
Current smoker	875 (84.5)	65 (0.90)	52 (0.69)	21 (0.28)	10 (0.13)	9 (0.12)	12 (0.16)
Former smoker	160 (15.5)	6 (0.45)	8 (0.59)	2 (0.15)	2 (0.15)	1 (0.07)	3 (0.22)
Smoking duration (years)							
Less than 30	253 (24.4)	12 (0.56)	9 (0.41)	1 (0.05)	4 (0.18)	3 (0.14)	1 (0.05)
30–40	572 (55.3)	37 (0.77)	29 (0.59)	11 (0.22)	5 (0.10)	6 (0.12)	7 (0.14)
40 or more	210 (20.3)	22 (1.35)	22 (1.27)	11 (0.63)	3 (0.17)	1 (0.06)	7 (0.40)
Cigarette consumption (per day)							
Less than 20	127 (12.3)	5 (0.47)	3 (0.28)	1 (0.09)	2 (0.19)	–	–
20–29	561 (54.2)	29 (0.61)	28 (0.58)	8 (0.16)	4 (0.08)	5 (0.10)	11 (0.23)
30–39	164 (15.8)	16 (1.19)	10 (0.70)	3 (0.21)	4 (0.28)	3 (0.21)	–
40 or more	183 (17.7)	21 (1.45)	19 (1.24)	11 (0.72)	2 (0.13)	2 (0.13)	4 (0.26)
Smoking (pack-years)							
20–39	405 (39.1)	13 (0.37)	10 (0.28)	2 (0.06)	4 (0.11)	2 (0.06)	2 (0.06)
40–59	360 (34.8)	24 (0.80)	25 (0.80)	7 (0.22)	5 (0.16)	5 (0.16)	8 (0.26)
60 or more	270 (26.1)	34 (1.62)	34 (1.51)	14 (0.62)	3 (0.13)	3 (0.13)	5 (0.22)

[a] Cancers of esophagus ($n = 1$), stomach ($n = 1$), intestine ($n = 2$), pancreas ($n = 1$), pleura ($n = 1$), soft tissue sarcoma ($n = 1$), kidney ($n = 1$), bladder ($n = 1$), prostate ($n = 1$), leukemia/lymphoma ($n = 2$).
[b] Stroke ($n = 4$), cerebral aneurysm ($n = 4$), myocardial infarction ($n = 2$).

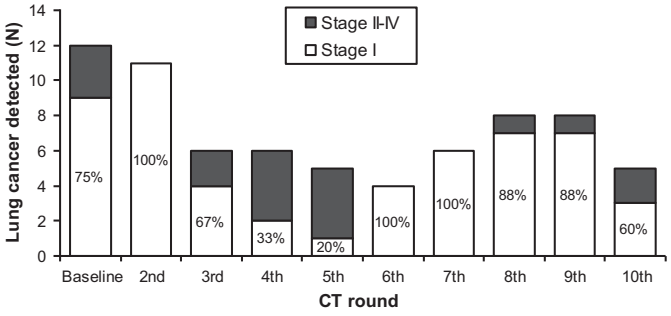


Fig. 2. Stage distribution of lung cancers detected by annual CT screening.

screening-detected lung cancers. By contrast, the number of lung cancers ($n = 48$) detected during the subsequent eight screening rounds was close to that predicted by the original Bach model ($n = 48.4$, $P = 0.49$) (Fig. 1). The proportion of stage 1 cancers diagnosed in any year varied from 20% to 100%, but the overall rate remained stable over the ten years (Fig. 2). Fig. 3 shows the cumulative incidence of lung cancers detected by annual screening, according to baseline smoking status and smoking history.

Complete tumor resection was achieved in 58 (80.5%) lung cancers. Five-year and ten-year survival were 64% and 58% overall, and 84% and 75% for stage I cases, respectively, (Fig. 4). Ten (12.1%) patients underwent invasive surgery for what turned out to be a benign lesion; there was no postoperative morbidity or mortality in these patients.

4. Discussion

We have found that the cancer detection rates at baseline and the second screening round were higher than predicted by the Bach model [12], but close to those predicted by the COSMOS model [11] recalibrated from the Bach model in order to predict lung cancers at baseline screening. This is the first validation of the COSMOS model in an independent population of current and recent heavy smokers.

The frequency of lung cancer detection during the subsequent eight annual screening rounds was lower than at baseline, but remained stable over the entire period, and was similar to that predicted by the original Bach model – designed to predict symptomatic cancers. Thus, the frequency of lung cancers over the last eight years of the study was very close to the expected frequency of symptomatic cancers in a high risk population, suggesting that few of these cancers were overdiagnosed (would have not

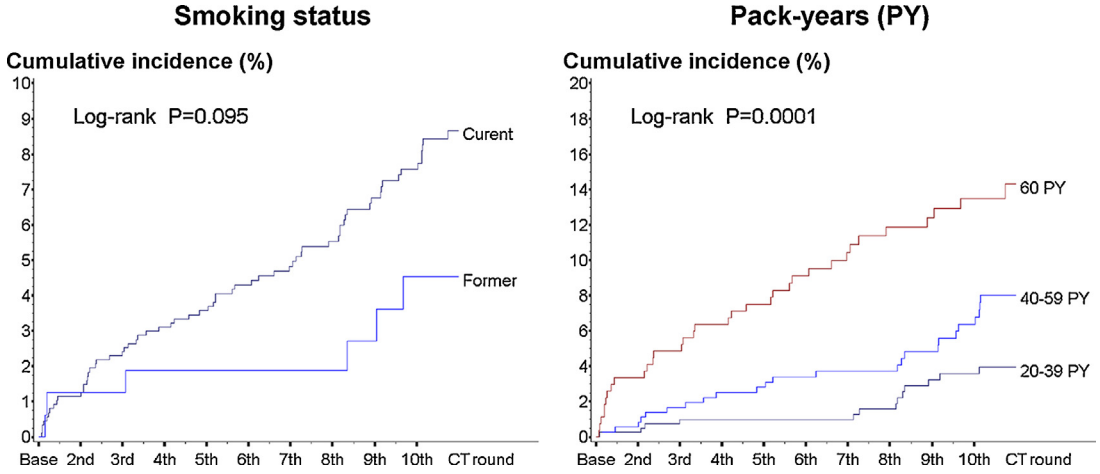


Fig. 3. Cumulative incidence of lung cancer detected by annual CT screening according to baseline smoking status and smoking history.

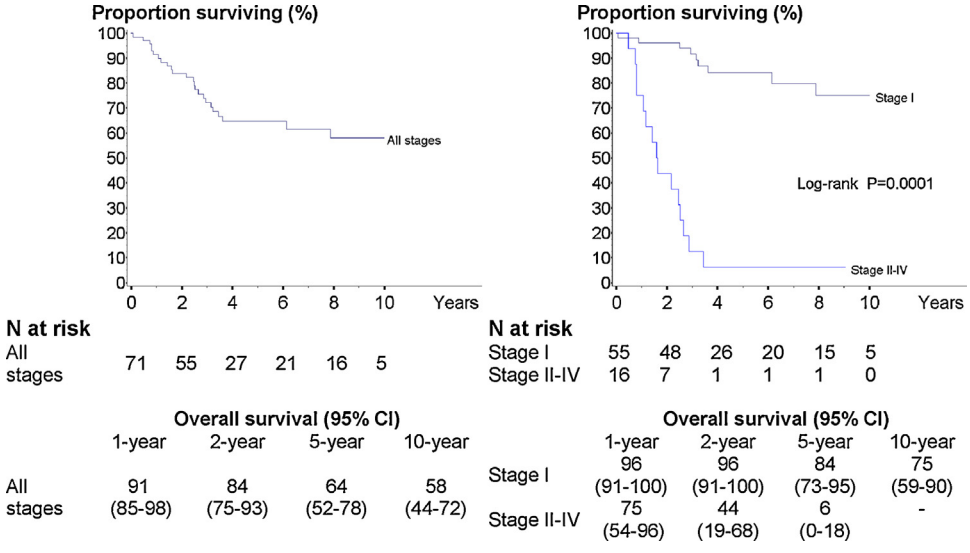


Fig. 4. Overall survival of 71 patients with screening CT-detected lung cancer.

became symptomatic in participant's lifetime). Note however, this inference seems at odds with our recent estimate, in a different population, that around 20% of screening detected-lung cancers might be overdiagnosed [13]. This difference might be due to overestimation of overdiagnosis in our previous paper, based on the sole criterion of long volume doubling time (VDT) and it is likely that a proportion of the cancers considered indolent or overdiagnosed based on a VDT >600 days, would have become symptomatic if left un-resected.

A 2007 study by Bach et al. [5] which, like the present study, compared the frequency of lung cancers diagnosed in a screened population with those predicted by Bach models, concluded that screening probably did not reduce lung cancer deaths. However in that study most (70%) participants were screened for only 3 or 4 years (median follow-up 3.9 years). The study [5] also found "no evidence of a decline" in the proportion of advanced cases diagnosed, while in the present study the proportion of advanced cases fluctuated but the rate of diagnosis of early stage cases was maintained over the entire ten-year period. The present experience therefore indicates that screening should be continued for over five years (either annually or every two to three years), and undermines the hypothesis that overdiagnosis is a major problem with lung cancer screening [14]. If overdiagnosis were a major phenomenon, the proportion of stage I cancers would be expected to decline after the first couple of screening rounds. Nevertheless a reliable estimate of the overdiagnosis rate can only come from randomized trials.

Another important finding of the present study is that the resection rate was good, and only a limited number of patients with what turned out to be benign disease, underwent invasive procedures, in accord other pilot single-arm studies [15–17].

Mortality data from other studies also support not discontinuing CT screening should after a few years. Thus, the 2011 paper from Henschke et al. [18] found that the two rounds of screening in the NYS cohort provided a mortality reduction that started in the fourth year and reached a maximum in the sixth to eighth years after enrollment. However, once screening stops, lung-cancer deaths are likely to increase and ultimately reach the same rate as in the absence of screening. The authors of the NLST trial [1] suggested that the reduction in lung cancer death rate would have been larger (than the 20% observed in 3 rounds) if screening had not been interrupted. A previous paper [19] from our group, on the cohort described in the present study, found that after 7 years of screening, lung cancer-specific mortality was reduced by 50% in the screened population compared to that in a cohort of smokers and former smokers matched for age and smoking intensity.

To conclude, results of 10 years of annual LDCT in our high risk cohort show that the lung cancer detection rate remained stable over this long period and, importantly, that the proportion of early stage cancers also remained stable, implying that screening should continue for beyond ten years. Finally our results provide the first validation of the COSMOS risk model [11] as it accurately predicted the frequency of lung cancers and the first and second screening rounds in the present cohort – independent of that used to derive the model. The original Bach model, designed to predict symptomatic lung cancers, accurately predicted incidental lung cancers on our screened cohort after the two initial screening rounds.

Conflict of interest statement

None declared.

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